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Can Intensity-Modulated Radiotherapy (IMRT) Be Used To
Reduce Toxicity And Improve Tumour Control In Patients With
Head And Neck Cancer?

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Glossary of Abbreviations

18-FDG	18F-fluorodeoxyglucose
3DCRT	Three dimensional conformal radiotherapy
CHART	Continuous, hyperfractionated accelerated radiotherapy
CRT	Conformal radiotherapy
CT	Computed Tomography
CTSU	Clinical Trials and Statistics Unit
CTV	Clinical target volume
DAHANCA	Danish Head and Neck Cancer Society
DCE	Dynamic contrast enhanced
DLT	Dose-limiting toxicity
dMLC	Dynamic MLC
DW	Diffusion weighted
EORTC	European Organisation for Research and Treatment of Cancer
FNA	Fine needle aspirate
GORTEC	Oncology and Radiotherapy Group for Head and Neck Cancer (France)
GTV	Gross tumour volume
HNSCC	Head and neck squamous cell carcinoma
HPV	Human Papilloma Virus
ICR	Institute of Cancer Research
IJV	Internal Jugular vein
IMAT	Intensity-modulated arc therapy
IMB	Intensity-modulated beams
IMRT	Intensity modulated radiotherapy
LENT-SOMA	Late effects of normal tissue – subjective, objective, management, analytical
MIMiC	Multivane Intensity Modulating Collimator
MLCs	Multi-leaf collimators
MRI	Magnetic resonance imaging
MSF	Multiple static fields
NCAT	National Cancer Action Team
NCGC	National Clinical Guideline Centre
NCIC	National Cancer Institute of Canada
NICE	National Institute for Health and Clinical Excellence
NTCP	Normal tissue complication probability
OAR	Organs at risk
PET-CT	Positron emission tomography-computerised tomography
PS-IMRT	Parotid sparing Intensity modulated radiotherapy
PTV	Planning Target Volume
QA	Quality assurance
QoL	Quality of life

RCT	Randomised controlled trial
RMH	Royal Marsden Hospital
RTOG	Radiation Therapy Oncology Group
RTTQA	Radiotherapy Trials QA group
SC	Spinal cord
TCP	Tumour control probability
TLDs	Thermo luminescent dosimeters
TMG	Trial Management Group
TPS	Treatment planning system
TROG	Tasmanian Radiation Oncology Group
TVD	Target volume delineation
UCSF	University of California San Francisco
UM	University of Michigan
US	Ultrasound
WHO	World Health Organisation

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I am grateful to my long term collaborators and staff in the Departments of Physics and Radiotherapy at The Royal Marsden Hospital and The Institute of Cancer Research past and present for keeping the ship afloat through thick and thin. Much of the work presented here was to them above and beyond the call of duty to push the envelope of what was possible to achieve in a busy hospital radiotherapy department. It is their attitudes and drive that make the Marsden what it is today. I am deeply grateful to the patients with whom I have made this journey, their willingness to take part in the clinical trials, their time and support of my efforts and the trust they put in me.

For this thesis I thank my supervisors, Robert Price, Sue Procter and Gill Craig at City and my close colleague Kevin Harrington for providing support and specialist supervision. I am indebted to the co-authors for their support and encouragement to complete this unusual form of PhD.

Finally, I thank my wife Melanie and my children Jessica, Jemima, James and George for their support and putting up with daddy being so busy all the time!

Abstract

Radiotherapy is commonly used in the treatment of head and neck cancer. For early stage tumours, conventional radiotherapy techniques have a high cure rate and low levels of long-term complications. Patients with more advanced cancers have much lower cure rates and high levels of treatment-related complications. Intensity-modulated radiotherapy (IMRT) is a new form of focussed radiation therapy. It has been used to reduce the radiation dose to normal tissue structures and increase the dose delivered to tumour bearing tissues. This potentially allows reduced side effects and increased tumour control compared to conventional radiotherapy. The rationale of this thesis was to test whether these twin goals could be achieved in head and neck cancer patients.

The first part of the thesis describes improvements in patient immobilisation, optimisation of techniques for neck irradiation, and evaluation of the technique in a busy radiotherapy department. It includes pre-clinical evaluation of IMRT for different tumour sites, the development of quality assurance programs and the conduct of a national randomised controlled trial of parotid-sparing IMRT. This trial concluded that IMRT significantly reduced patient-reported xerostomia, allowed recovery of saliva production and improved quality of life. The second part of the thesis describes pre-clinical evaluation of techniques to escalate radiation dose in patients with larynx and hypopharynx tumours. A phase I/II clinical trial showed that higher doses of radiation can be delivered at the expense of an increase in acute radiation toxicity but without a measurable increase in late radiation side effects. In the larynx and hypopharynx groups, a possible increase in local control was observed.

This thesis describes the process of evaluation of a new radiotherapy technology and could be used as a template for testing other new technologies in the future.

Chapter 1

A decade of research in head and neck cancer radiotherapy

1.1 Setting the scene

This PhD by prior publication presents a thesis of 10 research papers describing research work carried out between 2001 and 2011. The papers presented here are a development of earlier work undertaken during my clinical research fellowship at The Institute of Cancer Research (ICR) between 1998 and 2000 which was awarded MD (res) in 2001. My MD (res) supervisors were Steve Webb, Professor of Medical Physics, and David Dearnaley, Professor of Prostate Cancer Studies. I worked in the department of medical physics on a new form of radiotherapy called intensity-modulated radiotherapy (IMRT), a new technique aimed at focussing radiation in a more accurate way to treat cancer. This was a very interesting time working as the only doctor in a department of physicists and engineers to develop this treatment technique. I was able to demonstrate the potential advantages of IMRT to allow normal tissue sparing and escalation of radiation dose for more effective and safer treatment for a variety of tumours. In the MD (res) thesis I described new radiotherapy techniques for tumours of the thyroid (Nutting, Convery et al. 2001), parotid (Nutting, Rowbottom et al. 2001) (Rowbottom, Nutting et al. 2001), oesophagus (Nutting, Bedford et al. 2002) and prostate (Nutting, Convery et al. 2000). In 2000 I travelled to Memorial Sloane Kettering Hospital in New York where I worked with Dr Michael Zelefsky who was the first person to treat prostate cancer with IMRT. Later I spent a few weeks at the University of Michigan in Ann Arbor with my now great friend Dr Avi Eisbruch who taught me what he had learnt about applying IMRT to patients with head and neck cancer. I was amazed to see his patients who appeared to recover full function of speech and swallow, following IMRT - something I had rarely seen with conventional radiotherapy during my

training. On my return to the UK, we treated the first patient with IMRT at the Royal Marsden Hospital (RMH) in September 2000. This was the first delivery of IMRT in the UK, and was to a man with prostate cancer.

In 2001 I was appointed as Consultant in Clinical Oncology at the RMH and Honorary Senior Lecturer at the ICR. My main initial goal was to develop IMRT for the treatment of head and neck cancer patients as I had seen at the University of Michigan and to develop trials to see if IMRT was really of benefit for head and neck cancer patients compared to conventional radiotherapy. Radiotherapy is a complex treatment requiring close collaboration between clinical oncologists, medical physicists, and therapy radiographers. To develop, implement, and evaluate a new radiotherapy technique in clinical trials requires an even larger team comprising specialists in clinical trials (statisticians, trial managers, and data collectors), academic physicists, and other research staff. In the early years my work was achieved from a small close working team. Catherine Clarke, an excellent medical physicist who we recruited from University of California San Francisco (UCSF), provided medical physics leadership. Elizabeth Miles was appointed as a Research Radiographer and was responsible for developing departmental protocols for treatment of patients. As the project developed I began collaborations with the Clinical Trials and Statistics Unit (CTSU) at the ICR where Emma Hall and I built what is now an active head and neck trials group. For that reason the papers presented here have multiple authors and my contribution to the individual papers is detailed in Chapter 1 of this thesis.

When I started the IMRT research program at the RMH in 2001 I saw two major problems in head and neck cancer. First, for many tumour sites there were high levels of long-term treatment-related toxicity following radiotherapy (Mendes, Nutting et al. 2002). Second, for patients with advanced stage disease, there were poor rates of local tumour control and survival (Royal College of Pathologists 2005 (2nd Edition)). It appeared to me that the most important toxicities were due to the irradiation of non target organs. For example, xerostomia was the most commonly reported late radiation side effect and it was predominantly due to the irradiation of the parotid glands which generate 80% of the saliva. It seemed logical that development of radiation techniques which reduced the dose to these organs was likely to lead to improvements in long-term side effects (Nutting, Dearnaley et al. 2000). For advanced tumours with poor local control rates, there was a need to increase the delivered dose to improve local control and survival (Harrington and Nutting 2002). This formed the rationale for the research work presented in this thesis.

Head and neck cancer seemed an ideal site to test IMRT as the patient is easily immobilised with limited internal organ motion. The close anatomical relationship between the tumour tissues and critical normal tissue structures is challenging for conventional radiotherapy but IMRT seemed to offer the potential to spare some normal tissue structures and deliver higher doses to tumours. For squamous cell carcinomas, the close relationship between delivered radiation dose and probability of tumour control made head and neck cancer a very attractive model for testing dose escalation strategies.

As with all new technologies there was a learning curve in the first few months and years of applying this technique. At The ICR/RMH a clinical implementation process was underway for IMRT for a number of tumour sites. This process started with the identification of appropriate tumour sites and the design of efficient delivery techniques. Initial clinical testing of IMRT techniques in Phase I/II studies was followed by Phase III randomised studies to confirm the clinical benefits of these new techniques. In tumour sites when the delivered dose of radiation was standard, then I proceeded directly to a Phase III study once the radiotherapy technique had been worked out. If the tumour site being studied involved delivering higher radiation dose, then I felt it was more appropriate to study the technique in Phase I/II trials to assess safety of dose escalation before moving on to Phase III trials.

In this thesis I present a program of research in head and neck cancer IMRT designed to evaluate the ability of the technology to reduce the dose to a variety of organs at risk (OAR) and to test the potential of IMRT dose escalation to improve tumour control.

1.2 The Papers Submitted as part of this thesis

The full texts of the papers submitted for this PhD by prior publication are included at the end of the thesis.

Paper 1

Humphreys M, Guerrero Urbano MT, Mubata C, Miles E, Harrington KJ, Bidmead M, **Nutting CM**. Assessment of a customised immobilisation system for head and neck IMRT using electronic portal imaging. *Radiother Oncol*. 2005; 77:39-44.

Impact score 4.3

Role: CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. MH, CM, EM, and MB collected and analysed scan data. TGU and KH provided clinical support.

Paper 2

Nutting CM, Normile PS, Bedford JL, Harrington KJ, Webb S. A systematic study of techniques for elective cervical nodal irradiation with anterior or opposed anterior and posterior beams. *Radiother Oncol*. 2003; 69:43-51.

Impact score 4.3

Role: CN was first author, was responsible for the initial idea, provision of clinical material, plan production, data analysis and manuscript writing. PN, JB and SW produced treatment plans, KJH provided clinical support

Paper 3

Miles EA, Clark CH, Urbano MT, Bidmead M, Dearnaley DP, Harrington KJ, A'Hern R, **Nutting CM**. The impact of introducing intensity modulated radiotherapy into routine clinical practice. *Radiother Oncol*. 2005; 77:241-6.

Impact score 4.3

Role: CN was senior author, was responsible for the initial idea, patient recruitment, data analysis and manuscript writing. EM, CC, TGU, MB provided data for the manuscript. DD and KH provided clinical support.

Paper 4

Guerrero Urbano MT, Clark CH, Kong C, Miles E, Dearnaley DP, Harrington KJ, **Nutting CM**, PARSPORT Trial Management Group. Target volume definition for head and neck intensity modulated radiotherapy: pre-clinical evaluation of PARSPORT trial guidelines. *Clin Oncol (R Coll Radiol)*. 2007; 19:604-13.

Impact score 2.8

Role: CN was senior author, was responsible for the initial idea, provision of clinical material, data analysis and manuscript writing. TGU, CC and CK produced treatment plans, EM, DPD and KJH provided clinical support.

Paper 5

Clark CH, Hansen VN, Chantler H, Edwards C, James HV, Webster G, Miles EA, Guerrero Urbano MT, Bhide SA, Bidmead AM, **Nutting CM**; PARSPORT Trial

Management Group. Dosimetry audit for a multi-centre IMRT head and neck trial. *Radiother Oncol.* 2009; 93:102-8.

Impact score 4.3

Role: CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. CC, VH, HC, CE, HJ GW and MB collected and analysed treatment plans. EA, TGU, and SB provided clinical support.

Paper 6

Clark CH, Miles EA, Urbano MT, Bhide SA, Bidmead AM, Harrington KJ, **Nutting CM**; UK PARSPORT Trial Management Group collaborators. Pre-trial quality assurance processes for an intensity-modulated radiation therapy (IMRT) trial: PARSPORT, a UK multicentre Phase III trial comparing conventional radiotherapy and parotid-sparing IMRT for locally advanced head and neck cancer. *Br J Radiol.* 2009; 82:585-94.

Impact score 2.3

Role: CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. CC, EM, and MB collected and analysed scan data. TGU, KH and SB provided clinical support.

Paper 7

Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, Miles EA, Miah AB, Newbold K, Tanay M, Adab F, Jefferies SJ, Scrase C, Yap BK, A'Hern RP, Sydenham MA, Emson M, Hall E; PARSPORT trial management group. Results of a Phase III Multi-Center Randomized Controlled Trial of Parotid-Sparing Intensity Modulated versus Conventional Radiotherapy in Head and Neck Cancer, *Lancet Oncology* 2011;12(2):127-36

Impact score 14.5

Role: CN was first author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. JM, RAH, MS, ME and EH of the ICR CTSU provided data management, statistical support and trial management. KH, TGU, SB, EM, AM, KN, MT, FA, SJ, CS, and BY were clinical co-investigators.

Paper 8

Clark CH, Bidmead M, Mubata CD, Harrington KJ, **Nutting CM**. Intensity-modulated radiotherapy improves target coverage, spinal cord sparing and allows dose escalation in patients with locally advanced cancer of the larynx. *Radiother Oncol.* 2004; 70:189-98.

Impact score 4.3

Role: CN was senior author, was responsible for the initial idea, provision of clinical material, data analysis and manuscript writing. CC, MB and CM produced treatment plans, KJH provided clinical support.

Paper 9

Guerrero Urbano T, Clark CH, Hansen VN, Adams EJ, A'Hern R, Miles EA, McNair H, Bidmead M, Warrington AP, Dearnaley DP, Harrington KJ, **Nutting CM**. A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer. *Radiother Oncol*. 2007; 85:36-41.

Impact score 4.3

Role: CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. TGU, CC, VH, EA, MB, and AW produced treatment plans. EM, HM, DD, and KH provided clinical support. RAH was trial statistician

Paper 10

Miah AB, Bhide SA, Guerrero-Urbano MT, Clark C, Bidmead AM, St Rose S, Barbachano Y, A'Hern R, Tanay M, Hickey J, Nicol R, Newbold KL, Harrington KJ, Nutting CM. Dose-Escalated Intensity-Modulated Radiotherapy Is Feasible and May Improve Locoregional Control and Laryngeal Preservation in Laryngo-hypopharyngeal Cancers. *Int J Radiat Oncol Biol Phys*. 2012; 82(2):539-47

Impact score 4.6

Role: CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. AM, SB, TGU, CC, and MB produced treatment plans. MT, JH, RN, KN, and KH provided clinical support. SSR, YB and RAH were trial statisticians.

1.3 The Story

1.3.1 Head and neck cancer

Head and neck cancers include cancers of the upper aerodigestive tract (including the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx), the paranasal sinuses, and the salivary glands. Cancers at different sites have different clinical behaviours and variable histopathological types. Squamous cell carcinoma is by far the most common. The anatomical sites affected are important for functions such as speech, swallowing, taste, and smell, so the cancers and their treatments may have considerable functional sequelae with subsequent impairment of quality of life. Decisions about treatment are usually complex, and they must balance efficacy of treatment and likelihood of survival, with potential functional and quality of life outcomes. Patients and their carers need considerable support during and after treatment.

1.3.2 Incidence and epidemiology

Cancer of the mouth and oropharynx is the 10th most common cancer worldwide, but it is the seventh most common cause of cancer-induced mortality (Mehanna, Paleri et al. 2011). In 2002, the World Health Organization estimated that there were 600,000 new cases of head and neck cancer and 300,000 deaths each year worldwide, with the most common sites being the oral cavity (389,000 cases a year), the larynx (160,000), and the pharynx (65,000) (Boyle and Levin 2008). The male to female ratio reported by large scale epidemiological studies and national cancer registries varies from 2:1 to 15:1 depending on the site of disease. This is thought to be due to the higher exposure to carcinogens in alcohol and cigarette smoke in men than women. The

incidence of cancers of the head and neck increases with age. In Europe, 98% and 50% of patients diagnosed are over 40 and 60 years of age, respectively (Boyle and Levin 2008).

1.3.2.1 Geographical factors

A high incidence of head and neck cancer is seen in the Indian subcontinent, Australia, France, Brazil, and Southern Africa (World Health Organization and International Union Against Cancer 2005) . Nasopharyngeal cancer is largely restricted to southern China. The incidence of oral, laryngeal, and other smoking-related cancers is declining in North America and Western Europe, primarily because of decreased exposure to carcinogens, especially tobacco (Boyle and Levin 2008). In contrast, because of the 40 year temporal gap between changes in population tobacco use and its epidemiological effects, the worst of the tobacco epidemic has yet to materialise in developing countries. WHO projections estimate worldwide mortality figures from mouth and oropharyngeal cancer in 2008 to be 371,000. This is projected to rise to 595,000 in 2030 because of a predicted rise in life expectancy in South East Asia. Modest rises are predicted in Africa, the Americas, and the Middle East, whereas mortality in Europe is expected to remain stable (Mathers and Loncar 2006). This makes head and neck cancer a huge health burden worldwide for the foreseeable future.

Several retrospective analyses of tumour samples collected from patients recruited in randomised trials, as well as retrospective patient series, have shown recent changes in epidemiology and pathogenesis of head and neck cancers related to the human

papillomavirus (HPV), especially for oropharyngeal carcinoma. A rapid rise in HPV-related oropharyngeal cancers in particular has been shown in epidemiological studies from the developed world (Mehanna, Jones et al. 2010). For example, the United Kingdom has seen a doubling in the incidence of oropharyngeal cancer (from 1/100,000 population to 2.3/100,000) in just over a decade (Mehanna, Paleri et al. 2011). A recent retrospective study showed a progressive proportional increase in the detection of HPV in oropharyngeal squamous cell carcinomas in Stockholm over the past three decades: 23% in the 1970s, 29% in 1980s, 57% in 1990s, 68% between 2000 and 2002, 77% between 2003 and 2005, and 93% between 2006 and 2007 (Nasman, Attner et al. 2009).

1.3.2.2 Risk factors for head and neck cancer

The major risk factors are tobacco (smoking and smokeless products such as betel quid) and alcohol. They account for about 75% of cases, and their effects are multiplicative when combined (Conway, Hashibe et al. 2009). Smoking is more strongly associated with laryngeal cancer and alcohol consumption with cancers of the pharynx and oral cavity. Pooled analyses of 15 case-control studies showed that non-smokers who have three or more alcoholic drinks (beer or spirits) a day have double the risk of developing the disease compared with non-drinkers (odds ratio 2.04, 95% confidence interval 1.29 to 3.21) (Purdue, Hashibe et al. 2009) (Hashibe, Brennan et al. 2007).

1.3.3 Diagnosis of head and neck cancer

Patients with head and neck cancer present with a variety of symptoms, depending on the function of the site where the tumour originates. Laryngeal cancers commonly present with hoarseness, whereas pharyngeal cancers often present late with dysphagia or sore throat. Many often present with a painless neck node. Patients with head and neck cancer can present with non-specific symptoms or symptoms commonly associated with benign conditions, such as sore throat or ear pain.

1.3.3.1 Investigation of head and neck cancer

Examination of any lesion of the head or neck should include careful examination of the patient's neck and mucosal surfaces (Paleri, Staines et al. 2010). Flexible nasolaryngoscopy allows detailed examination of the nasal cavities, postnasal space, base of the tongue, larynx, and hypopharynx.

Examination under anaesthetic and biopsy allows assessment of the size, histopathological nature and extent of the primary tumour. FNA or core biopsy can provide cytological evidence of nodal metastasis (van den Brekel, Castelijns et al. 1993).

1.3.3.2 Imaging

Computed tomography (CT) scanning from the skull base to the diaphragm is the first line investigation to assess nodal metastasis and identify the primary tumour site and tumour size. CT scanning has an important role in planning the extent of local therapies, such as surgery and radiotherapy (Newbold, Partridge et al. 2006).

Magnetic resonance imaging (MRI) is indicated for oral cavity and oropharyngeal tumours; in some cases it provides better information than CT, because of the absence of interference from dental amalgam and the better delineation of soft tissue extension. It can also be used for treatment planning (Ahmed, Schmidt et al. 2010).

Ultrasound (US) -guided fine needle aspiration (FNA) of tumour contents performed by experienced practitioners is highly accurate and is used by some centres to diagnose nodal metastasis as part of disease staging (van den Brekel, Castelijns et al. 1993).

The new technique of fusion positron emission tomography-computerised tomography (PET-CT) has become one of the most important diagnostic tools for head and neck cancers. It combines normal CT scanning with functional imaging using 18F-fluorodeoxyglucose (18F-FDG), which is taken up preferentially by cells with high metabolic activity, especially cancer cells (Newbold, Partridge et al. 2008). This technique can therefore help identify occult primary tumours, which are relatively uncommon and not detected by examination and conventional imaging (Newbold, Partridge et al. 2008). The technique may also have a role in the assessment of persistent nodal disease after treatment and in the monitoring and follow-up of patients with head and neck cancer in the longer term, but sufficient evidence to support this is not yet available (Isles, McConkey et al. 2008).

1.3.4 Treatment of head and neck cancer

Management is increasingly being delivered by specialists, whose main interest is cancers of the head and neck. Multidisciplinary care has now become the standard of care, often encouraged by national guidelines and protocols (National Institute for Health and Clinical Excellence 2004) (Scottish Intercollegiate Guidelines Network 2006). The complexities of combined surgery and radiotherapy, as well as rehabilitation, means that a team of health professionals is needed to deliver high quality care to patients treated for head and neck cancer. An ideal team usually includes head and neck surgeons from different disciplines, clinical and medical oncologists, clinical nurse specialists, speech and language therapists, dieticians, psychologists, restorative dentists, prosthodontists, and social workers. Although we have no data to prove that multidisciplinary treatment has improved care, intuitively and anecdotally that seems to be the case.

Radiotherapy and surgery are the two most common curative treatments for cancers of the head and neck. The choice of treatment modality depends on individual factors related to the site of the tumour and stage, but also patient preference.

1.3.4.1 Early stage tumours

Case series, often retrospective and from single centres, have shown that for early stage tumours in many head and neck subsites, surgical excision or radiotherapy have similar cure rates but a different side effect profile (Bhalavat, Fakhri et al. 2003). Radiotherapy may offer better organ preservation, and for some cancers where function is important this is the treatment of choice. For example, radiotherapy allows

preservation of natural speech and swallowing in carcinomas of the tongue base. For some sites (such as the oral tongue), mainly retrospective single centre case series have shown that surgical excision alone may be curative, and that it is associated with a highly satisfactory functional outcome by retaining natural speech and swallow as assessed by a variety of validated techniques and patient surveys (Dwivedi, Chisholm et al. 2011) (Bhalavat, Fakih et al. 2003).

1.3.4.2 Advanced tumours

For advanced squamous cell carcinoma of the head and neck, single modality treatment (surgery or radiotherapy) is associated with poorer outcomes (Bhalavat, Fakih et al. 2003), and randomised studies have shown that combined use of surgery and postoperative radiotherapy, or combined chemotherapy and radiotherapy, offer the highest chance of achieving a cure (VA Laryngeal Cancer Study Group 1991; Bhalavat, Fakih et al. 2003) .

1.3.4.3 Patients with HPV-related cancer

Retrospective analyses of patients with oropharyngeal carcinoma show that HPV positive tumours seem to respond better to a variety of treatments, including chemoradiotherapy or surgery and radiotherapy than those who are HPV negative (Fakhry, Westra et al. 2008) (Ang 2010) (Licitra, Perrone et al. 2006). Because these patients are generally younger, they may survive for several decades with substantial side effects and functional impairment as a consequence of the treatment they receive, and this may have implications for carers, the health system, and social care (Harris,

Thorne et al. 2011). The anticipated loss of quality adjusted life years in this subgroup of head and neck cancer makes it even more important to minimize long-term toxicity.

1.3.5 Role of radiation therapy in head and neck cancer

Head and neck cancer is commonly treated with radiotherapy. High doses of radiation, typically 60-70 Gy, are required to eradicate tumours successfully. The close proximity of tumours to radiosensitive normal tissues means that, for many patients, successful cure is associated with sequelae of long-term radiation damage to these normal tissues. These include general tissue fibrosis and atrophy leading to stiffness of the tissues. Furthermore, several specific organ dysfunctions are observed. These include severe dryness of the mouth (xerostomia) due to damage to salivary glands leading to difficulties with speech, swallowing and poor oral hygiene. Swallowing difficulties are common due to damage to the muscles and nerves of the pharynx (Mendes, Nutting et al. 2004).

1.3.5.1 Conventional radiotherapy

Conventional radiotherapy techniques have for many years used simple parallel-opposed fields to treat head and neck cancer. Typically treatment was planned using orthogonal plain radiographs using a simulator and field borders were based on standard anatomical bony landmarks. While these techniques provided adequate tumour coverage, there was little opportunity to spare adjacent normal tissues, leading to many of the side effects detailed above.

1.3.5.2 Three dimensional conformal radiotherapy

Three dimensional conformal radiotherapy (3DCRT) became available for the treatment of head and neck cancer in the 1990s. This technique used 3-dimensional anatomical data in the form of a CT scan to identify more accurately the position and shape of the tumour target. Multi-leaf collimators (MLCs) allowed individual beam shaping which conformed the radiation dose more closely to the tumour and reduced the volume of normal tissue irradiated. While this had clinical benefits for some tumour types (e.g. prostate cancer see Table 1.1), in head and neck cancer there was little impact on late normal tissue radiation reactions because the key organs at risk were still within the high dose volume (Bhide and Nutting 2010).

Site	Author	Benefits
Prostate	Dearnaley 1994	46% and 41% reduction of dose to rectum and bladder
Paranasal sinus	Adams 2001	Reduced optic nerve dose by 10%, parotid gland dose by 30%, potential to dose escalate
Thorax	Nutting 1999	Reduced lung irradiation, improved target homogeneity
Oropharynx	Eisbruch 1998	Reduced parotid gland irradiation
Brain	Khoo 1999	Reduced normal tissue irradiation by 40%

Table 1.1 The benefits of 3-dimensional radiotherapy for a variety of tumour sites

1.3.5.3 Intensity-modulated radiotherapy

Intensity-modulated radiotherapy (IMRT) was developed in the late 1990s and represented progress in conformal radiotherapy where each beam was not only geometrically shaped, but also the intensity of radiation varied across the beam

(Figure 1.1). This permitted the delivery of dose distributions with concave isodose shapes (Bhide and Nutting 2010).

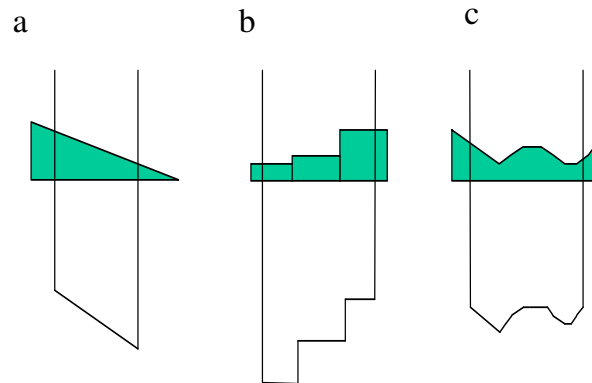


Figure 1.1 Examples of simple methods of intensity-modulation a) wedge filter, b) Partial transmission block and c) tissue compensator.

Reproduced (Nutting, Dearnaley et al. 2000)

IMRT combines several intensity-modulated beams. The resultant isodoses are highly conformal, and uniquely can yield a concave distribution. IMRT therefore offers a significant advance in conformal therapy (Webb 1998), by improving conformality and reducing radiation dose to radiosensitive normal tissues close to the tumour even if they lie within a concavity in the PTV (Brahme 1988).

1.3.5.4 Production of intensity-modulated beams

Intensity-modulated beams (IMB) can be produced in a number of ways (Webb 1997):

1.3.5.4.1 Metal compensators

A specifically manufactured metallic compensator is milled or moulded so that a variable thickness of the absorber is presented before the radiation beam. Production of compensators is relatively simple but expensive and time consuming. They are heavy and may be difficult to position accurately in the linear accelerator head. In practice this limits the number of IMB that can be delivered (Webb 1998), and this method is rarely used in current clinical practice.

1.3.5.4.2 Multiple static fields (MSF)

Each treatment field is divided into several smaller segments or sub-fields which are delivered sequentially (the “step and shoot” method). Each segment shape is defined by a multi-leaf collimator or shaped blocks. The addition of several segments produces an IMB. This type of IMRT can be delivered with technology already available in centres using an MLC to treat patients with 3DCRT, and is currently being used in Europe and the United States to treat patients with cancer of the prostate, head and neck, lung, breast, liver, brain, and other sites (Boyer and Yu 1999) (De Neve W 1996) (Eisbruch, Marsh et al. 1998). The current use of these techniques is based on observed dosimetric advantages as well as early reports of encouraging clinical outcomes (Eisbruch, Ship et al. 1996; Eisbruch, Marsh et al. 1998; Zelefsky, Leibel et al. 1998). To produce the required conformality, four to nine beam directions may be required depending on the complexity of the Planning Target Volume (PTV) (Boyer and Yu 1999) (De Neve W 1996) (Eisbruch, Marsh et al. 1998). Each field may consist of three to twenty sub-fields which are delivered in succession (Figure 1.2).

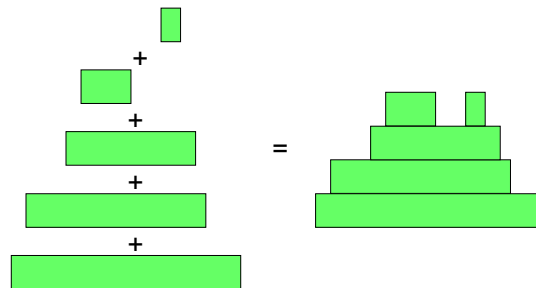


Figure 1.2 The generation of an intensity-modulated beam by addition of multiple static fields

For highly modulated beams, the total number of monitor units delivered per beam is often much higher than for conventional radiotherapy. These factors increase treatment time from around ten minutes for a conformal treatment delivery to fifteen to twenty-five minutes for IMRT (De Neve W 1996). Higher dose rates and optimisation of the sequence of delivery of segments have been used to minimise treatment times (De Neve W 1996). Physical problems with the use of an MLC to define segments include accuracy of MLC leaf placement, interleaf radiation leakage, the tongue and groove effect, and the accuracy of delivering small numbers of monitor units to some segments (Hansen and Evans 1998).

1.3.5.4.3 Dynamic MLC (dMLC)

Modulation of beam intensity by pairs of moving MLC leaves characterises this technique (also known as the “sliding window” technique). The IMB is constructed from a series of one-dimensional IMB formed by the differential speed profile of the

leading and trailing MLC leaves (Figure 1.3)(Convery and Rosenbloom 1992) (Stein, Bortfeld et al. 1994). Each leaf pair in the MLC leaf bank moves through a series of control points determined by an interpreter which converts the required intensity distribution into speed profiles for each leaf pair (Boyer and Yu 1999).

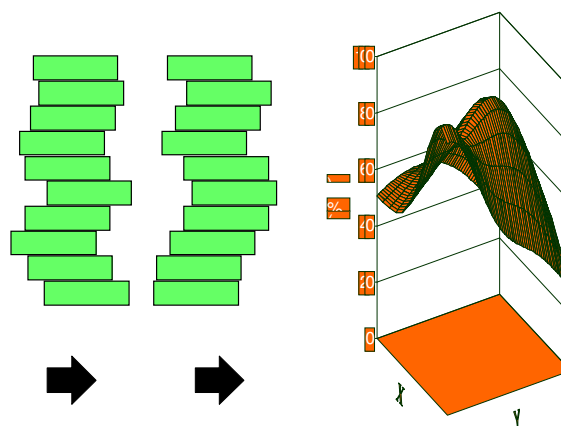


Figure 1.3 The delivery of an intensity-modulated beam using a sliding window technique

Delivery times are quicker than for multiple static fields; typical delivery time for a five-field prostate treatment is 14 minutes (McNair, Adams et al. 2003). The leaf movements of the MLC during treatment must be accurate, as these produce the IMB. Leakage and transmission of radiation between or through MLC leaves must be taken into account in the dose calculation. Leakage occurs both between adjacent leaves, and between the ends of opposing leaf pairs. MLCs produced by different manufacturers vary greatly in this respect. Transmission of radiation through MLC leaves is less than 1.5-2% although larger transmission of up to 2.5-3% have been measured at the interlocking leaf edge (Galvin, Smith et al. 1993), (Jordan and Williams 1994). The phenomenon known as the “tongue and groove” effect is

clinically significant in that it can cause tumour overdose or underdose (Sykes and Williams 1998), but can be removed by “synchronisation” (van Santvoort and Heijmen 1996; Webb 1997).

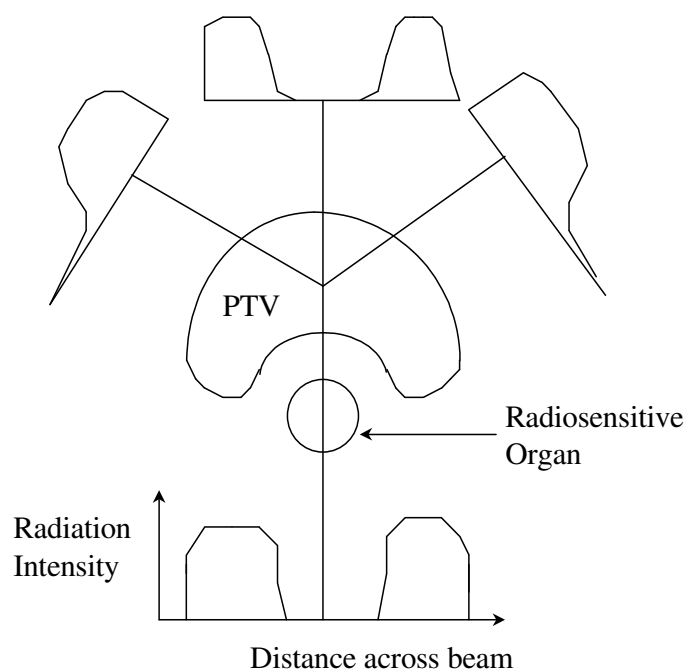


Figure 1.4 The generation of a concave dose distribution from the summation of several intensity modulated beams. Reproduced from Nutting et al 2000

Dynamic leaf movement during the treatment delivery, combined with continuous arcing of the gantry is known as intensity-modulated arc therapy (IMAT) (Yu 1995; Boyer and Yu 1999). This technique has the advantages of quick treatment time (5-10 minutes), and may allow the use of fewer intensity levels than dMLC. IMAT is currently being implemented in many radiation oncology departments (Yu and Tang 2011).

1.3.5.4.4 Tomotherapy

Tomotherapy describes IMRT techniques which irradiate the target slice by slice. The NOMOS Corporation developed the first commercially available tomotherapy machine, the Multivane Intensity Modulating Collimator (MIMiC) which was used in several centres in the United States (Carol, Grant et al. 1996; Grant and Woo 1999). A helical tomotherapy device was designed by Mackie (Mackie, Holmes et al. 1993) and is now in widespread use throughout the USA and Europe (Mackie, Balog et al. 1999) (Burnet, Adams et al. 2010).

1.3.6 Role of IMRT in head and neck cancer

In head and neck radiotherapy there are many clinical situations where radiosensitive normal tissues lie within a concavity surrounded by the planning target volume (PTV). The treatment of patients with tumours of the larynx, pharynx, or thyroid are good examples. The clinical target volume (CTV) often includes a midline target, and bilateral cervical lymph nodes, producing a horseshoe-shaped PTV with the spinal cord within the concavity (De Neve W 1996). Homogeneous irradiation of these PTVs to radical doses (50-66 Gy) with conventional external-beam radiotherapy is difficult. Typically parallel-opposed photon portals are matched to electron beams. This technique leads to dose inhomogeneity at the photon-electron match-line, and may under dose the posterior cervical and deep cervical lymph nodes close to the spinal cord. Such under dose may result in failure to achieve local tumour control. This shape of PTV can be treated homogeneously using IMRT without the need for electrons (Figure 1.4). The dose to the spinal cord can be kept well within tolerance (De Neve W 1996) and permits tumour dose escalation (Figure 1.5).

While there were many reasons to expect good outcomes with IMRT in the head and neck there were also many unknown factors and some potential risks. First, IMRT was a complex technique to plan and deliver where small errors in planning or treatment delivery could lead to failure to deliver adequate dose to the tumour risking tumour recurrence. Second, the techniques of efficient delivery were unknown. Third, the use of multiple beams led to the deposition of larger areas of low dose irradiation than conventional radiotherapy and the consequences of this were unclear. There were particular risks about the effects of low dose radiation on second malignancy, and on growth of soft tissue and bone in paediatric cancer patients.

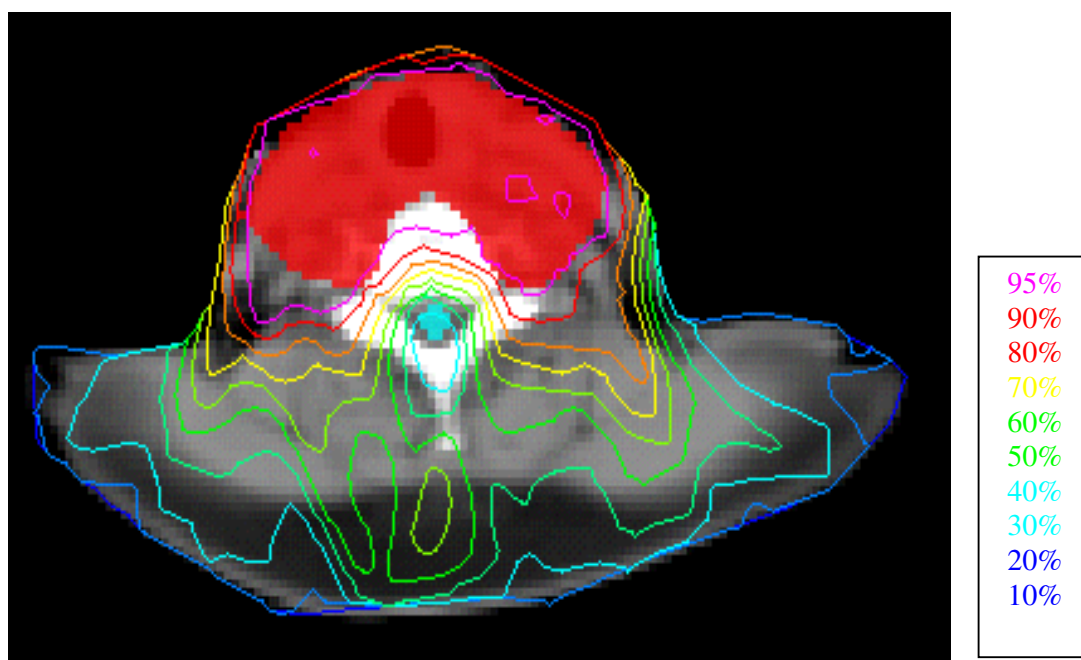


Figure 1.5 An IMRT dose distribution to treat the thyroid bed and adjacent lymph nodes (solid red) while sparing the spinal cord (blue) in a patient with thyroid carcinoma.

From the above, it can be seen that head and neck cancer represents an ideal model system for testing IMRT in the clinic and to investigate the concerns expressed above. Several factors are relevant here. First, conventional and 3DCRT as practiced in head and neck cancer are associated with significant toxicity due to irradiation of normal tissues close to the target volume. IMRT using highly conformal dose distributions and ability to generate concave dose distributions should translate into reduction in organ at risk doses and reduced toxicity. Second, the ability to reduce the volume of normal tissue to be irradiated allows the opportunity to deliver higher radiation doses in an attempt to increase local tumour control. The next section outlines a program of work to implement IMRT at the RMH, the first centre to use this technique in the UK, and then to develop research protocols to answer the questions as to whether IMRT can reduce toxicity and improve tumour control in patients with head and neck cancer.

1.4 Thesis Road Map

In Chapter 2, I seek to answer the first question posed in the title “Can intensity-modulated radiotherapy be used to reduce toxicity in head and neck cancer patients?” First, I discuss an evaluation of our patient immobilisation system which needed to be assessed before treating head and neck cancer patients with IMRT at RMH (paper 1). At the same time, I performed an evaluation of the role of neck irradiation with IMRT (paper 2). Radiotherapy departments are usually very busy so there were initial concerns as to how efficient the new technique would be within the RMH radiotherapy department. A time and motion study is presented to determine the additional resources required to deliver IMRT (paper 3). Paper 4 presents an analysis of two tumour types where IMRT was tested through planning studies. Once these issues had been resolved, we started IMRT at RMH. In the UK we aspire to practice evidence-based medicine based on randomised controlled trial (RCT) data. In 2003, I was successful in my bid to win a clinical trial grant from Cancer Research UK to carry out a RCT called PARSPORT to evaluate whether parotid gland-sparing IMRT could lead to a reduction in long-term xerostomia in head and neck cancer patients. In order to do this, I needed to develop IMRT protocols which could be used in multiple UK radiotherapy departments. Papers 5 and 6 describe the process of national implementation and quality assurance required for the trial. Finally in paper 7, I present the results of the randomised trial which was published in *Lancet Oncology* in 2011. The impact on international head and neck radiotherapy practice are discussed.

In Chapter 3, I seek to answer the second posed question “Can IMRT improve tumour control in patients with head and neck cancer?” I chose to study tumours arising in

the larynx and hypopharynx as these tumours were associated with poor levels of local control and also were tumour sites where organ preservation was key for maintaining the normal functions of speech (larynx cancers) and swallowing (hypopharynx cancers). Three papers are presented. Initially I carried out a theoretical planning study to assess if the delivery of additional dose, to improve local tumour control, was possible using IMRT (paper 8). Radiation dose escalation is a potentially dangerous treatment approach as the extra radiation dose may cause an increase in damage to normal structures such as cartilage, bone or soft tissues close to the tumour. In oncology, we typically use Phase I studies to determine the safety of new treatments in patients. I, therefore, designed a Phase I radiation dose escalation trial for patients with tumours of the larynx and hypopharynx and thyroid. Papers 9 and 10 describe the acute and late side effects in the larynx and hypopharynx trial. As a consequence of these results, I designed a second RCT (ARTDECO) to compare standard dose radiation with escalated dose radiation in this patient group to test the hypothesis that increase in radiation dose would lead to increase in tumour control and possible overall survival in head and neck cancer patients.

Chapter 2

**Can intensity-modulated radiotherapy be used
to reduce toxicity in head and neck cancer
patients?**

Papers in this chapter

1. Humphreys M, Guerrero Urbano MT, Mubata C, Miles E, Harrington KJ, Bidmead M, **Nutting CM**. Assessment of a customised immobilisation system for head and neck IMRT using electronic portal imaging. *Radiother Oncol*. 2005; 77:39-44.
2. **Nutting CM**, Normile PS, Bedford JL, Harrington KJ, Webb S. A systematic study of techniques for elective cervical nodal irradiation with anterior or opposed anterior and posterior beams. *Radiother Oncol*. 2003; 69:43-51.
3. Miles EA, Clark CH, Urbano MT, Bidmead M, Dearnaley DP, Harrington KJ, A'Hern R, **Nutting CM**. The impact of introducing intensity modulated radiotherapy into routine clinical practice. *Radiother Oncol*. 2005; 77:241-6.
4. Guerrero Urbano MT, Clark CH, Kong C, Miles E, Dearnaley DP, Harrington KJ, **Nutting CM**, PARSPORT Trial Management Group. Target volume definition for head and neck intensity modulated radiotherapy: pre-clinical evaluation of PARSPORT trial guidelines. *Clin Oncol (R Coll Radiol)*. 2007; 19:604-13.
5. Clark CH, Hansen VN, Chantler H, Edwards C, James HV, Webster G, Miles EA, Guerrero Urbano MT, Bhide SA, Bidmead AM, **Nutting CM**; PARSPORT Trial Management Group. Dosimetry audit for a multi-centre IMRT head and neck trial. *Radiother Oncol*. 2009; 93:102-8.

6. Clark CH, Miles EA, Urbano MT, Bhide SA, Bidmead AM, Harrington KJ, **Nutting CM**; UK PARSPORT Trial Management Group collaborators. Pre-trial quality assurance processes for an intensity-modulated radiation therapy (IMRT) trial: PARSPORT, a UK multicentre Phase III trial comparing conventional radiotherapy and parotid-sparing IMRT for locally advanced head and neck cancer. *Br J Radiol.* 2009; 82:585-94.

7. **Nutting CM**, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, Miles EA, Miah AB, Newbold K, Tanay M, Adab F, Jefferies SJ, Scrase C, Yap BK, A'Hern RP, Sydenham MA, Emson M, Hall E; PARSPORT trial management group. Results of a Phase III Multi-Center Randomized Controlled Trial of Parotid-Sparing Intensity Modulated versus Conventional Radiotherapy in Head and Neck Cancer. *Lancet Oncology* 2011; 12(2):127-36

2.1 Introduction

Radiotherapy for head and neck cancer is a complex process. To achieve high quality treatment, it is important to achieve a series of individual goals. These are often referred to as the “radiotherapy chain” where each link has to be strong to achieve a good treatment outcome.

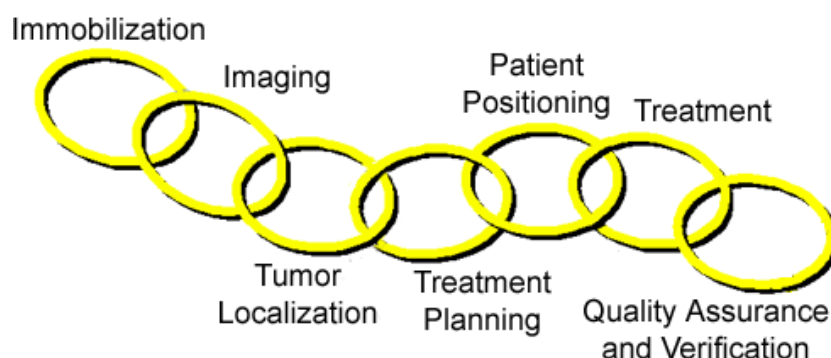


Figure 2.1 the Radiotherapy Chain

The links in the chain are accurate immobilisation of the patient, good quality CT imaging, accurate definition of the target volume and OARs, high quality treatment planning, accurate treatment delivery and quality assurance of the treatment delivery.

2.2 Review of Immobilisation (paper 1)

When we started the head and neck IMRT program the radiotherapy chain had to be revisited. One of the main differences between conventional radiotherapy and IMRT is the steep dose gradients that are produced around tumour targets and OARs seen on IMRT plans. It is, therefore, critical that the immobilisation of the patient is as accurate and reproducible as possible to ensure that the deposition of radiation dose is

correct. Furthermore, the performance of the immobilisation system needs to be known in order to add appropriate margins to the Clinical Target Volumes (CTVs) when generating Planning Target Volumes (PTVs).

Paper 1 reports the assessment of a customised immobilisation system for head and neck IMRT. Figure 1 in that paper shows the new 4 point immobilisation shell. It differed from our previous immobilisation shell in that it extended down to the shoulders and over the skull vertex and had 4 points of attachment rather than the traditional 2 points. This study showed the accuracy of daily set up in 20 patients measured using 354 electronic portal images. In this study, we demonstrated that 94% of translational displacements were $\leq 3\text{mm}$, and 99% $\leq 5\text{mm}$. Looking back at this study, the findings have been robust. The overall systematic error was 0.9 mm (± 1.0 SD) in the right-left, 0.7 mm (± 0.9 SD) in the superior-inferior, and -0.02 mm (± 1.1 SD) in the anterior-posterior directions. The corresponding SDs of the random errors were ± 0.4 , ± 0.6 , and ± 0.7 mm. We used the Van Herk formula (van Herk, Remeijer et al. 2000) to calculate the estimated CTV-PTV margins and found them to be 2.9, 2.6 and 3.3 mm respectively. Based on this we adopted a 3 mm CTV-PTV margin for our head and neck IMRT. The use of electronic portal imaging in this study was a real advantage. First, it allowed computer-assisted matching – much more accurate than working from traditional portal films, and second, it also calculated the errors within the computer program reducing the chance of operator error. One area of concern is that many centres delivering IMRT have adopted 3 mm margins based on our data without doing their own departmental study. Between one radiotherapy centre and another there are many potential differences in equipment which could impact on the

performance of an immobilisation system, such as couch stiffness, use of a head board, type of material used to make the shell, type of attachment of the shell to the couch, and skill of the mould room staff. For these reasons, I would encourage each centre to carry out their own assessment of their systems rather than adopting published data. This paper sets out the methods which might be adopted by a centre wishing to make these measurements for themselves.

As technology has advanced, current studies have shifted away from imaging the bone tissues with portal imaging, towards imaging the soft tissues, or even the tumour itself with MV/kV cone-beam CT (Bhide and Nutting 2010). This has led us to realise that while the bones of the head and neck region may be immobilised during a course of radiotherapy, the soft tissues may change considerably during treatment. For example, several authors have recently demonstrated that the parotid salivary glands shrink and their centre of gravity moves medially during the course of radiotherapy (O'Daniel, Garden et al. 2007), the external contour of the patient may also change significantly due to weight loss and, of course, the tumour itself may shrink considerably during a course of treatment. At the present time it is not clear exactly what effects these factors are likely to have on the delivered dose to the tumour and the OAR. In particular it is not known whether the small dose differences seen in studies are sufficient to affect patient outcomes. In a study in our centre (Bhide and Nutting 2010), we demonstrated that most of the soft tissue changes occur between the planning scan and the second week of radiotherapy. Theoretically, it is possible to adapt your radiotherapy plan during the course of treatment to take these changes into account. This approach had been called “adaptive radiotherapy”, but in practice

this process is not in widespread use because re-planning is so time consuming. Most centres, including mine, would only re-plan a patient's treatment if the immobilisation system started to fail e.g. due to severe weight loss causing positional error of >3 mm.

2.3 How to treat the neck nodes: IMRT or Conventional technique? (Paper 2)

In 2001, there were fewer than 10 academic centres worldwide treating head and neck patients with IMRT and reporting the implementation or results of the technique (Nutting, Rowbottom et al. 2001). The most common head and neck tumour sites being treated were tumours of the pharynx, where IMRT was being used for parotid gland sparing. Tumours of the pharynx have a high risk of nodal metastasis to the anterior cervical lymph node chains which need to be included in the target volume for a radiation treatment. Two schools of thought existed. Some centres, such as University of Michigan and Memorial Sloan-Kettering, treated the primary tumour and the neck with IMRT (Marsh, Eisbruch et al. 1996). Advantages were that IMRT provided a more conformal plan and allowed better coverage of the lymph nodes. Disadvantages were that because of the use of multiple fields, some of the OAR were included in the low dose bath which exposed organs such as the larynx, oesophagus and spinal cord to higher radiation doses than the conventional anterior neck field with midline shielding. The second school, mainly centres on the west coast of the US such as UCSF, preferred to use IMRT fields to treat the primary tumour in the oropharynx and then match to a conventional anterior neck field below the hyoid (Chao, Low et al. 2000). Stated advantages were that it minimised dose to the OARs, especially the larynx, reduced treatment time and complexity and, for some treatment

machines with small MLC field length, it was a necessity. Disadvantages were that the conventional anterior neck field was not conformal and risked underdosing some of the lymph node groups.

Paper 2 represents an attempt to study the latter point and determine the optimal technique for cervical node irradiation in this setting. With conventional radiotherapy, typically either a single anterior photon field or anterior and posterior parallel-opposed fields were used. Single anterior fields were known to under dose the posterior cervical nodes, but these were only at very high risk in patients with carcinoma of the nasopharynx. Moderate risk was seen in patients with carcinoma of the oropharynx, larynx and hypopharynx (Candela, Kothari et al. 1990). There was considerable variation in technique between centres (Nowak, Wijers et al. 1999). A consensus statement had recently defined a method of localisation of cervical lymph nodes using CT imaging (Gregoire, Coche et al. 2000). The methods of target volume definition had been developed by Wijers (Wijers, Levendag et al. 1999) and Nowak (Nowak, Wijers et al. 1999). This study systematically studied several techniques of cervical node irradiation using the cervical node volume definitions to determine PTVs. Conventional radiotherapy techniques (CRT) using single and opposed fields were studied in this paper using moderate (6 MV) and high (10 MV) energy photons. The use of IMRT to improve dose homogeneity in the neck was also assessed as a second part of this study.

The main findings of this study were that IMRT using opposed fields gave the best dose distributions with optimal mean dose and dose homogeneity, and that this was

better than any of the conventional techniques either using opposed beams of either 6 or 10 MV. This was particularly important for cervical lymph node levels II and V which extend posteriorly in the neck as shown in Figure 5 of the paper. As a consequence of these data, we concluded that IMRT should be used to treat the cervical lymph nodes as part of our treatment program.

One of the benefits of this research was the clinical algorithm I developed. The most common clinical scenarios are shown in the algorithm in Figure 6. These include irradiation of the whole cervical lymph node chain (levels I-V), or selective nodal irradiation. The most common regions for selective anterior-posterior irradiation are levels III and IV, or IV alone, when the upper neck is included in lateral fields which also irradiate the primary tumour site. If irradiation of the posterior (level V) nodes or upper deep cervical nodes (level II) is required, then the opposed field IMRT technique with either 6 MV or 10 MV energy gave the best target coverage and dose homogeneity which should maximise tumour control probability (TCP) and minimise normal tissue complication probability (NTCP). This is due to the posterior position of level V and the posterior part of level IIB.

If the aim is to irradiate electively level III and IV but not II or V, (e.g. when the primary tumour and upper neck are irradiated with lateral fields), then single field CRT with 6 MV or 10 MV produced the best target coverage and IMRT has no significant additional benefit. If level IV is to be irradiated alone, then 6 MV or 10 MV single field CRT is the simplest technique.

In practice, the overriding priority for irradiation of most pharyngeal cancers is to prevent radiation-induced xerostomia by sparing the parotid glands. The technique used for this is described in paper 5, but typically uses 5-7 non-opposed radiation beams to irradiate the tumour targets. This beam arrangement is not the same as those anterior and posterior beam position techniques presented in paper 2, so some additional aspects of technique were developed to protect the midline structures of the anterior neck from irradiation. This comprised a non-anatomical avoidance structure which was constrained to doses of less than 30 Gy and thus minimized the dose to the larynx and cervical oesophagus as much as possible (see paper 5).

2.4 Time and motion studies in IMRT: delivering a complex treatment in a busy department cost and staff implications (paper 3)

With the introduction of more complex treatments such as IMRT, the potential increased use of specific resources, such as time and staff, needed to be assessed and justified. At the time of publication of paper 3, an increasing number of radiotherapy departments in Europe were aiming for clinical implementation of IMRT and initial experience from other centres was becoming available (Adams, Convery et al. 2004; Boehmer, Bohsung et al. 2004; Teo, Ma et al. 2004; Venencia and Besa 2004; Zhu, Schultz et al. 2004) . However, increased workload remained a major concern in the UK. There were little data available regarding planning and treatment times. These were important for the acceptance of IMRT from both the patients' perspective and ultimately for integration of a change in practice into the routine clinical workload.

At the Royal Marsden Hospital, our team had adopted single phase IMRT delivery to reduce planning and treatment times (Butler, Teh et al. 1999; Wu, Mohan et al. 2003).

In paper 3 I present the comparison of our novel single phase IMRT technique (described below and in Paper 5) to the previously used conventional radiotherapy technique. Conventional treatment required multiple portals and sequential field reductions. Additional significant gains were anticipated in patients with advanced head and neck cancer eliminating the complexity of photon and electron field matching and multiple phase treatments (Clark, Bidmead et al. 2004).

In the radiotherapy department, we measured time taken for clinicians, radiographer and treatment planners to produce plans for conventional radiotherapy and IMRT. The detailed description of the tasks is given in paper 3.

The main findings of this study were that IMRT planning and delivery took longer than conventional treatment planning. Clinician time was increased by 2.3 hrs for IMRT, radiographer time was reduced by 1.6 hrs, and physics time was increased by 4.9 hrs compared to conventional radiotherapy. A learning curve was observed over the first 11 patients treated both for patient-specific QA and duration of treatment time (see paper 3 Figures 2 and 3).

Since this paper was published in 2005, there have been significant advances in IMRT techniques. First, greater computational power is available for planning computers which are also running more efficient optimisation software. This has now shortened planning time to a maximum of 60 minutes per case (Bidmead, personal communication 2011). Second, more rapid delivery techniques are now available. At its most simple, this relates to more accurate and robust MLC design, but a new technique of intensity-modulated arc therapy – IMAT; (Yu and Tang 2011) has now

come into common usage. This is an IMRT technique where the gantry of the linear accelerator rotates during IMRT delivery. The advantages of this technique are the reduction in delivered monitor units and, therefore, faster treatment delivery compared to the standard fixed field IMRT used in our study. Recent papers suggest that the delivery times may be almost halved by IMAT compared to IMRT (Lee, Chao et al. 2011; Stieler, Wolff et al. 2011). Another question is what is the level of quality assurance required for IMRT plans? In the early days of IMRT, it was advised to perform quality assurance on each patient's treatment plan. This would include measurement of dose deposition by ion chamber and thermo luminescent dosimeters (TLDs) inside a phantom. This was a complex and time consuming procedure, particularly for physics staff in the radiotherapy department. Nowadays, in departments experienced in the IMRT technique a QA "sampling" process is used where typically 1 in 5 plans are subjected to a full QA measurement by delivery of the treatment to a phantom, and a pre-treatment independent monitor unit check is used for the remaining cases (Georg, Nyholm et al. 2007). These advances in QA techniques have substantially reduced the time required to prepare an IMRT plan in centres where large numbers of patients are treated with IMRT.

Clinician time spent performing target volume delineation (TVD) remains an issue at present, with TVD taking anything from 1-4 hours. Auto-contouring software has been assessed, but at the present time is not sufficiently accurate for routine clinical use (Wang, Garden et al. 2008) .

The findings of this paper have been used by the National Cancer Action Team (NCAT) to develop UK national recommendations as to the resources required for UK radiotherapy departments to implement IMRT for patients (Department of Health 2011).

2.5 Prioritising what to treat with IMRT: the planning studies (paper 4)

Radiotherapy planning studies offer the possibility to simulate radiotherapy treatment “in silico” for the purpose of identifying and quantifying potential improvements in outcome for one radiotherapy technique versus another (Nutting, Bedford et al. 2002) (Cardinale, Benedict et al. 1998; Eisbruch, Marsh et al. 1998; Khoo, Oldham et al. 1999). Overall, I performed planning studies for several head and neck tumour sites. The planning studies for parotid gland IMRT (Nutting, Rowbottom et al. 2001; Rowbottom, Nutting et al. 2001), and thyroid IMRT (Nutting, Convery et al. 2001) were presented in my MD (res) thesis. In this section two further published planning studies are presented. First, I performed a study to see if IMRT could be used to reduce the optic nerve dose in patients with cancer of the maxillary sinus cancer (Adams, Nutting et al. 2001). This represented a particularly difficult challenge in treating this tumour site, and I thought that IMRT had the potential to reduce the risk of radiation-induced loss of vision. Second, I performed a study of parotid gland sparing in oropharyngeal cancer (paper 4) to assess the likely reduction in radiation-induced xerostomia using the PARSPORT trial guidelines for TVD

For both studies, actual patient data (CT scans) of the disease in question were imported into a treatment planning system (TPS). Target volumes and organs at risk

were localized, and different treatment techniques were applied. In both papers, 3-dimensional conformal radiotherapy plans were compared to intensity-modulated radiotherapy plans.

Descriptive statistics were used to compare dose-volume data for tumour targets and organs at risk using dose and volume to predict the chances of complications. Normal tissue complication probability (NTCP) was similarly modelled for the parotid gland in paper 4. This type of methodology is still in widespread use in the current literature. The use of these techniques on small groups of patients rapidly provides information as to which technique is superior and provides some estimate of the size of the clinical benefit that might be anticipated. Theoretical planning studies have the advantage that they are relatively quick to perform, and statistically easy to analyse. The use of repeated testing of a variety of techniques in one individual allows the use of the statistically efficient paired t-test for normally distributed data and the Mann Whitney U test for non-normal data distribution. The use of planning studies does, however, have some drawbacks. The models used for NTCP are still relatively experimental, and while they may help rank plans in order of quality, the absolute value of NTCP is probably not very accurate. Furthermore, deciding which plan is the best out of a series is not always straightforward and the investigator may have to be prepared to weigh up the “pros and cons” of each dose distribution. This process may be biased by the clinician’s opinion as to what the clinical priorities or goals are for a particular tumour site.

The planning study of maxillary sinus cancer demonstrated that IMRT plans produced consistently lower doses delivered to the optic nerve and chiasm. The average maximum optic nerve dose was 56.4 Gy with IMRT compared to 65.7 Gy with 3DCRT plans. This difference of over 9 Gy was clinically important as it meant that patients with this tumour type could be safely offered a higher prescribed radiation dose to their tumour which should translate into improved local tumour control. IMRT plans also produced lower radiation doses to the brain and salivary gland tissue. These effects were of less clinical importance, but may reduce the risk of other side effects of radiotherapy.

The planning study for oropharyngeal cancer was more complex. Xerostomia is the most prevalent long-term complication following radiotherapy for head and neck cancer in patients who require bilateral neck irradiation and is associated with significant deterioration in the patient's QoL (Jensen, Hansen et al. 1994; Bjordal and Kaasa 1995; Wijers, Levendag et al. 2002). By 2001, IMRT had been shown to achieve significant reductions in the dose delivered to the parotid glands and several small single institution phase 2 studies had suggested lower xerostomia rates and improvements in quality of life (QoL) (Ship, Eisbruch et al. 1997; D'Hondt, Eisbruch et al. 1998; Eisbruch, Marsh et al. 1998; Eisbruch, Dawson et al. 1999; Kuppersmith, Greco et al. 1999). Most of these early clinical reports failed to give clear protocols for TVD, making reproducibility difficult. The ability to reduce radiation dose to the parotid gland was largely determined by its proximity to the PTV (Chao, Low et al. 2000) and, therefore, is significantly affected by differences in TVD.

I thought that in the UK there was an opportunity to carry out a multi-centre randomised controlled trial of parotid-sparing IMRT versus conventional radiotherapy. Agreement was reached amongst the trial participants as to the methods of TVD. The CTV definition guidelines used in this paper are important. This was the first time that primary tumour target outlining guidelines for a trial had been published in the literature. Key features were that I recommended that the entire oropharyngeal mucosa was included in the CTV 1, from the superior aspect of the soft palate to the hyoid bone. Laterally, on the involved side, the CTV1 extended to the mandible and included the ipsilateral parapharyngeal space. The contralateral parapharyngeal space was spared (see Figure 1 in paper 4). I used data from several sources to come to these conclusions. First, the data from pathological studies suggests that submucosal spread of squamous cell carcinoma is common and can extend over 1cm from the clinical or radiologically visible tumour edge. This phenomenon accounts for the high rates of local recurrence from partial pharyngeal surgery. Second, conventional radiotherapy techniques based on sound anatomical principles had irradiated the whole oropharynx for tumours approaching the midline for decades, and the local control rates with this technique were well described. Moving away from this principle of treatment risked higher levels of local tumour recurrence in the IMRT arm.

These guidelines differ from other researchers e.g.(Chao, Low et al. 2000), who prefer to use anatomically grown CTV from the GTV. In reality, the two different approaches lead to similar CTVs for all but very small primary tumours. Figure 1 and 2 in paper 4 demonstrate typical target volumes. For the outlining of CTV 2, the

elective lymph node volumes, we used the then recently published DAHANCA, EORTC, GORTEC NCIC, RTOG consensus guideline, but with a British modification, namely additional inclusion of the supraclavicular fossa down to the clavicles. This was done as UK oncologists felt that these areas were occasionally seen as sites of tumour recurrence. Since the PARSPORT trial, I have removed this “British modification” and reverted to the standard international consensus for one of the subsequent trials – e.g. the ART DECO protocol.

Conventional plans and IMRT plans were constructed as detailed above. With conventional plans, I sought to use the type of treatment planning in common UK clinical practice, such that any potential improvements with the IMRT plans could be compared to the UK standard of practice. This has sometimes been criticised because at the time of publication some radiotherapy departments in Europe and the USA were already using more complex treatment methods (e.g. 3-dimensional conformal radiotherapy, and forward-planned IMRT) to treat these patients. For a particular country, with an established standard of care for cancer treatment I think it is important that for a clinical trial, that “standard” treatment arm of the trial should represent the prevalent national practice at the time of trial design. Strict planning requirements were set for plan assessment as given in table 1 of paper 4.

This planning study was unusual in that the endpoint of the study was the predicted normal tissue complication probability (NTCP) (Kutcher, Burman et al. 1991) for salivary gland function.

At the time, there were two parameter sets proposed in the literature (see Table 2.1), and so we had to calculate NTCP using both parameter sets using the BIOPLAN software (Sanchez-Nieto and Nahum 2000) .

	Eisbruch <i>et al.</i>		Roesink <i>et al.</i>	
Parameter	TD50	m	TD50	m
Mean	28.4	0.18	39	0.45
95% confidence interval	25-34.7	0.1-0.33	34-44	0.33-0.65

Table 2.1 Eisbruch and Roesink parameters for parotid NTCP

The main results of paper 4 were that, for the PTVs, the dosimetric goals were achieved with adequate target coverage of the PTV1 and 2, and that spinal cord tolerance was observed (Figure 3 paper 4). However, for IMRT plans the dose to the parotid glands, especially the contralateral parotid, were significantly reduced, and the dose homogeneity to PTV2 was significantly better.

The calculated NTCP values are shown in Table 2.2. Both parameters showed highly statistical differences in predicted NTCP, however, as will be seen later in this chapter, neither parameter set was accurate in predicting subsequent clinical outcomes.

	Eisbruch et al (1999)			Roesink et al (2001)		
	IMRT	3D-RT	<i>p</i>	IMRT	3D-RT	<i>p</i>
Contralateral parotid	22.3 ± 10.3	100.0 ± 0.0	0.00007*	20.1 ± 3.5	98.7 ± 2.7	0.000004*
Ipsilateral parotid	100.0 ± 0.0	100.0 ± 0.0	NA	92.2 ± 11.0	99.6 ± 0.6	0.2

(*p*<0.05) *Statistical significance (*P* <0.05) using the Student *t* test

Table 2.2 Mean (± 1 standard deviation) NTCP values for IMRT vs. 3DCRT

Looking back, this area of head and neck oncology practice has moved forward significantly since the publication of paper 4 in 2007. Studies have shown a wide variety of target volume delineation amongst clinicians (Rasch, Steenbakkers et al. 2005). In the early days of parotid gland-sparing IMRT, there was concern about the risk of recurrence in the spared tissue around the parotid. This risk was uncertain at the beginning of the trial and was included as a risk in the patient information sheet for the PARSPORT trial. It was one of the aspects of the trial that both myself and the patients were concerned about. A review of the literature in this area shows that only one recurrence has been reported in the spared tissue adjacent to the parotid gland (Chao, Ozyigit et al. 2003; Eisbruch, Marsh et al. 2004) (Bussels, Maes et al. 2004) .

Nasopharyngeal cancer is rare in the UK, but represents a specific case where parotid gland sparing may be considered. IMRT is commonly used in Hong Kong and China where this cancer type is most prevalent, but occasional tumour recurrences have been seen in the parotid gland, especially in cases where extension of tumour along the Eustachian tube allows lymphatic drainage to the intraparotid nodes.

In the University of Michigan experience, Eisbruch et al (2004) found no recurrences in the contralateral neck, cranial to the sub-digastric nodes and the authors felt that the crossing of the posterior belly of the digastric muscle and IJV was a safe superior margin for the contralateral level. So the consensus emerged that it was safe to place the margin of the upper neck node fields at the bottom of the transverse process of C1 (Gregoire, Levendag et al. 2003) in the node negative neck and where there is no specific clinical indication to include the jugular fossa (Prins-Braam, Raaijmakers et al. 2004).

In our study, parotid-sparing IMRT achieved reductions of the mean dose to the contralateral parotid gland to 22 Gy, below the threshold suggested by Eisbruch et al (1999) for preservation of function. We also found reductions in the volume of ipsilateral parotid irradiated to 45 Gy and 60 Gy. Roesink et al (2001) reported some recovery when 40-80% of the gland was irradiated to 35-45 Gy and it may be that these observed reductions in volume irradiated could possibly translate to a small recovery of function in the ipsilateral parotid gland.

Calculated NTCP values for the contralateral parotid with PS-IMRT were 20-22% suggesting that xerostomia may be significantly reduced but not eliminated (Eisbruch, Dawson et al. 1999) (Roesink, Moerland et al. 2001). This general observation was subsequently disproved and is discussed later in this chapter.

Very recently it has become apparent that regions of the human parotid gland are not homogeneous in their ability to secrete saliva. Animal data from rat parotids (van

Luijk, Faber et al. 2009) suggests that the cranial and caudal compartments of the rat parotid contribute differently to saliva production. Recent data from our group suggest that this is analogous to the deep and superficial lobes of the human parotid gland (Miah 2011).

If these two planning studies are compared and contrasted, we start with the following two observations:

1. For Paranasal sinus cancers, IMRT reduced the dose to the optic nerve and may reduce the risk of radiation-induced optic nerve damage and blindness (Adams, Nutting et al. 2001).
2. For oropharyngeal cancers, IMRT can be used to reduce the dose to the parotid salivary tissue and that the IMRT technique should, in theory, allow recovery of parotid gland function such that xerostomia may be reduced or avoided (paper 4).

While “in-silico” planning studies offer the potential to test possible benefits of one dose distribution against another, the results of such studies are not sufficient to change practice. For this, actual clinical outcome data are required, ideally in the context of a well designed randomised controlled clinical trial. The planning study is helpful in determining the likely size of a clinical benefit (for example the differences in NTCP for parotid in paper 4) which may help guide sample size calculations for trials.

Of the two clinical scenarios given above, I considered that they represented two very different scenarios in terms of their potential to develop into practice-changing clinical trials.

First, xerostomia is an important long-term side effect of radiotherapy to the head and neck region which can be measured subjectively, objectively and with quality of life instruments (Jensen, Hansen et al. 1994; Bjordal and Kaasa 1995; Wijers, Levendag et al. 2002). The complication is common and the disease site also prevalent in the UK. At the same time there were a number of potential risks with the IMRT. First, the tissue around the parotid gland was not going to receive a tumouricidal dose, and therefore there was concern that tumour recurrences might be seen in the area close to the parotid gland. Second, the addition of multiple intensity modulated beams each day over a period of 6 weeks may not always deliver a homogeneous high radiation dose to the tumour and therefore tumour control might be compromised. Third, the delivery of low dose radiation to other tissues may have unexpected long-term consequences. I, therefore, decided to design a randomised controlled trial of conventional technique vs. IMRT to test whether IMRT would reduce the xerostomia rates in patients. This trial (PARSPORT) will be detailed later in this chapter. All of the risks and potential benefits detailed above were included in the PARSPORT trial patient information sheet.

By contrast, I did not think that it was possible to develop the theme of the maxillary sinus tumours into a randomised clinical trial. Radiation-induced optic nerve damage is a very serious late radiation side effect with a low predicted incidence which may take years to manifest (Martel, Sandler et al. 1997). In terms of trial design that would

mean a low number of events necessitating very large trial patient numbers over a long period of time. Second, paranasal sinus tumours are very rare such that any large randomised trial would not be feasible. Third, in paranasal sinus cancer, it would not be considered ethically appropriate to randomise patients to standard treatment arms which carried a risk of such serious late radiation complication as blindness.

It has been stated that this last argument could also be applied to PARSPORT (i.e. how can you ethically randomise patients to receive an above-tolerance dose to an OAR?). My response has been that in order to advance our specialty and develop new techniques, it is required that randomised controlled trials should be used when possible. In retrospect, I still maintain that the decision for a randomised controlled trial was correct. It will be seen later in this chapter that 47 patients were randomised in the PARSPORT trial to receive conventional radiotherapy, and approximately 80% of them were rendered xerostomic as a consequence. The process of the trial allowed us to deliver evidence of the benefits of IMRT which now is being recommended for all patients in the UK, Europe and abroad as the standard of care. It also encouraged implementation of IMRT in UK centres, provided education and training.

2.6 The PARSPORT trial: Preparations for a UK IMRT group and the challenge of delivering a high quality multicentre trial (paper 5 and 6)

In 2002, I started to work on the design of a randomised controlled trial of conventional radiotherapy vs. IMRT. At that time, there were limited reports in the literature of the outcome of head and neck IMRT.

At the University of Michigan (UM), IMRT was used to spare salivary gland tissue in patients irradiated for head and neck tumours. PTV included the primary tumour, ipsilateral cervical lymph nodes, and contra-lateral cervical lymph nodes up to and including the sub-digastric node. If the contralateral parapharyngeal space and parotid gland were judged to be at very low risk of harbouring occult metastases, they were spared, as were the submandibular salivary glands (Eisbruch, Ship et al. 1996; Eisbruch, Marsh et al. 1998). Patients were treated with a forward-planned “step-and-shoot” IMRT technique using multiple non-coplanar photon beams, and low-weighted electron fields (personal observation UM 1999). A beams eye view facility was used to select beam orientations that avoided the parotid gland (Marsh, Eisbruch et al. 1996). Unstimulated and stimulated salivary flow was measured from each parotid gland before and after radiotherapy and then at three, six, and twelve months. In fifteen patients treated with this parotid-sparing technique, IMRT improved the minimum dose, and reduced dose inhomogeneity to the primary tumour and lymph node regions compared to standard three-field conformal plans. IMRT reduced the radiation dose to the contralateral parotid gland to 32% compared to 93% for the standard plan. Smaller, statistically significant, reductions in the dose to the oral cavity, contralateral submandibular gland, and spinal cord were also seen but are unlikely to be clinically significant. One to three months after irradiation, the mean stimulated salivary flow from the contralateral parotid gland was 60% (SD 49%) of pre-treatment measurements (Eisbruch, Ship et al. 1996). Longer follow-up of eleven of these patients showed that spared parotid glands, which received a mean dose of 19.9 Gy, recovered 63% of their pre-treatment stimulated salivary flow rates at one year compared to only a 3% recovery for treated parotid glands which received 57.5

Gy (Ship, Eisbruch et al. 1997; D'Hondt, Eisbruch et al. 1998) (Table 2.3). At the time of this report, it was not clear what the relationship was between salivary flow rates (an objective measurement) and patient reported symptoms of dry mouth (subjective).

	<i>Spared parotid</i>	<i>Treated parotid</i>	<i>p value</i>
Pre-radiotherapy	0.40 ± 0.22 ml/min	0.36 ± 0.31 ml/min	N/A
Completion of RT	0.12 ± 0.07 ml/min	0.008 ± 0.02 ml/min	0.0004
3 months	0.20 ± 0.21 ml/min	0.003 ± 0.01 ml/min	0.05
6 months	0.24 ± 0.17 ml/min	0.006 ± 0.02 ml/min	0.001
1 year	0.25 ± 0.02 ml/min	0.011 ± 0.03 ml/min	0.006

Table 2.3 Mean stimulated salivary flow (± SD) after parotid-sparing IMRT

An analysis of eighty-eight patients treated with parotid-sparing IMRT allowed correlation of radiotherapy dose with salivary flow measurements to produce dose-response curves for parotid gland function. A mean dose threshold was found for both stimulated (26 Gy), and unstimulated (24 Gy) saliva flow rates, such that glands receiving mean dose below or equal to the threshold showed substantial preservation of the saliva flow following radiotherapy, which may continue to improve over time. By contrast, most glands receiving mean doses above the threshold produced little saliva and had no recovery over time (Eisbruch, Dawson et al. 1999). A subsequent published analysis did not reveal increased risk of nodal relapse in the vicinity of the spared parotid gland (Dawson, Anzai et al. 2000).

De Neve et al (1999) from the University of Gent reported the results of treatment of three patients with recurrent or second primary tumours of the nasopharynx, oropharynx, and hypopharynx with IMRT. All patients had been previously treated with radical radiotherapy; tumour dose 66-70 Gy, spinal cord dose 44-45 Gy, and had inoperable disease. An IMRT technique was used to re-treat the tumour (minimum target dose 48-65 Gy), with a concave dose distribution to avoid the brain stem and spinal cord (maximum spinal cord dose 21-34 Gy, maximum brainstem dose 67 Gy). Two patients achieved complete remission, but relapsed within one year of radiotherapy, and the other patient remained in partial remission seven months after treatment. No patient developed myelopathy, although the follow-up period was short. The same author has reported an IMRT technique for the irradiation of tumours in the neck which extend into the upper mediastinum. This technique has been used in the treatment of tumours of the thyroid, larynx and pharynx and would allow target dose escalation up to 70-80 Gy while restricting maximum spinal cord dose to 50 Gy (De Neve W 1996).

Boyer et al (1997) reported the results of a planning and delivery study where three patients with head and neck tumours were planned on the PEACOCK inverse planning system (now updated to CORVUS, NOMOS Corporation, Sewickley, PA), and the plan was delivered to a humanoid phantom using nine equispaced fields by a dynamic MLC technique. For a patient with nasopharyngeal carcinoma, 96% of the primary tumour PTV reached the goal dose of 72 Gy, although part of the gross tumour volume (GTV) received 90 Gy. A goal dose of 54 Gy was prescribed to the lymph node chains but 12% of this PTV was under dosed, with a minimum dose of

26.5 Gy. Parotid and spinal cord sparing were achieved with delivered doses below clinical tolerance. Similarly, for tumours of the larynx and ethmoid sinus, mean target doses were achieved and normal tissue structure sparing was successful, although target dose inhomogeneity was high. (Goitein and Niemierko 1996) have calculated that such dose inhomogeneity may lead to large reductions in the probability of tumour control. However, in comparison with standard techniques, the precise location of lower dose regions and effects, for example, of patient movement as well as the accuracy of the planning algorithm need to be considered in determining the desired tolerance of such dose inhomogeneities.

The first clinical report of twenty-eight patients with a spectrum of head and neck tumours treated with the MIMiC tomotherapy apparatus (NOMOS Corporation, Sewickley, PA) has been published from the Baylor College of Medicine (Butler, Teh et al. 1999; Kuppersmith, Greco et al. 1999) . Ten patients were treated for tumour recurrence after previous conventional radiotherapy, and in eighteen patients IMRT was part of the primary treatment. Patients were initially immobilised using an invasive fixation device (Talon, NOMOS Corporation, Sewickley, PA) which attached to screws placed in the inner table of the skull vertex, although currently half of their patients are immobilised in a standard thermoplastic mask (Engler, Curran et al. 1994). After CT scanning, inverse treatment planning was performed with the objective of minimising the dose to parotid glands, brain, orbits, optic nerves, and brainstem, depending on tumour site. Treatment was well tolerated with acute toxicity equivalent to conventional radical radiotherapy. A high degree of parotid sparing was demonstrated in suitable patients, with less than 20% of the total parotid volume

receiving greater than 20 Gy. Clinical follow-up of these patients is short, and although only one of twenty patients treated definitively has recurred locally, long-term results are not yet available.

Using the above data, I designed a simple randomised controlled trial where patients at high risk of radiation-induced xerostomia would be randomised to either standard technique radiotherapy or IMRT. The primary end-point was the incidence of high grade xerostomia reported by patients using the LENT-SOMA (late effects of normal tissue – subjective, objective, management, analytical) scoring system. Secondary endpoints were clinician-reported outcomes of RTOG subjective xerostomia grade 2 or more, measured saliva flow, and quality of life. I submitted my initial trial proposal to CRUK who requested a full application. At that stage I started to collaborate with The Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU). Together with a trial manager and statistician we developed the protocol and were awarded full funding in 2003.

At the start of PARSPORT, detailed procedures for the implementation of IMRT had not yet been established in the UK and, although some centres in the UK had started IMRT programs (Clark, Mubata et al. 2002) (James, Scrase et al. 2004), most centres joining the study had not yet implemented head and neck IMRT. In addition, only some early recommendations in general implementation had been published in the USA (Ezzell, Galvin et al. 2003; Galvin, Ezzell et al. 2004), as well as some initial quality assurance recommendations for IMRT in the head and neck (Marcie, Aletti et al. 2003; Zefkili, Tomsej et al. 2004). Prior to opening the trial, I had to form a Trial

Management Group (TMG) consisting of the principal investigator from each centre as well as physicists, radiographers, statisticians and trial managers. The TMG agreed a trial protocol which included the TVD guidelines and QA requirements. A rigorous QA programme to cover all aspects of the patient pathway, from target volume definition to verification, was designed for participating centres to ensure parity of treatment planning, pre-treatment verification and delivery across the different institutions. The program also served to give the centres a structure on which to base their IMRT protocol and provided guidance and support for clinical implementation.

As many centres were starting IMRT, there was also an element of teaching required in the set-up process and this was provided at the trial launch day, and by running regular IMRT courses at RMH. A dosimetry audit was carried out after the centres had joined the trial and patients had been entered.

The main results of the dosimetry audit (paper 6) were that while each centre was using different equipment (planning systems and linear accelerators) to deliver IMRT, that they could all reach agreement as to a standard process to deliver the trial treatments. Furthermore the adoption of the outlining guidelines presented in paper 4 was acceptable, and that the medical physicists in each department were able to produce treatment plans which fulfilled the criteria laid out in the trial protocol document. This observation would be confirmed a few years later when the trial outcome reports found that over 90% of treatment plans (91% conventional and 98% of IMRT plans) had been delivered within protocol. In total 10 UK centres completed the entire pre-trial QA process of which 2 had no prior experience of IMRT planning

or delivery. Since this piece of work was completed, there have been other trials of IMRT in head and neck cancer and other tumour types. The success of our experience has been used to set up a National Radiotherapy Trials QA group (RTTQA) and has developed an IMRT accreditation program for centres entering IMRT trials of breast and prostate cancer in the UK. Similar programs have also been implemented in Europe (EQUAL-ESTRO) and in the US (RTOG QA). It is now widely held that rigorous QA is an essential part of any trial where radiotherapy is an important component of the treatment.

As well as the departmental processes and the treatment planning, an equally important aspect is that the delivery of IMRT on the linear accelerator is accurate and that the radiation dose is reproducible in all participating cancer centres. This importance of this has recently been demonstrated in a trial carried out by the TROG group (Peters, O'Sullivan et al. 2010). They performed a trial of chemoradiation with the addition of a hypoxic cell sensitizer in head and neck cancer. The primary endpoint of the trial was not met, but in an interesting retrospective analysis they looked at the outcomes of patients whose radiotherapy had been given according to the protocol, and compared that to patients who had minor or major deviations from the protocol. It was seen that major deviations to the protocol led to a reduction in tumour control and survival of 10-20%.

In paper 6, I present the outcome of a dosimetry audit which we performed for all the centres that entered patients into the PARSPORT trial. This consisted of treatment

planning system tests, fluence verification films, combined field films and dose point measurements inside a head and neck phantom.

The results of this study were that, from the 6 participating centres, the standard deviation of the dose measurements was within $\pm 2.5\%$. As a consequence of this work, a national recommendation was made that a 3% tolerance was appropriate for dose points within the PTV for multi-centre IMRT trials.

2.7 PARSPORT trial results (paper 7)

I undertook a randomised controlled trial between Jan 21, 2003, and Dec 7, 2007, that compared conventional radiotherapy (control) with parotid-sparing IMRT. We randomly assigned patients with histologically confirmed pharyngeal squamous cell carcinoma (T1–4, N0–3, M0) at six UK radiotherapy centres between the two radiotherapy techniques (1:1 ratio). A dose of 60 or 65 Gy was prescribed in 30 daily fractions given Monday to Friday to the primary tumour site and involved lymph nodes and 54Gy to elective lymph node regions. Randomisation was by computer-generated permuted blocks and was stratified by centre and tumour site. Our primary endpoint was the proportion of patients with grade 2 or worse xerostomia at 12 months, as assessed by the LENT SOMA scale. Analyses were done on an intention-to-treat basis, with all patients who had assessments included. Long-term follow-up of patients is ongoing. This study was registered with the International Standard Randomised Controlled Trial register, number ISRCTN48243537.

The Consort diagram (paper 7 Figure 1) shows the outcomes of patients entered into the trial. Table 1 shows the patient characteristics. Again, the trial represents a typical head and neck population, being typically male aged just under 60 years. The majority of patients had oropharynx tumours and most had stage III-IV disease. Approximately 40% of patients had induction chemotherapy which was well balanced between the arms. The mean contralateral parotid gland dose was 25.4 (range 23.2-28) Gy for IMRT patients and 61 (range 54.6-63.8) Gy in conventional radiotherapy patients. Corresponding ipsilateral parotid gland doses were 47.6 (range 39.9-54.5) Gy and 61 (range 57.0-64.4) Gy respectively (paper 7, Table 1).

Figures 2a and 2b in the paper show the proportion of patients with high grade ($\geq$ G2) xerostomia using both the LENT SOMA and the RTOG scoring systems. They both show a similar pattern, with xerostomia rates in the conventional arm of 70.8-86.2% (LENT SOMA Conventional arm) compared to recovery in the IMRT arm: 38.5% at 12 months, 31.4% at 18 months, and 29% at 24 months. The RTOG data show a similar pattern. The RTOG definition of G2 xerostomia is slightly different being “partial or persistent dryness of the mouth with little or no response on stimulation” compared to the LENT SOM definition of “complete dryness of the mouth”.

Other acute side effects of radiotherapy were not reduced by IMRT (paper 7, table 2). Unexpectedly, acute fatigue was more common in the IMRT patients. The cause for this remains unknown, but subsequent research suggests that the dose to the brain was higher with IMRT than conventional radiotherapy, and that this might be the underlying cause.

The patient-reported xerostomia was supported by the saliva collection results which showed that patients who had received IMRT had a higher chance of producing measurable quantities of saliva compared to conventional radiotherapy patients.

The EORTC QLQ-C30 instrument was used to measure global quality of life. At 24 months after radiotherapy, there was an 11.1 point score difference between IMRT patients and those treated with conventional radiotherapy. This represents a clinically significant difference in global QoL for patients who received IMRT.

The PARSPORT trial showed a significant reduction of radiation-induced xerostomia for patients treated with IMRT compared with conventional radiotherapy by use of both LENT SOM and RTOG scales. Furthermore, the trial showed recovery of saliva flow by quantitative measurements, and improvements on QoL measures associated with xerostomia. To my knowledge, this trial is the first to show that parotid-sparing IMRT reduces xerostomia in head and neck squamous cell carcinoma. A consistently higher QLQ-C30 global and QLQ-HN35 dry mouth score was reported in patients who received IMRT; between group differences at 24 months were clinically but not statistically significant. Xerostomia questionnaire results showed changes in favour of IMRT in all eight questions but these differences were not large enough to reach statistical significance, probably because of the small number of patients that completed this questionnaire. Although an association between measurable saliva flow and presence of grade 2 or worse xerostomia was recorded, there was not perfect concordance. We postulate that this could be because of differences in patient

perception of the xerostomia symptom or because of other factors such as submandibular gland or oral cavity dose or co-morbidity. Detailed analyses of the distribution of dose to the salivary tissue including parotid glands and other minor salivary glands, and its correlation with clinical outcomes are ongoing. Initial results suggest that there is no correlation between submandibular gland dose and xerostomia.

A limitation of our trial was that it was not possible to mask the treatments from patients or clinicians because of differences in treatment delivery. Assessments were therefore unblinded. However, results that relate to multiple secondary endpoints support the primary analysis and the size of the observed effect is unlikely to be due entirely to assessment or reporting bias. After our trial was designed, several small non-randomised studies and one case-control study (Fang, Tsai et al. 2007) of parotid-sparing IMRT have been published with a range of endpoints including saliva flow rate, patient-reported symptoms, and QoL (see summary table 2.4). These studies reported apparent improvements for IMRT over conventional radiotherapy.

Two small single-institution randomised phase 3 trials of IMRT in nasopharyngeal cancer have also reported benefits of IMRT over conventional radiotherapy. Pow and colleagues (Pow, Kwong et al. 2006) reported an increase in stimulated whole saliva flow rate in patients receiving IMRT in a randomised trial of 51 patients with early-stage nasopharynx cancer. QoL was assessed with EORTC QLQ-C30, QLQ-HN35, and the SF36 health survey and although QoL scores for some domains were better for IMRT patients, no improvements in patient-reported dry mouth symptoms on the

HN35 questionnaire were noted. Kam and colleagues (Kam, Leung et al. 2007) reported a reduction in observer-rated severe xerostomia (RTOG grade 2 or worse) with IMRT (39% vs. 82%; $p=0.001$) in 60 patients with early-stage nasopharyngeal cancer. The results of the PARSPORT trial are thus likely to be generalisable to all head and neck tumours for which conventional radiotherapy is used.

In our study, fewer cases of acute dermatitis were recorded in patients treated with IMRT than in those treated with conventional radiotherapy, although differences were not statistically significant at the 1% level, probably because of reduced dose to skin. The proportions of patients that reported grade 2 or worse acute xerostomia and grade 2 or worse salivary gland changes also showed reductions, albeit not statistically significant. Late xerostomia side effects thus accord with acute side effects; this suggests that late radiation-induced xerostomia is a consequential effect.

We did not attempt to spare the submandibular or mucosal minor salivary glands within the planning target volume in our trial. It is possible that further reductions in severe xerostomia can be achieved by sparing these tissues, but this might risk underdosing crucial target tissues. Unexpectedly, acute fatigue was greater in patients treated with IMRT, which could be due to the greater radiation dose to non-tumour tissues. In an unplanned dosimetry review in a subset of patients, mean radiation doses to the posterior fossa were 20–30 Gy in the patients treated with IMRT compared with about 6 Gy in patients treated with conventional radiotherapy, which could account for the recorded difference in acute radiation induced fatigue. Late fatigue data were not collected because lethargy is not a recognised long-term side-

effect of radiotherapy. There was no significant association between the giving of neoadjuvant chemotherapy and either acute fatigue or xerostomia. The addition of concurrent chemotherapy to altered fractionation radiotherapy remains experimental and was not used in our study.

Further research is needed to establish the effect of concurrent chemotherapy on xerostomia. Apart from salivary gland changes and radiation-induced xerostomia, other late side-effects of conventional radiotherapy were not altered by IMRT.

Our trial was too small to detect small differences in, or conclude non-inferiority of, locoregional progression free survival (PFS) or overall survival (OS). Although patients continue to be followed up for long-term survival, to show non-inferiority in overall survival to no more than 5% at 2 years (80% power, one sided 5% significance) would need a randomised controlled trial of more than 900 patients. In this, and other, head and neck IMRT studies most tumour recurrences happen within the high-dose volume. Recurrences have not been noted in the spared parotid tissue in patients treated with IMRT or surgery, suggesting that a large study to show non-inferiority in this tumour type is probably both impractical and inappropriate. Our trial has shown a clinically and statistically significant reduction in xerostomia, improved salivary flow, and improved QoL, and thus strongly supports a role for IMRT in HNSCC.

In the next chapter I will move away from the question of reducing normal tissue radiation toxicity and present data on the use of IMRT to increase radiation dose to head and neck tumours in an attempt to improve local tumour control.

Table 2.4 Summary table of published literature on parotid-sparing IMRT for head and neck cancer

Study	Mean Parotid Dose in Gray (Gy)				Benefit from IMRT		
	IMRT	RT	Conventional	Conformal	Xerostomi a	Functiona l	QoL
Pow (Pow, Kwong et al. 2006) Mean (SD; Range)	Ipsilateral Contralateral	42Gy (4.7; 31.3-51.2) 41.3Gy (5.4; 33.1-51.8)	n.a	-	-	Yes	No
Vergeer (Vergeer, Doornaert et al. 2009) Mean (SD)	Ipsilateral Contralateral	28.7Gy (11.9) 23.3Gy (11.2)	Bilateral 43.0 Gy	-	Yes	Yes	Yes
Jabbari (Jabbari, Kim et al. 2005) Mean (Range)	Ipsilateral Contralateral	50Gy (38.7-67.8) 21.8Gy (14-35.5)	Bilateral 55.0 Gy	-	Yes*	-	Yes
Fang (Fang, Tsai et al. 2007)	n.a		n.a	n.a	-	Yes	Yes
Fang (Fang, Chien et al. 2008) Mean (Range)	Right Left	47.64Gy (23.42-63.55) 46.84Gy (21.44-64.37)	-	Bilateral 60.0 Gy	-	No	No
Graff (Graff, Lapeyre et al. 2007) Mean	Bilateral Mean dose <30Gy: For one or both parotids in 63.5% of patients For both parotids in 23.8% of patients Mean dose <26Gy: For one or both parotids in 34.9% of patients	33.7Gy	n.a	-	-	Yes	No
McMillan (McMillan, Pow et al. 2006) Mean (Range)	Right Left	38.4Gy (29.6-46.1) 40.4Gy (29.7 – 53.4)	-	-	-	-	-
Scrimger (Scrimger, Kanji et al. 2007) Mean (SD)	Total Parotid Volume Spared Parotid Volume	27.1Gy (16.5) 18.4Gy (10.5)	-	-	-	-	-

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Lin (Lin, Kim et al. 2003)	n.a			-	-	-	-	-
Parliament (Parliament, Scrimger et al. 2004)	Right Spared Parotid volume	22.8Gy (17.8 – 27.8)						
Mean (Range)	Left Spared Parotid volume	20.9Gy (17.9 – 24)		-	-	-	-	-
	Total Parotid Volume	30.0Gy (26.9 – 33.1)						
Nutting [2011]	Ipsilateral	47.6Gy (range 39.9-54.5)	Ipsilateral					
Mean	Contralateral	25.4Gy (range 23.2-28)	Contralateral	-	Yes	-	n.a	
			60Gy					
			60Gy					

SD Standard deviation
RT Radiotherapy
QoL Quality of Life
IMRT Intensity Modulated Radiotherapy

Chapter 3

Can IMRT increase tumour control?

Papers in this chapter

Paper 8

Clark CH, Bidmead M, Mubata CD, Harrington KJ, **Nutting CM**. Intensity-modulated radiotherapy improves target coverage, spinal cord sparing and allows dose escalation in patients with locally advanced cancer of the larynx. *Radiother Oncol*. 2004;70:189-98.

Paper 9

Guerrero Urbano T, Clark CH, Hansen VN, Adams EJ, A'Hern R, Miles EA, McNair H, Bidmead M, Warrington AP, Dearnaley DP, Harrington KJ, **Nutting CM**. A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer. *Radiother Oncol*. 2007; 85:36-41.

Paper 10

Miah AB, Bhide SA, Guerrero-Urbano MT, Clark C, Bidmead AM, St Rose S, Barbachano Y, A'hern R, Tanay M, Hickey J, Nicol R, Newbold KL, Harrington KJ, **Nutting CM**. Dose-Escalated Intensity-Modulated Radiotherapy Is Feasible and May Improve Locoregional Control and Laryngeal Preservation in Laryngo-hypopharyngeal Cancers. *Int J Radiat Oncol Biol Phys*. 2012; 82(2):539-47

3.1 Introduction

This chapter focuses on three papers (papers 8-10) that aim to explore the potential of IMRT to deliver higher radiation doses to larynx and hypopharynx tumours. Paper 8 is a theoretical treatment planning exercise and then papers 9 and 10 present the results of a clinical trial in patients suggesting that improvements in tumour control may be observed. The chapter concludes with a summary of a randomised trial which is currently recruiting patients in the UK. The chapter highlights the difficulty of conducting Phase I trials in radiotherapy and shows how I progressed the ideas through preclinical evaluation, through to Phase I, and then into a Phase III trial.

Classical radiobiological teaching holds that increases in local tumour control can be anticipated with increasing radiation dose delivered to a tumour (Fu, Pajak et al. 2000), and that this may translate into improvements in overall survival. Squamous cell carcinoma of the head and neck has a high alpha/beta ratio and so this approach is anticipated to be particularly effective.

Radical chemoradiation or surgery (laryngectomy/pharyngo-laryngectomy) with or without adjuvant radiation/chemoradiation has traditionally been the main treatment options for locally advanced tumours of the larynx and hypopharynx. Concomitant cisplatin chemoradiotherapy can achieve locoregional failure-free rates of 60–65% at 2 years, with a laryngeal preservation rate of 35– 65% The Department of Veterans Affairs Laryngeal Cancer Study Group (1991); (Lefebvre, Chevalier et al. 1996; Forastiere, Goepfert et al. 2003). These treatment modalities offer similar overall survival rates when compared with surgery and have demonstrated improved

locoregional control and laryngeal preservation rates over the last 30 years (Marcial, Pajak et al. 1987; Lee, Cosmatos et al. 1995). This is particularly important in the maintenance of normal function, especially breathing and swallowing.

A meta-analysis confirmed improved locoregional control and overall survival when altered, as opposed to standard, fractionation regimens were delivered (Bourhis, Overgaard et al. 2006). Unfortunately, combining concomitant chemotherapy with altered fractionation using conventional radiotherapy techniques can cause severe normal tissue toxicities and consequential morbidity (Maciejewski, Skladowski et al. 1996; Jackson, Weir et al. 1997).

IMRT delivers radiation more conformally and reduces the volume of normal tissue in the high-dose volume. Paper 8 aimed to test whether IMRT would produce a better dose distribution and allow dose escalation by modest hypofractionation in patients with tumours of the larynx and hypopharynx.

3.2 Application of the IMRT technique to locally advanced larynx and hypopharynx cancers (paper 8)

External beam radiotherapy for advanced cancer of the larynx and hypopharynx represents a difficult challenge for treatment planning because the PTV, which includes the larynx and bilateral cervical lymph nodes, is wrapped around the spinal cord (SC).

Typically in the UK, with conventional radiotherapy, lateral-opposed photon portals are used to treat the PTV up to cord tolerance and then reduced photon fields are matched to high-energy electrons bilaterally to treat the posterior cervical lymph nodes (Perez and Brady 1987; Dobbs, Barrett et al. 1999). This produces a concave dose distribution surrounding the SC, but there are areas of potential under dose in the photon–electron match line that may account for a proportion of patients who relapse in the cervical nodes.

A radiation dose of 65–70 Gy is required to eradicate macroscopic tumour in the larynx and involved lymph nodes, and 50 Gy elective irradiation to the cervical lymph nodes (Fletcher 1972). These doses are in excess of SC tolerance (absolute maximum of 48 Gy in 2 Gy fractions), and without careful treatment planning the patient is at risk of radiation-induced myelopathy due to the proximity of the target volume to the SC.

In the treatment of carcinoma of the larynx and hypopharynx, IMRT may offer the potential to improve target coverage and increase the sparing of the organs at risk (OAR). The primary aim of the study in paper 8 was to investigate whether IMRT could improve coverage of the larynx and nodal PTVs compared to conventional techniques whilst maintaining SC sparing. The second aim of the study was to investigate if dose escalation was technically possible within SC tolerance. A planning study was performed using the principles outlined in Chapter 2.

The main findings of paper 8 were that IMRT plans had better dose distributions than conventional plans (see paper 8 figures 2-7 and tables 2-4). Figure 3.1 shows a typical patient dose volume histogram and demonstrates the increase in minimum dose delivered to PTV 1 and 2 and also the reduced dose to the spinal cord with IMRT. The reduction in spinal cord dose was such that dose escalation to greater than 67 Gy was possible within spinal cord tolerance. Target dose homogeneity was improved with IMRT plans.

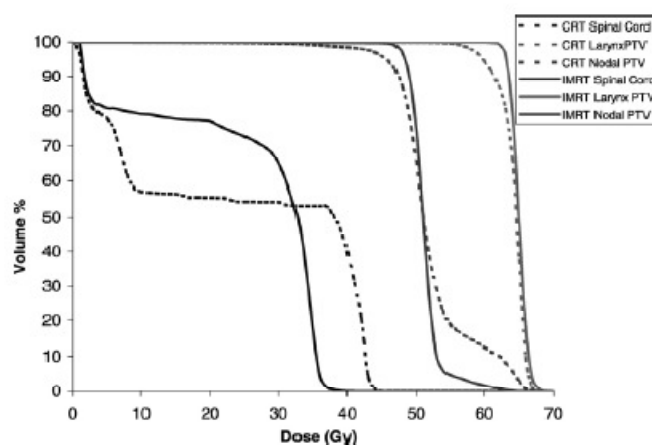


Figure 3.1 A dose-volume histogram showing data for a conventional and IMRT plan for a typical patient. The CRT plan data are shown as dotted lines and the IMRT is in solid lines. The IMRT data show a significant improvement in target coverage and dose inhomogeneity as well as improved cord sparing.

3.3. Development of a clinical dose escalation trial

The goals of radiotherapy for locally advanced (T3-4, N+) carcinoma of the larynx and hypopharynx are local control, survival and quality of life—specifically voice/larynx preservation. For T3N0 cases, the local control and survival rates with

radiotherapy alone are 50–60 and 60–70%, respectively. Two-thirds of patients will survive with a functional larynx (The Department of Veteran Affairs Laryngeal Cancer Study Group 1992). Other larynx-preserving approaches include the use of induction and/or concomitant chemoradiation (The Department of Veteran Affairs Laryngeal Cancer Study Group 1992; Lefebvre, Chevalier et al. 1996), and radiotherapy dose escalation. Dose escalation strategies have employed accelerated, hyperfractionated, and continuous, hyperfractionated accelerated radiotherapy (CHART) schedules which show an increase in local control and support the hypothesis of a steep dose–response relationship for squamous cell carcinoma of the head and neck (Fu, Pajak et al. 2000). Induction chemotherapy schedules have not been shown to have a significant effect on improving overall survival, although cisplatin doublets may increase the response rate and increase local tumour control.

Concomitant chemo-radiation strategies are now the standard of care in locally advanced head and neck cancer. In a large meta-analysis, concomitant chemo-radiation had a 9% advantage over radiotherapy alone (Pignon, Bourhis et al. 2000). Such strategies may carry increased normal tissue toxicity, and there is uncertainty as to the net effect on the therapeutic ratio (Henk 1997).

3.3 Design of a dose escalation trial (paper 9)

Putting all the above evidence together, I designed an IMRT schedule which combined induction chemotherapy and concomitant chemo-IMRT using a moderately accelerated fractionation scheme. I hoped that this would offer the benefits of induction and concomitant chemoradiation and at the same time that the accelerated

IMRT would be more tolerable for patients than acceleration delivered by conventional radiotherapy techniques. The dose and fractionation technique is shown in Table 3.1.

	PTV 1	PTV 2
Dose level 1	63.0Gy 28# (2.25Gy) BED _{10Gy} 66.6, BED _{3Gy} 110.3 Log cell kill 10.12	52Gy 28# (1.85Gy) N/A
Dose level 2	67.2Gy 28# (2.4Gy) BED _{10Gy} 72.8, BED _{3Gy} 121.0 Log cell kill 11.06	56Gy 28# (2.0Gy) N/A
Conventional 70Gy 35#	70Gy 35# (2Gy) BED _{10Gy} 74.1, BED _{3Gy} 116.67 Log cell kill 10.26	50 Gy 25# (2Gy) N/A

Table 3.1 Dose schedules used in the dose escalation trial

The proposed radiotherapy technique had several potential risks. First, I was proposing an accelerated radiotherapy schedule with concurrent chemotherapy. As detailed above, other studies that used more accelerated techniques had demonstrated severe acute toxicity with this approach. Second, I had proposed delivering greater than 2 Gy per fraction (2.2 Gy in the first dose level (DL1), and 2.4 Gy in the second dose level (DL2)). Within PTV 1 were some normal tissue structures with a low alpha: beta ratio which may have increased risk of normal tissue injury when delivering greater than 2 Gy per fraction. I was particularly concerned about the risk of laryngeal cartilage necrosis and also cervical oesophagus strictures.

These safety concerns led me to the decision to evaluate this technique using a phase I trial design. Phase I trials have traditionally been used to assess the safety of new drugs in patients with incurable recurrent cancer for whom there are very few treatment options. Typically, increasing doses of the drug under evaluation are administered to small numbers of patients over a short period of time until acute dose-limiting toxicity (DLT) is reached. Once DLT is established, then the previous non-toxic dose level is usually taken forwards into Phase II trial testing (Harrington, Billingham et al. 2011).

In radiation oncology, phase I trials are problematic. First, DLT for most radiation techniques are late effects which may take months or years to appear and may be progressive over time. Second, we were proposing to evaluate this dose escalation strategy in previously untreated patients who had a reasonably good chance of long-term cure, even with standard dose radiation.

With this in mind, I designed a quite conservative dose escalation strategy and wrote into the protocol stringent safety stopping rules based on $\geq$ G3 toxicity (see paper 9). The trial design was to enrol 15 patients for each dose level initially, expanding to 30 if a late toxicity was reported. The main expected toxicities were late, specifically laryngeal cartilage necrosis, and oesophageal stricture.

Phase I stopping rules were, that if 0/15 had $\geq$ G3 toxicity (defined as a radiotherapy toxicity requiring surgery to correct it) then $\geq$ 20% risk of $\geq$ G3 late complications was excluded with 95% power. If 1-2 of 15 developed $\geq$ G3 toxicity then that cohort

should be expanded to 30 patients to improve statistical power. If 1 or 2 of 30 had $\geq$ G3 toxicity then the incidence of $\geq$ G3 toxicity was estimated at 0-17% or 0-22%, respectively. If $>2/30$ had $\geq$ G3 toxicity then the predicted grade $\geq$ G3 toxicity would be 2-27% with 95% power which would be deemed too unsafe to continue and the recruitment to the trial would be stopped.

3.4 Clinical Results of the dose escalation trial (Paper 10)

Overall, 60 patients were recruited to the study. The patient characteristics are given below.

	DL1 63Gy/ 28F	DL2 67.2Gy/28F
No of patients	29	31
Median follow up months (range)	49.0 (35.7- 78.3)	35.7 (17.7-62.8)
Age (years) Mean	58 (35-80)	63 (43-85)
Sex Male Female	23 (79.3) 6 (20.7)	24 (77.4) 7 (22.6)
Performance status 0 1	24 (82.8) 5 (17.2)	30 (96.8) 1 (3.2)
Primary Tumour Site Larynx Hypopharynx	17 (58.6) 12 (41.4)	16 (51.6) 15 (48.4)
TNM Stage I II III IVA IVB	1 (3.4) 1 (3.4) 12 (41.3) 13 (44.8) 2 (6.9)	0 0 16 (51.6) 15 (48.3) 0
Neoadjuvant chemotherapy Yes No	29 (100) 0	29 (93.5) 2 (6.5)
Concomitant chemotherapy given	29 (100)	30 (97)

Table 3.2 Patient Characteristics; DL = Dose level; F = fractions

The trial participants were typical of the head and neck population being predominantly male aged around 60. The balance of larynx and hypopharynx tumours was, by chance, similar which was fortunate because the prognosis stage for stage is not the same, being worse for hypopharynx cancers. Ninety-three percent of cases were stage III or IV, although two patients with earlier stage hypopharynx cancers were included in DL1.

Acute toxicity is presented in Figure 1 and 2 and Table 3 of paper 9 and updated in Table 2 of paper 10. Late radiotherapy toxicity is presented in Table 3.3 below.

Overall 3 patients had $\geq$ G3 late toxicity. In the first 15 patients in DL1, no patient had toxicity. On that basis we proceeded to DL2. In dose level 2, two toxicities were observed. One oesophageal stricture which was treated conservatively and one stricture which failed dilatation and required laryngopharyngectomy (no tumour found on pathology). While the data on DL2 were maturing, we returned to DL1 and treated another 15 cases to that dose. This was done to increase the statistical power of the DL1 patient group. One of those second 15 cases developed a benign stricture and required dilatation. Overall the G3 toxicity rate was 5% for DL1 and 8% for DL2. (Table 3.3)

	Number of patients by late toxicity grade at 1 year (%)									
	Dose Level 1 n=29					Dose Level 2 n=31				
	0	1	2	3	4	0	1	2	3	4
Skin	16 (76)	4 (19)	1 (5)	0	0	21 (88)	3 (12)	0	0	0
Mucosa	12 (57)	9 (43)	0	0	0	17 (71)	7 (30)	0	0	0
Subcutaneous Tissue	18 (86)	3 (14)	0	0	0	15 (63)	7 (30)	2 (7)	0	0
Larynx	9 (43)	7 (33)	5 (24)	0	0	6 (25)	14 (58)	4 (17)	0	0
Oesophagus	15 (71)	5 (25)	0	1 (5)	0	15 (60)	7 (29)	0	1 (4)	1 (4)
Salivary Gland	10 (48)	9 (43)	2 (9)	0	0	9 (38)	13 (54)	2 (8)	0	0
Spinal Cord	21 (100)	0	0	0	0	24 (100)	0	0	0	0

Table 3.3 Type and Frequency of Late Radiotherapy Adverse Effects (N=60)

Treatment outcome at 2 years is presented in Table 3.4. The locoregional control rate appeared higher in DL2 than DL1 (85.9% vs. 70.8%), as did the laryngeal preservation rate (96.4% vs. 88.7%). Kaplan Meier curves for local control and survival are presented in paper 10.

	DL1 n=29 %- (95% CI)	DL2 n=31 %- (95% CI)
Median Follow Up	51.2 months range 12.1-77.3	36.2 months range 4.2-63.3
Local control rates	70.8 (49.7-84.3)	85.9 (66.7-94.5)
Locoregional control rates	67.6 (46.7-81.7)	81.8 (61.6-92.1)
Loco-regional progression free survival	64.2 (43.5-78.9)	78.4 (58.1-89.7)
Disease free survival	61.5 (58.8-89.9)	78.4 (58.1-89.7)
Larynx preservation rate	88.7 (68.5-96.3)	96.4 (77.2-99.5)
Overall survival	72.4 (52.3-85.1)	74.2 (55.0-86.2)

Table 3.4: Treatment outcomes at 2 years

3.5 Design of ART DECO, a dose escalation trial

In some studies, locally advanced head and neck cancer has benefited from altered radiotherapy fractionation regimens (pure acceleration or altered fractionation with a higher total dose) (Overgaard, Hansen et al. 2003; Overgaard, Mohanti et al. 2010). The RTOG 9003 study concluded that hyperfractionation or accelerated fractionation with concomitant boost provided significantly better locoregional control when compared with conventional fractionation (54.5% vs. 46.0% at 2 years) (Fu, Pajak et al. 2000). Accelerated radiotherapy, compared with a conventional treatment of 7 weeks, can achieve maximum shortening in treatment time of 2 weeks, with the high grade mucositis being the DLT and any further acceleration requiring a reduction of dose. Further dose escalation schedules with conformal radiotherapy techniques had been unsuccessful because of unacceptable acute and or late toxicity. Maciejewski et al. (1996) compared a 70 Gy in 35 daily fractions over 7 days per week fractionation

schedule versus a 5 days per week schedule and found an unacceptably high incidence of severe acute reactions and consequential late effects in the accelerated arm. Jackson et al. (1997) randomized 66 Gy in 33 daily fractions once daily vs. twice daily. The trial was discontinued early because of an increase in Grade 4 toxicity in the accelerated arm. Phase III trials have demonstrated a lower incidence of patient-reported toxicities with IMRT when compared with conformal radiotherapy techniques in the treatment of oropharyngeal (Nutting 2009) and nasopharyngeal cancers (Pow, Kwong et al. 2006; Kam, Leung et al. 2007). However, dose escalation IMRT studies in the treatment of locally advanced head and neck cancers are sparse.

In my sequential cohort Phase I/II study, both accelerated hypofractionated radiotherapy regimens with induction and concomitant chemotherapy were found to be deliverable without treatment breaks. Dose Level 2 confirmed that dose escalation is feasible with an increase in acute toxicities, but with similar late radiation toxicity at two years. The Phase I goals of the study were therefore met.

During our study, Madani et al. reported the results of their Phase I dose escalation trial (Madani, Duthoy et al. 2007). They assessed the feasibility of positron emission tomography-guided focal dose escalation using IMRT. Patients received 25 Gy in 10 daily fractions to a sub-volume within the GTV. Standard 2.16 Gy per fraction was applied to the remainder of the volume and then to the combined target volumes for the remaining 22 fractions. There were two cases of DLTs (Grade 4 dermatitis and Grade 4 dysphagia) out of the 18 reported cases. The second dose level delivered 30 Gy in 10 fractions to the positron emission tomography-defined volume within the

GTV. The study was stopped after a treatment-related death (sepsis and renal failure) at the second dose level.

This gave me grave concerns about proceeding further with dose escalation. The trial by Madani had escalated radiation doses by about 20% compared to our trial where an estimated 10% dose escalation had been achieved. This was obviously a very disturbing observation and I felt that increasing another dose level with our technique may run into severe acute toxicity problems. At the same time, we were analysing the locoregional control data and I realised that the DL2 results suggested an improvement in local control and larynx preservation rate without increasing long-term toxicities.

Lee et al. (2007) reported a retrospective review of laryngeal and hypopharyngeal cancers treated with concurrent chemotherapy and IMRT. All patients experienced RTOG $\geq$ G2 pharyngitis during treatment. Two-year percutaneous endoscopic gastrostomy dependence rates were 31% and 15% for hypopharyngeal and laryngeal cancers, respectively. Percutaneous endoscopic gastrostomy dependence was related to pharyngeal stricture, high-grade dysphagia, or laryngeal aspiration (Lee, O'Meara et al. 2007). Our study defined very conservative stopping rules: the incidence of high-grade dysphagia at 1 year was 6% in DL2, whereas incidences reported in the literature are around 30% (Jeremic, Shibamoto et al. 2000; Staar, Rudat et al. 2001; Lee, O'Meara et al. 2007). The mean dose delivered to the inferior constrictor muscles in DL2 was 68.1 Gy (range, 65.5–69.3 Gy). We observed no cases of laryngeal cartilage necrosis or laryngectomy for a dysfunctional larynx. Patients with

successful organ preservation also maintained acceptable function. In our study, no formal functional outcome measures of speech and swallow were undertaken. These will be included in our subsequent studies alongside quality of life parameters.

The RTOG has described age, tumour stage, primary site (larynx/ hypopharynx), and neck dissection after chemoradiation as factors associated with severe late toxicity after concomitant chemoradiation for locally advanced squamous cell cancer of the head and neck (Machtay, Moughan et al. 2008). They also demonstrated that the peak incidence of severe toxicity occurs at 3 years after treatment. In our study there has been no increase in incidence of high-grade (Grade ≥ 3) radiation-related late toxicities at 2 to 3 years compared with the reports at 1 year. Within the limitations of this small study, improved treatment outcomes were reported in DL2. Local control rates at 2 years in the two cohorts were 70.8% and 85.9% in DL1 and DL2, respectively, with larynx preservation rates at 2 years of 88.7% and 96.4%. The difference between these two outcome measures is explained by the patients either being unfit for salvage surgery or that the disease was deemed inoperable. Locoregional control rates at 2 years for the two dose levels with a median follow-up of 24 months for DL1 and 21 months for DL2 were reported as 65% and 85%, respectively (Nutting, Miah et al. 2009). To emphasize, the study was too small to determine differences in locoregional control and survival, and the Phase I/II trial design was inappropriate to assess this outcome in detail. However, the potential difference in overall response rates and locoregional recurrences between the two cohorts could be due to increased radiobiological effectiveness of DL2. It has been suggested that DL1 represents an inferior radiobiological effective dose. However,

when we compare DL1 outcomes with those reported in the literature using conventional dose and fractionation, the locoregional control rates are similar at 60–65% at 2 years for laryngeal cancers. With longer median follow-up of 51.2 months for DL1 and 36.2 months for DL2, an improvement in locoregional control is maintained.

As a consequence of the improved locoregional control and larynx preservation rates and concerns about acute toxicity of further dose escalation, I decided to proceed to examine the DL2 schedule in a randomised controlled trial. The trial schema is presented below in Figure 3.2.

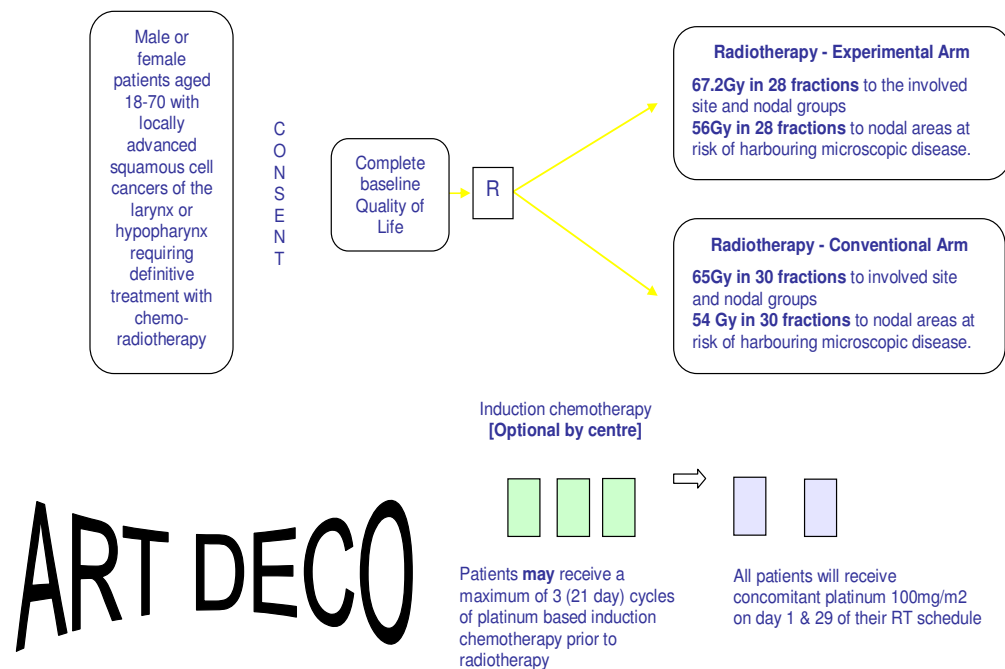


Figure 3.2 ART DECO phase III trial schema

In this trial, which opened to recruitment in 2011, patients with locally advanced squamous cell carcinoma of the larynx or hypopharynx are randomised to receive either UK standard dose IMRT (65 Gy in 30 fractions) or the DL2 schedule. Patients in both treatment arms will receive concomitant chemotherapy with cisplatin and can also receive induction chemotherapy at the investigator's discretion. The trial is stratified by treatment centre and each centre will provide their own induction chemotherapy schedule such that different chemotherapy schedules will be balanced on both arms of the study by the randomisation process. The primary endpoint is to determine whether there is an improvement of locoregional failure-free rate at 2 years compared with standard-dose chemotherapy-IMRT. In conjunction with recently published consensus guidelines for laryngeal preservation studies, we will also evaluate laryngeal and oesophageal dysfunction and associated quality of life (Lefebvre and Ang 2009). At the time of writing approximately 20 patients have been randomised within this clinical trial.

This Chapter has demonstrated the progression of medical scientific discovery through preclinical evaluation, to early phase trials, and then the design of a Phase III RCT in head and neck cancer patients. In the final chapter I will review some of the methodological ideas used in this thesis as well as the research and development infrastructure in the UK which led to this method of research. I will explore some of the ethical issues around the RCT design and suggest some future directions for research.

Chapter 4

Conclusions and Future Directions

4.1 Introduction

In this thesis I have explored the use of IMRT to reduce toxicity and improve tumour control rates for patients with head and neck cancer. Chapter 2 detailed the resolution of obstacles for local and then national implementation and evaluation of IMRT through a randomised controlled trial. This trial demonstrated a clinically and statistically significant benefit in reduction in xerostomia, the main long term side effect of head and neck radiotherapy. This trial provided proof-of-principle that IMRT could be used to reduce parotid gland radiation dose compared to conventional radiotherapy leading to reduced symptoms and improved quality of life, while maintaining tumour control rates.

Currently a second randomised controlled trial called COSTAR (principal investigator Nutting) is recruiting patients in the UK. This trial aims to reduce radiation-induced hearing loss in patients who are being treated with adjuvant radiotherapy to the parotid following surgical resection of a malignant parotid tumour. The trial design is similar to the PARSPORT trial, and the endpoint of this trial is high frequency hearing loss measured by an audiogram one year after radiotherapy. The COSTAR trial is predicted to close in autumn 2012 and results should be available in late 2013.

4.2 Methodological issues

The randomised controlled trial methodology is widely accepted as being the gold standard for evaluation of a new health care intervention (Moher, Hopewell et al. 2010). Evidence from RCTs is designated level II evidence – “evidence from at least

one properly designed RCT". (National Health and Medical Research Council (Australia) 1998). This form of trial design helps reduce spurious causality and avoid bias or confounding factors. Results of RCTs may be combined to produce systematic reviews, the highest hierarchy of evidence-based medicine (Level I evidence (Oxford centre for evidence based medicine (2009)). However, RCTs have their own limitations and risks (Black 1996; Sanson-Fisher, Bonevski et al. 2007). Among the most frequently cited scientific drawbacks are limitations of external validity, cost, time, and statistical problems. The validity of a RCT result for the general population may be affected by where the trial was performed, the characteristics of the patients entered into the trial, the outcome measures chosen and the completeness of data collection. Furthermore, the informed consent process has the potential to introduce a systematic bias by patient selection. RCTs are expensive to perform and may take many years to recruit and follow up patients to the chosen endpoint. RCTs are subject to both type I (false positive) and type II (false negative) errors. A typical trial design using $p < 0.05$, will have a 1:20 chance of a type I error. Despite these drawbacks, global healthcare systems typically demand data from RCTs to decide on major changes in clinical practice, especially when assessing new high-cost technology. In the UK the Department of Health is responsible for developing and assessing evidence to inform development of medical technology for the benefit of patients and the public. The National Institute for Health and Clinical Excellence (NICE) develops evidence-based guidelines on the most effective way to diagnose, treat and prevent ill health. NICE generates Clinical Guidelines as well as performing Technology Appraisals. As part of the process of evaluation of a new intervention, NICE reviews evidence collated by the National Clinical Guideline Centre (NCGC) which

systematically reviews the evidence for that technology. Selection of relevant studies and assessing their quality are some of the most important tasks in this process (NICE guidelines manual 2009). The following quotation is taken from their manual: “Well-conducted randomised controlled trials are more likely than non-randomised studies to produce similar comparison groups, and are therefore particularly suited to estimating the effects of interventions”. Therefore in the UK the RCT is critical for evaluation of health care technology for clinical implementation in the NHS.

The design of both the PARSPORT and COSTAR trials has taken account of these factors. While the studies have been performed in the UK, both trials are relatively small. This was due to the large difference in outcome of the primary endpoint expected between the two arms of the trials. The trial participants were selected in that they had to fulfil all the inclusion and exclusion criteria of the trial. A small number of subjects were unable to join the trial because they refused to be randomised. This was usually because they had read that IMRT was “new” technology with possibly better outcomes than conventional radiotherapy. Other patients refused randomisation because of concerns about potential increased relapse rates in the untreated areas around the parotid gland which was a risk which was mentioned in the patient information sheet, and discussed during informed consent. One patient who refused randomisation travelled to the USA for IMRT. During the trial recruitment period, IMRT was not available in the UK outside of a trial. The choice of outcome measure in the PARSPORT trial (i.e. severe xerostomia ($\geq$ G2)) could be criticised, and if I had chosen a lower toxicity ($\geq$ grade 1 for example) then

the results of the trial may have been different, as G1 xerostomia is still reported by many patients treated with IMRT.

Two studies published in the New England Journal of Medicine in 2000 suggested that RCTs and observational studies overall produced similar results (Benson and Hartz 2000; Concato, Shah et al. 2000). However a study in 2001 published in Journal of the American Medical Association (Ioannidis, Haidich et al. 2001) concluded that discrepancies beyond chance do occur, and differences in the estimated size of a difference between two treatments are seen between RCTs and observational studies. Such differences may influence healthcare providers' decisions in funding new technologies. This raises an ethical dilemma with radiation oncology trials of normal tissue toxicity. Patients treated in the conventional arm of the PARSPORT trial suffered permanent dry mouth which will affect their QoL for their whole lifetime. This was predicted, but unproven, at the time of trial design (see below). As a consequence of the PARSPORT trial and associated research, IMRT has been accepted to be superior to conventional radiotherapy for reducing xerostomia and over 250,000 patients worldwide can potentially benefit from IMRT each year.

4.3 Evidence base in 2002 compared to 2006/7

In 2002 when the trial was conceived, there were two theoretical planning studies from University of Michigan that showed IMRT delivered a lower radiation dose to the parotid salivary tissue (Eisbruch, Marsh et al. 1998; Eisbruch, Ten Haken et al. 1999). In addition there were early clinical reports from three US centres reporting reduction in xerostomia in head and neck IMRT patients (Ship, Eisbruch et al. 1997;

Kuppersmith, Greco et al. 1999; Chao, Low et al. 2000). One study had demonstrated maintenance of saliva flow following parotid sparing IMRT (D'Hondt, Eisbruch et al. 1998). While promising, these studies were inadequate to make any conclusions about parotid gland sparing radiotherapy at that time. The reports were heterogeneous and contained small numbers of patients with no comparative groups. It is important at this point to also take into account the perceived disadvantages of parotid-sparing IMRT at that time. First, IMRT was still in its infancy, a new treatment available in a small number of specialist centres with no long term clinical outcome data. Second, the IMRT technique used multiple complex radiation beams which led to a less homogeneous radiation dose with significant variation in dose within the tumour compared to conventional radiotherapy. There were concerns as to whether this might lead to reduced tumour control rates if there were areas of low dose within the tumour, and specifically if parotid sparing IMRT would lead to geographical miss of tumour cells close to or within the parotid tissue (Dawson, Anzai et al. 2000). Third, the technique was time-consuming and therefore costly. As discussed in Chapter 2, there was an opportunity to test this technology in a RCT as there was clinical equipoise as to whether IMRT was overall beneficial to head and neck patients.

It could be argued that a large multi-centre observational study in the UK would have been an alternative approach to the PARSPORT RCT, and may have come to the same conclusion without having to render patients xerostomic in the control arm. By contrast, in 2007 when the trial closed to recruitment, and 2009 when the results were first reported, the situation had changed. There were a number of larger Phase II single institution trials reporting consistently better recovery of saliva flow in patients

treated with parotid sparing IMRT (Parliament, Scrimger et al. 2004; McMillan, Pow et al. 2006; Fang, Tsai et al. 2007; Graff, Lapeyre et al. 2007; Scrimger, Kanji et al. 2007). One case-control study (Jabbari, Kim et al. 2005) showed that IMRT reduced xerostomia rates and improved quality of life. Two small randomised controlled studies in nasopharyngeal cancer from Asia, (Pow, Kwong et al. 2006; Kam, Leung et al. 2007) showed increases in saliva flow and reduction in xerostomia in IMRT patients compared to conventional radiotherapy. In respect of the PARSPORT trial it is clear that the position of clinical equipoise existed appropriately up until 2006-2007 when the studies by Pow et al (2006) and Kam et al (2007) were published. This was contemporaneous with the closure of recruitment of PARSPORT. In retrospect, the period 2003-2007 was a window of opportunity for performing this trial and I do not think that it would have been possible to continue recruitment to PARSPORT beyond that time.

The PARSPORT trial sample size was not large enough to statistically prove that the local tumour control rates were equivalent for both arms of the trial. In order to achieve this aim a much larger sample size would have been required, which was not felt to be feasible. This remains a major criticism of the PARSPORT trial as while reduction in toxicity was demonstrated, equivalent local control was not statistically proven and so any overall gain in the therapeutic ratio remains uncertain (discussed on p77, chapter 2).

In Chapter 3 I have presented data to show that dose escalation to larynx and hypopharynx cancers was theoretically possible with IMRT (paper 8). Papers 9 and

10 show clinical data from a non-randomised trial that suggests that this approach is safe, and also that it may lead to an improvement in local tumour control. The study design used in paper 9 and 10 is a sequential cohort design and the numbers of patients studied are too low to lead to any statistically valid conclusions about differences in outcomes between the two dose levels. However the ARTDECO trial is powered to measure a difference in local control rates between standard dose, and escalated dose IMRT.

The potential consequences of irradiation of more tissue to low dose with IMRT remain uncertain. Parotid-sparing IMRT uses multiple beam directions and increases the radiation dose to some non-target structures such as the brain stem and cerebellum. This may well be the reason why increased acute fatigue was observed in the IMRT arm of the PARSPORT trial. This was an unexpected finding which is almost certainly a real observation ($p < 0.01$), but had not been identified in any of the observational studies performed by other groups. The MD Anderson Cancer Centre reported an increase in acute normal tissue toxicity with IMRT and suggested that more careful avoidance of non-target structures should be performed (Rosenthal, Chambers et al. 2008). The low-dose irradiation of these and other tissues may be shown in the long term to be detrimental to patients, for example increased risk of cerebro-vascular disease or second malignancy. These toxicities would be expected to take years to manifest and are not part of the data collection of the RCT protocol.

4.4 Ethical issues

At the time of the PARSPORT trial design, and throughout the recruitment period, there was clinical equipoise amongst the investigators regarding the risks and benefits of parotid-sparing IMRT based on the potential benefits and risks given above. As with many advances in medical science, the results, when viewed retrospectively looked very predictable especially when viewed in the context of the additional advances in knowledge that occurred during the recruitment period. However, I have often been asked “Surely it is self evident that reducing the radiation dose to the salivary glands will maintain saliva production – how could you ethically randomise patients?” Since the introduction of RCTs, there has been concern from medical professionals and lay people that this experimental design requires patients to potentially sacrifice their own best interests for the benefit of future patients, or the population as a whole (Edwards, Lilford et al. 1998). Investigators have an obligation and a responsibility to ensure that patients do not come to any harm as a consequence of trial participation (World Medical Association Medical Ethics Committee 1999). This can be addressed on several levels. First, when possible, patients and carers should be involved at the stages of clinical trial design to ensure that what is being proposed in a trial is acceptable to potential participants. Second, before a trial starts, approval of an ethics committee must be sought. Third, informed consent must be obtained from competent patients (Williams 1994). These points are largely procedural and are legal requirements through Good Clinical Practice (GCP) (General Medical Council 2006 (updated 2009)). What is more difficult is the evaluation of developments which occur during trial recruitment after the initial protocol approval. Developments in the clinical science are part of the remit of a data monitoring

committee, but participating investigators may have their personal equipoise affected by peer pressure to continue a trial, personal investment of time and effort, or other reasons (Taylor and Kelner 1987; Tobias and Souhami 1993). In respect of the PARSPORT trial it is clear that the position of clinical equipoise existed appropriately up until 2006-2007 when the studies by Pow et al (2006) and Kam et al (2007) were published. This was contemporaneous with the closure of recruitment of PARSPORT.

4.5 Future directions

In the future I would like to see the development of studies aimed at improving swallowing following radiotherapy. The pharyngeal muscles are adversely affected by high dose radiotherapy and chemo-radiotherapy, with up to 50% of patients complaining of swallowing abnormalities after treatment (Roe 2011). The pathophysiology of this problem is poorly understood, but does seem to be related to the dose delivered to the pharyngeal muscles. Whether the problem is due to atrophy and fibrosis of the muscles themselves, or due to loss of neurological function is uncertain. Certainly it may be possible to achieve reductions in the extent of irradiation of these structures with IMRT and this could translate into improved swallowing function. In order to do this then I believe that better imaging of the extent of tumour may be required to give us more certainty in the definition of the target volume and thus the safety of reducing margins around GTV. This should be tested in a RCT with endpoints of swallowing and QoL. This thesis could be seen as a template for evaluation of other new radiotherapy techniques such as this in the future.

One consistent observation from current radiotherapy studies is that despite advances in radiotherapy techniques there are still a proportion of patients in whom the tumour exhibits primary radiation resistance. These tumours are characterised by persistence through radiotherapy or rapid recurrence soon after completion of treatment. These recurrent or persistent tumours occur within the high dose volume of PTV1 and are associated with a very poor prognosis. It is postulated that the reasons for primary radiotherapy resistance are due to a number of factors including hypoxia, tumour proliferation or ability to rapidly repair radiation induced DNA damage.

In the future a number of different strategies will be used to try and overcome these issues. First, are the physical strategies. The processes of hypoxia or proliferation may be imaged using a number of functional imaging techniques. These include the use of radiopharmaceutical tracers for example ^{18}F -misonidazole or CuATSM for hypoxia, or dynamic MRI techniques such as dynamic contrast enhanced (DCE) or diffusion weighted (DW) MRI. At the present time these techniques are experimental, but in the future if they show adequate sensitivity and stability these may provide targets for radiation dose escalation to subvolumes contained within tumours. Radiation doses of up to 150% of current prescriptions may be needed to overcome the relative radioresistance of hypoxia for example.

Second, there are pharmaceutical approaches. The normal cellular response to DNA damage is to enter cell cycle arrest to allow repair of DNA damage. In normal cells this process is mediated by the intracellular protein p53 which recognises and initiates

repair of DNA. In many tumours p53 is mutated and the tumour cell relies on another pathway through Chk1 to allow cell cycle arrest and DNA repair. Therefore in some tumour cells with mutated p53 it may be possible, by Chk1 inhibition, to block this alternative DNA repair pathway and therefore render cells more sensitive to DNA damage. Such strategies may be tumour specific as most normal tissues have intact p53 and therefore will continue to repair DNA damage in normal cells in the usual way. There are now a number of drugs which may inhibit this DNA repair process in tumour cells and these will be tested in clinical trials in the next few years.

In summary, I believe that we have only just started to scratch the surface of what is possible with modern radiation technology. The next decade will see further advances in technology and our understanding of cancer biology which will allow more accurate radiation delivery to tumours and will translate into further reductions in side effects and improvements in tumour control rates

Paper 1

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Head and neck radiotherapy

Assessment of a customised immobilisation system for head and neck IMRT using electronic portal imaging

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Abstract

Purpose: To evaluate set-up reproducibility of a cabulite shell and determine CTV-PTV margins for head and neck intensity-modulated-radiotherapy.

Materials and methods: Twenty patients were entered into the study. A total of 354 anterior and lateral isocentric electronic portal images (EPIs) were compared to simulator reference images.

Results: About 94% of all translational displacements were ≤ 3 mm, and 99% ≤ 5 mm. The overall systematic error was 0.9 mm (± 1.0 SD) in the Right-Left, 0.7 mm (± 0.9 SD) in the Superior-Inferior and -0.02 mm (± 1.1 SD) in the Anterior-Posterior directions. The corresponding SDs of the random errors were ± 0.4 , ± 0.6 and ± 0.7 mm. The estimated margins required from CTV-PTV were calculated according to the Van Herk formula was 2.9, 2.6 and 3.3 mm, respectively.

Conclusions: This head and neck immobilisation system is of sufficient accuracy for its use with IMRT treatments and a 3 mm CTV-PTV margin has been adopted.

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Keywords: Immobilisation; Head and neck; IMRT; Electronic portal imaging

Introduction

The delivery of head and neck IMRT requires accurate knowledge of accuracy of patient set-up. This is accounted for by margins added to clinical target volume (CTV) to produce planning target volume (PTV). Both random and systematic errors occur [3,7–11,18]. The introduction of IMRT and the initiation of PARSPORT (a randomised study of parotid sparing IMRT) prompted reassessment of the head and neck immobilisation system, in order to determine the correct CTV to PTV margins.

Materials and methods

Patients and immobilisation method

20 patients receiving radiotherapy for head and neck tumours close to bony structures suitable for image matching were entered into the study. Patients were treated on a 2100 CD Varian linear accelerator (Varian Medical Systems, Palo Alto, CA) using a *Tufnol-Sandwich* head and neck board. The head-board was fully integrated into the Varian exact couch in a fixed position. Each patient was immobilised on a head support pad using a customised

Cabulite (co-polyester) head and shoulder shell attached to the head-board using a positive fixing mechanism with four fixation points, two either side of the head and two either side of the shoulders (Fig. 1).

Imaging protocol

Prior to treatment all patients had anterior and lateral (orthogonal) isocentric simulator reference images taken. The simulator images were acquired on the Acuity digital simulator (Varian Medical Systems) and transferred into Vision 6.1 as the reference images. They were then used for comparison with their corresponding megavoltage portal images. Anterior and lateral isocentric EPIs were taken on the treatment machine using a Varian amorphous silicon detector (Portal vision aS500, Varian Medical Systems). Images were taken and assessed daily during the first week of treatment and weekly thereafter. A match template was drawn on the reference images by contouring stable anatomical structures. Matching of the images was performed off-line on the third day. If there was field placement error of more than 3 mm in any axis on three consecutive days, the isocentre was adjusted to correct for this error. Where adjustments were required, further images were

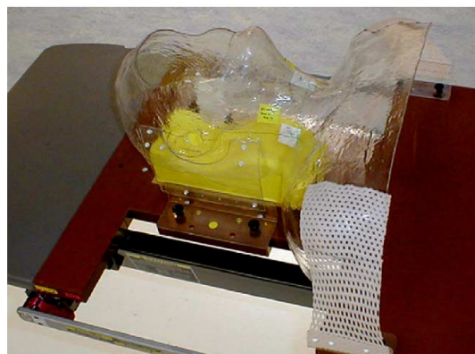


Fig. 1. Customised shell attached to wooden board using four fixation points.

taken until two consecutive images were within the pre-established tolerance limits. A single observer matched the portal images to the simulator reference images in all patients, thereby eliminating inter-observer variability.

Image analysis

All images were analysed using the Vision 6.1 image matching software (Varian Medical Systems). The comparison between the reference and portal images was performed using the template matching technique as previously described. Field sizes for the reference images were acquired from the VARIS database but are automatically extracted by software from the differential gradient around the portal image edge. The software then automatically calculates the magnification factors allowing direct comparison between the reference and portal images. The software allows improvement of the image quality using different filters and contrast enhancement tools.

The field edges of both the reference and the portal images were automatically matched and the match template projected on to the portal image. The match template was then manually adjusted using rotation and translation to get the best correspondence between the template and the anatomical landmarks seen on the portal image. The software then calculated displacement errors of the portal image relative to the reference image. The deviations observed were expressed as translational and rotational displacements of the field.

Statistical analysis

This was a prospective observational study. Displacements in the supero-inferior (S-I), right-left (R-L) and antero-posterior (A-P) directions were measured in millimetres and rotational displacements in degrees, both on the anterior and lateral images. Superior, right and posterior movements were defined as positive and inferior, left and anterior as negative.

For each individual patient, the systematic error is given by the mean value of all the displacements measured during the course of treatment. The overall (group) systematic error is expressed by the mean of all individual means.

For the whole population the distribution of systematic errors in each direction is expressed by the standard deviation (SD) from the values of the mean displacements of all individual patients [15].

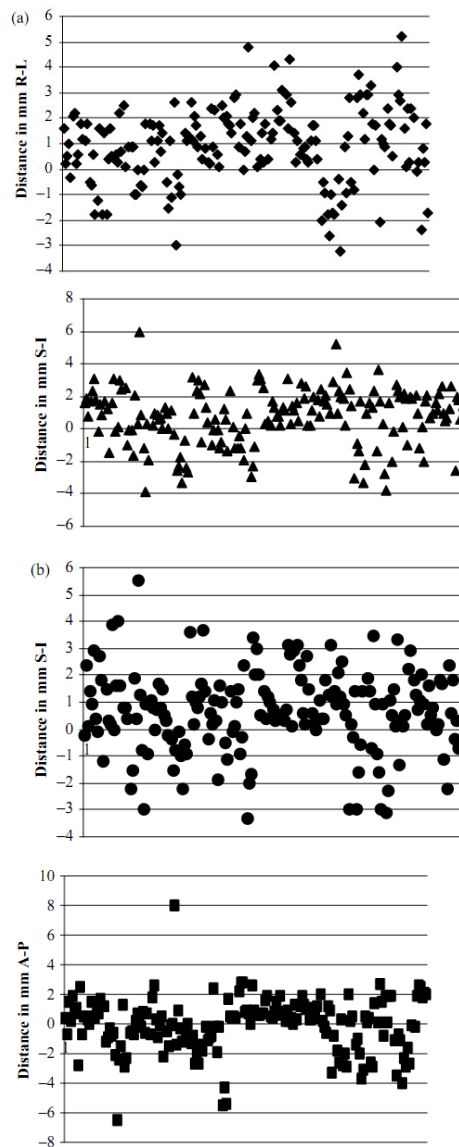


Fig. 2. Scatter plot of distribution of set-up measurements for (a) anterior fields showing Right-Left and Superior-Inferior directions. Each diamond represents one measurement (total 177); (b) lateral fields showing Anterior-Posterior and Superior-Inferior directions. Each diamond represents one measurement (total 177).

The distribution of the random errors for each individual patient is expressed by the SD of the measured displacements. The overall (group) SD of the random error is given by the SD of all individual SDs [16].

The cumulative probability of total translational errors occurring in the anterior and lateral images was calculated. The formula described by van Herk et al to obtain the CTV-PTV margins was used to calculate an estimate of the CTV-PTV margins in all directions: $\text{Margin} = (2.5 \times \text{SD of the group systematic error}) + (0.7 \times \text{SD of the random error})$ [15].

Results

354 images were obtained from 20 patients. About 1062 displacements were measured, 177 in each direction: S-I, R-L and rotational in the anterior images and S-I, A-P and rotational in the lateral images.

Overall displacements

The absolute values of total errors measured in both the anterior and lateral images are depicted in Fig. 2. In absolute terms, of all translational displacements, 94% were ≤ 3 mm and 99% ≤ 5 mm; 99% of all rotational displacements were $\leq 3^\circ$ (Fig. 3). The probability of a translational displacement being < 3 mm was 95% in both the anterior and lateral images in all directions.

Per patient displacements

The mean ($\pm$ SD) translational displacements per patient in the anterior and lateral images in each direction are shown in Fig. 4.

Systematic errors

The overall (group) systematic error was 0.9 mm (± 1.0 SD) in the R-L, 0.7 mm (± 0.9 SD) in the S-I and -0.02 mm (± 1.1 SD) in the A-P directions. Separate analysis of the S-I systematic error on the anterior and lateral images gave the same result (0.7 mm) with SD ± 1.0 and ± 0.8 , respectively. Rotational overall systematic error was 0.2° (± 0.4 SD) on the anterior images and 0.5° (± 0.5 SD) on the lateral images.

Random errors

The SD of the random errors was ± 0.4 mm in the R-L, ± 0.6 mm in the S-I and ± 0.7 mm in the A-P direction. The SD of the random error in the S-I direction on the anterior and lateral images was the same (± 0.6 mm). The SD of the random rotational errors was $\pm 0.2^\circ$ on the anterior and $\pm 0.3^\circ$ on the lateral images.

Estimated margin calculation

The estimated margin from CTV to PTV calculated according to the formula suggested by van Herk et al was 2.9 mm in the R-L direction, 2.6 mm in the S-I direction and 3.3 mm in the A-P direction. For practical purposes, adoption of a 3 mm margin in each direction would encompass $> 95\%$ of all positioning errors.

Discussion and conclusions

Many different immobilisation devices and materials have been used and previously evaluated [1-8,12-14,17]. Our study shows that using a customised Cabulite shell SD of systematic errors of approximately 1 and 0.6 mm for random

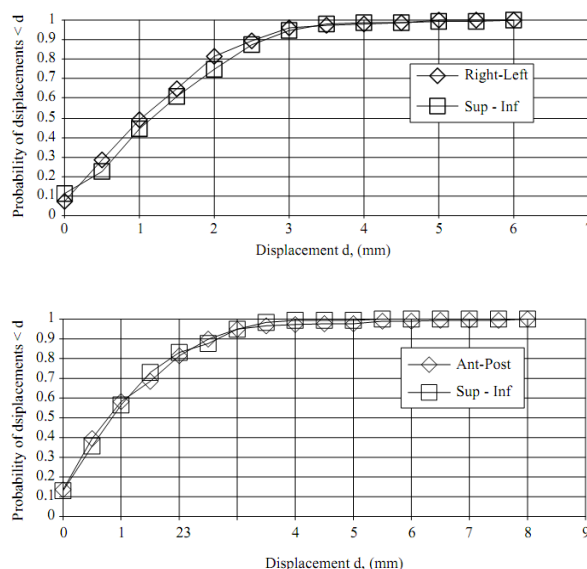


Fig. 3. Graphs depicting the cumulative probability of translational errors on the anterior and lateral images.

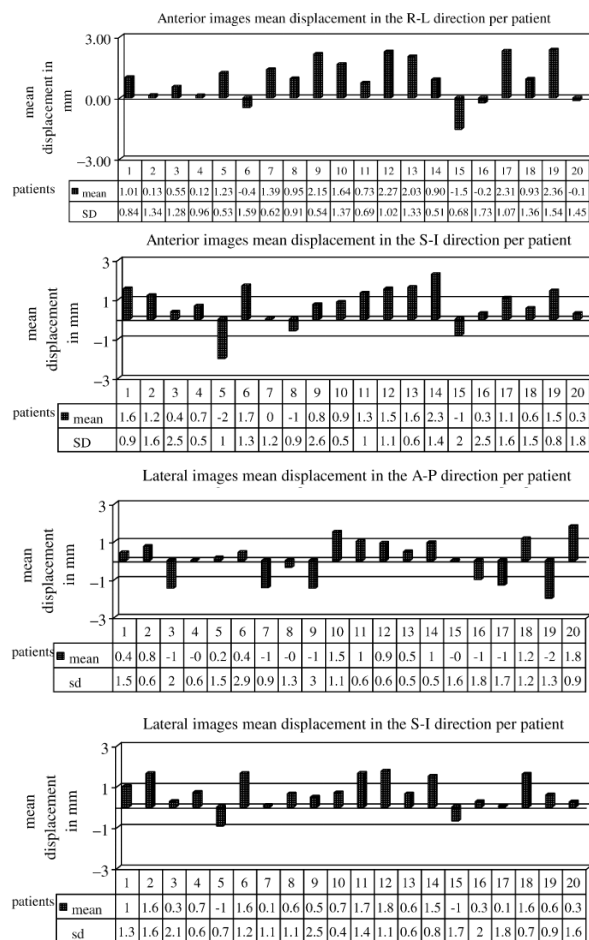


Fig. 4. Graphs depicting the mean ($\pm$ SD) displacement per patient in the anterior and lateral images in all directions.

errors can be obtained. This compares well to the published data (Table 1), although the methodology used in most of these reports used film portal images and manual matching rather than EPI and computer-assisted matching. In addition,

separate analysis of the anterior and lateral images showed no difference in the errors and their standard deviations in the S-I direction, suggesting negligible intra-fraction motion. For the rotational errors standard deviations of

Table 1
Results of other studies of head and neck immobilization

Reference	Immobilisation method	Result
Bel [1]	Head cast	SD of systematic error 1.8 mm, SD of random error 1.4 mm
Bentel [2]	Orfit	Mean set-up error 5-10 mm
Bentel [2]	Cabulite	Mean set-up error 3-4 mm
De Boer [4]	PVC cast	SD of random and systematic error of 1.5-2 mm
Gilbeau [5]	Posifix or head/shoulder cast	SD of random and systematic error of <2.4 mm
Hess [6]	Cast	Absolute Deviations, 50% <3 mm, and 95% <9 mm

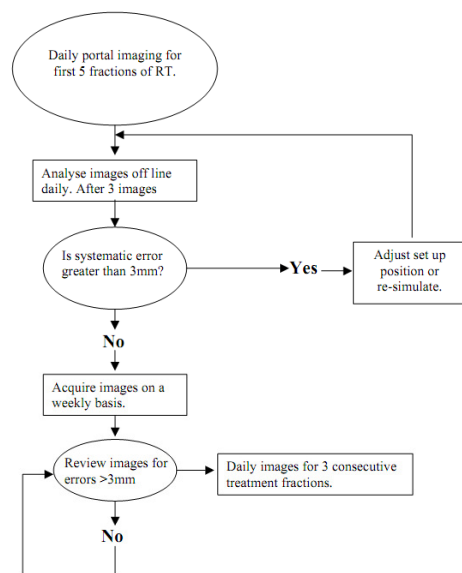


Fig. 5. Electronic portal imaging protocol for isocentre verification at RMH.

approximately 0.5° for the systematic and 0.3° for the random errors were found. This is important as it has been shown that rotational errors larger than 3° can lead to a reduction in the accuracy in the measurement of the translational error if not taken into account [15].

In our study, 94% of all translational displacements were ≤ 3 mm and 99% were ≤ 5 mm. The results presented in this paper confirm that the system currently used at our institution is of sufficient accuracy for use with IMRT treatments and the margin from CTV to PTV and OAR (spinal cord) to PRV has been set at 3 mm. Fixation of the immobilisation system to the treatment couch may be an important factor and we suggest that our results are due at least in part to the use of four fixation points. Individual plastic masks are rigid and transparent and can be cut out to allow skin sparing without losing their rigidity and avoid skin marks on the patient. In addition they do not interfere with the delivery of radiotherapy and the attenuation of the radiation beam through the plastic is minimal.

In our study the simulator images were used as the reference to which the portal images were compared. This is a potential source of small systematic errors. Hurkmans et al. summarised the reported standard deviations of the systematic and random errors in the head and neck region as between 1.6–4.6 mm and 1.1–2.5 mm, respectively, with no clear directional dependence, and suggested a SD of 2 mm or less for both the systematic and random error to be considered 'state of the art' [9]. We have shown that with careful immobilisation and use of a radiographer led portal

imaging protocol (Fig. 5) even better results can be obtained.

Given that different immobilisation systems show different degrees of accuracy, it is essential that each individual centre performs an assessment of their immobilisation system in order to determine their own CTV to PTV and PRV margins prior to the implementation of IMRT.

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Paper 2



Radiotherapy and Oncology 69 (2003) 43–51

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A systematic study of techniques for elective cervical nodal irradiation with anterior or opposed anterior and posterior beams

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Abstract

Purpose: To assess target coverage and dose homogeneity using conventional radiotherapy (RT) and intensity-modulated RT (IMRT) with anterior and posterior beams for elective irradiation of the cervical lymph nodes in patients with head and neck cancer.

Materials and methods: A planning study was performed in six patients who had undergone radical RT for head and neck cancer. RT plans to irradiate the cervical lymph nodes using a single anterior field, or opposed anterior and posterior fields, with 6 or 10 MV photons were compared. Plans using IMRT for missing-tissue compensation were also studied. An algorithm was developed to guide clinicians to the most appropriate treatment technique depending on the nodal groups to be irradiated.

Results: With 6 MV single field (SF) irradiation significant under-dose (minimum dose <70% of prescription dose) was seen in nodal groups II and V, due to their posterior position. With SF 10 MV the mean dose to level II was higher ($p < 0.001$) and dose homogeneity to levels Ib and II was improved. Using opposed fields (OF), minimum doses to the nodes in levels II and V were improved. OF using 10 MV showed significant advantage over 6 MV with reduction of maximum doses to levels II, III and V. SF 10 MV IMRT improved maximum doses to levels Ib and II compared to SF 6 MV IMRT. OF IMRT gave the best dose distributions with optimal mean dose and dose homogeneity. Beam energy made no difference with OF IMRT.

Conclusions: The optimal technique for elective cervical node irradiation depends on the lymph node levels within the PTV. If irradiation of the level II or V nodes is required, then the OF IMRT technique with either 6 or 10 MV gives the best dose distributions. In the absence of IMRT, then OF conventional techniques are best. If the aim is to irradiate levels III and IV or level IV only, then 6 MV SF non-IMRT is the simplest technique.

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Keywords: Head and neck carcinoma; Elective cervical lymph node irradiation; Radiotherapy techniques; Intensity-modulated radiotherapy

1. Introduction

Head and neck cancer represents 500,000 new cancer cases per year world-wide. Radiotherapy (RT) is delivered to the primary site and the elective nodal regions in the majority of patients. Elective irradiation of the cervical lymph nodes has been shown to reduce the incidence of cervical node metastases in the treatment of head and neck cancer by 20–30% [4,8,9,16]. The survival benefit is estimated at 5–10%. The dose required to control micro-metastatic disease in cervical lymph nodes is thought to be 44–50 Gy [7,15], and

shows a dose response [3,10,17]. Anterior or anterior and posterior radiation portals are frequently used to irradiate elective nodal regions. Typical conventional neck node fields may extend from the mastoid process to below the clavicle, including levels Ib–V (level Ia is very close to the midline, and lies beneath spinal cord shielding). The neck may be irradiated unilaterally or bilaterally, and may make up only part of a treatment schedule. In other situations part of the nodal irradiation (typically level II) may be included in lateral opposed portals, and anterior or opposed anterior and posterior beams used to treat only the lower lymph node levels (selective irradiation of III and IV) [5]. In this setting the retropharyngeal nodes are usually incorporated in the primary tumour target volume.

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The optimal technique for cervical node irradiation in these settings is uncertain. Typically either a single anterior photon field or anterior and posterior opposed fields (OF) are used. Single anterior fields are known to under-dose the posterior cervical nodes, but these are only at very high risk in patients with carcinoma of the nasopharynx. Moderate risk is seen in patients with carcinoma of the oropharynx, larynx and hypopharynx [3]. There is considerable variation in technique between centres [11]. Recently a consensus statement has defined a method of localisation of cervical lymph nodes using CT imaging [5]. The methods of target volume definition have been developed by Wijers et al. [18] and Nowak et al. [11]. This study systematically applies several techniques of conventional cervical node irradiation using the new cervical node volume definitions to determine planning target volumes (PTV). Conventional radiotherapy techniques (CRT) using single and OF are studied in this paper using moderate and high energy photons. Areas of under-dose are identified, and quantified using the different techniques.

Intensity-modulated radiotherapy (IMRT) has been used to improve dosimetry in a number of tumour sites [13]. There are significant changes in contour of the head and neck region that do impact on the dose distribution to the cervical region. It has been shown that IMRT improves dose homogeneity at a number of tumour sites [1,12,14]. The use of IMRT to improve dose homogeneity in the neck is also assessed as a second part of this study.

2. Methods

2.1. Patients and target volumes

Six consecutive patients who had been treated with radical external beam RT for head and neck cancer were studied. All patients had been immobilised in a customised thermoplastic shell and had undergone a supine planning CT scan of the neck and upper thorax with images taken at 5–10 mm intervals from skull-base to upper mediastinum.

CT data were transferred by a local network to an ADAC Pinnacle³ planning system (Philips Radiation Oncology Systems, Milpitas, CA).

The guidelines of Gregoire et al. [5] were used to define the clinical target volume (CTV) of lymph node groups I–V. These cervical lymph node levels are defined as follows: Ib, submandibular; II, upper deep cervical; III, middle deep cervical; IV, lower deep cervical; V, posterior triangle. For each patient, the CTV for each nodal group Ib–V and spinal cord were outlined on each image in accordance with ICRU 50 [6]. An isotropic 2 mm margin was added in three dimensions to each nodal CTV to account for uncertainties of patient movement within the shell. This created the PTV for each nodal group. The overall envelope of the PTVs for all groups formed the total PTV, on which treatment planning was based.

2.2. Conventional radiotherapy planning

Conventional radiotherapy planning was carried out using Pinnacle³. The prescribed dose to the cervical nodes was 50 Gy in 25 fractions. In order to achieve consistency, and allow simple plan comparison, this prescription was performed by assigning 50 Gy to the mean dose for the entire PTV. The 100% dose then typically corresponded to a point mid-way between the superior and inferior field borders at 2–3 cm depth. This approximately reproduced the type of dose distributions generated by our current method of dose prescription in the neck. For each patient, plans were produced using single fields (SF) or OF of 6 or 10 MV. A margin of 6 mm was allowed between the edge of the PTV and the field edge to allow for penumbra, and a midline block of 15–20 mm in width was used to shield the spinal cord (Fig. 1). Dose distributions were calculated using a collapsed cone convolution algorithm [2] using

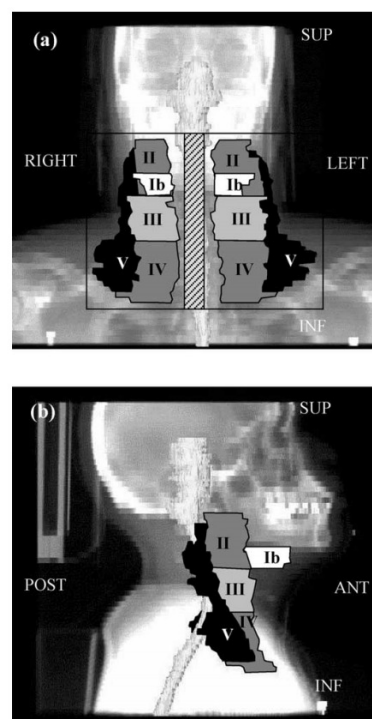


Fig. 1. (a) Anterior and (b) lateral digitally reconstructed radiographs of the neck region, showing the position of CTVs for lymph node levels Ib–V and the spinal cord. In (a), the beam's eye view of the treatment field is shown, together with the position of the spinal cord block.

beam data from a 6/10 MV Elekta linear accelerator (Elekta Oncology Systems, Crawley, UK).

2.3. Intensity-modulated radiotherapy planning

IMRT planning was also performed on Pinnacle³ for SF and OF plans with 6 and 10 MV photons. A 6 mm margin between the PTV and the field edge was used as for the CRT plans, thereby defining the area over which fluence could be modulated. Two objectives were used in the inverse planning module within Pinnacle³: a uniform dose of 50 Gy in 25 fractions to the total PTV, and a maximum dose of 45 Gy to the spinal cord. These two objectives were equally weighted. The treatment planning system then performed an iterative gradient-descent optimisation using a cost function based on the difference between the prescribed objectives and the calculated dose distribution at each iteration. For each plan, 50 iterations were used. Dose was calculated using a pencil beam algorithm during the inverse planning to provide sufficient speed, with collapsed cone convolutions after five iterations and at the end of the optimisation.

2.4. Comparison of treatment plans

For each patient and nodal group, the mean PTV dose and dose range were calculated. The maximum spinal cord dose was recorded for each plan and dose-volume histograms (DVHs) were calculated. Results from the different techniques were tested for normal distribution using quantile–quantile plots, and were found to be normally distributed. The mean statistics were therefore compared using a paired Student's *t*-test. *p*-Values of less than 0.05 were considered statistically significant. Small differences of <1.0 Gy were considered clinically irrelevant even if statistically significant.

3. Results

3.1. Single field conventional irradiation

A transverse section showing the dose distribution for SF 6 MV CRT is given in Fig. 2a. Mean DVHs for all six patients for nodal groups Ib–V, spinal cord and the whole PTV are shown in Fig. 3. The mean, minimum and maximum doses to the nodal levels Ib–V are given in Table 1. With SF 6 MV irradiation, the mean doses to all lymph node groups were within $\pm 10\%$ of the target dose, but the minimum doses to levels II and V were very low, 34.8 ± 1.8 and 31.0 ± 5.6 Gy, respectively. Examination of the cross-sectional dose distributions confirmed that it was the posterior part of level II and much of level V that were under-dosed with the SF 6 MV technique (see Fig. 2a). When SF 6 MV was compared to SF 10 MV, there was an increase in mean dose to level II (45.1 ± 1.8 to 46.3 ± 1.4 Gy, $p < 0.001$). No significant differences in the mean dose

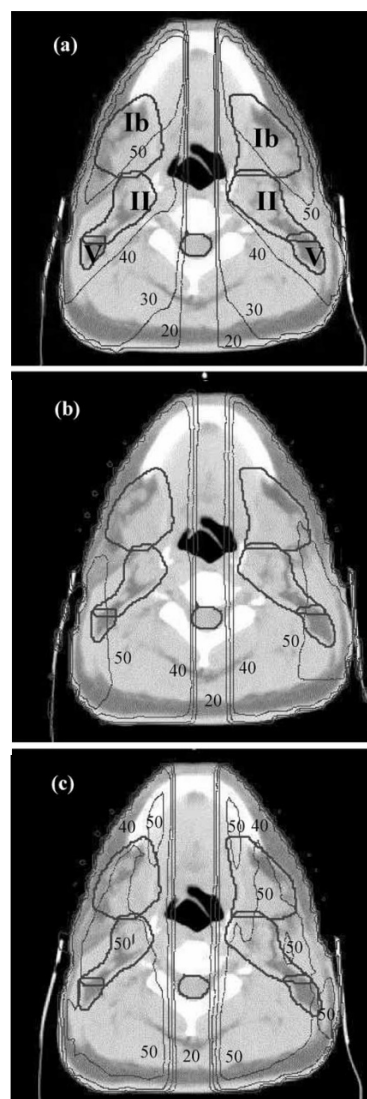


Fig. 2. Transaxial slice through the upper neck showing PTV for lymph node levels Ib, II and V. (a) CRT with single 6 MV anterior field, (b) CRT with anterior and posterior opposed 6 MV fields, and (c) IMRT technique with opposed 6 MV fields. Isodose values are given in Gy.

were seen in the other nodal groups. The minimum doses to levels Ib and II were higher (43.5 ± 3.4 to 44.7 ± 3.5 Gy, $p < 0.001$, and 34.8 ± 1.8 to 36.6 ± 2.0 Gy, $p < 0.001$, respectively) and to level IV was lower (45.2 ± 5.2 to

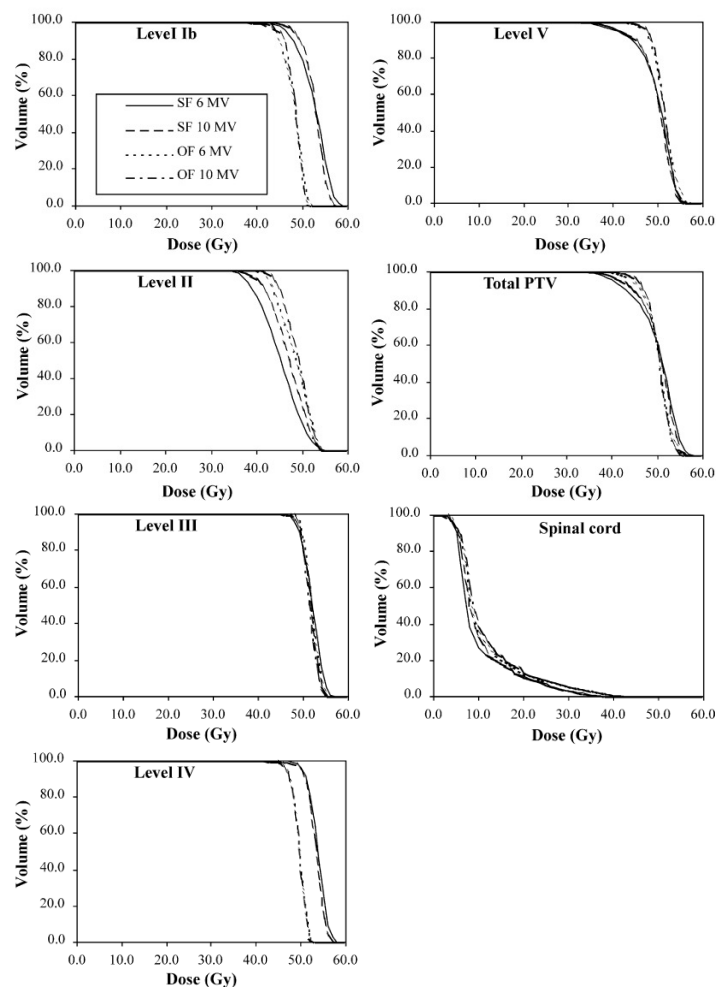


Fig. 3. DVHs for CRT showing the dose distribution for each nodal PTV, the total PTV and the spinal cord. SF, single field, OF, opposed fields.

43.1 ± 5.0 Gy, $p = 0.005$). There were no significant differences in minimum doses for level III or V. The maximum doses to levels Ib and III were reduced with SF 10 MV (57.9 ± 0.9 to 56.6 ± 0.8 Gy, $p < 0.001$, and 55.5 ± 1.1 to 54.5 ± 1.1 Gy, $p < 0.001$, respectively). No other differences were observed. Overall, SF 10 MV was considered better than the SF 6 MV technique because of the improvements in mean, maximum and minimum doses to levels Ib and II, despite a lower minimum dose to level IV.

3.2. Anterior and posterior opposed conventional irradiation

The 6 MV opposed irradiation (OF 6 MV) produced mean doses of $\pm 5\%$ of the target dose. The minimum doses to levels II and V were low at 40.4 ± 1.9 and 36.6 ± 7.5 Gy, respectively (Table 1, Fig. 2b). OF 6 MV was compared to OF 10 MV. There were no significant differences in mean or minimum doses between the two techniques for any nodal group. The maximum doses to levels II, III and V

Table 1
Mean, minimum and maximum doses to the PTV for each lymph node level using SF and OF CRT

	SF 6 MV	SF 10 MV	OF 6 MV	OF 10 MV
Level Ib mean	52.5 ± 1.1	52.5 ± 0.7	47.8 ± 1.3	48.0 ± 1.1
Level Ib minimum	43.5 ± 3.4	44.7 ± 3.5	42.2 ± 4.8	42.8 ± 5.2
Level Ib maximum	57.9 ± 0.9	56.6 ± 0.8	51.2 ± 0.9	50.6 ± 0.8
Level II mean	45.1 ± 1.8	46.3 ± 1.4	48.1 ± 1.6	48.6 ± 1.2
Level II minimum	34.8 ± 1.8	36.6 ± 2.0	40.4 ± 1.9	41.1 ± 2.4
Level II maximum	54.2 ± 0.9	53.3 ± 0.7	54.8 ± 1.4	53.8 ± 1.3
Level III mean	51.8 ± 0.9	51.3 ± 0.8	51.6 ± 0.9	51.1 ± 0.8
Level III minimum	44.2 ± 2.5	43.7 ± 2.9	44.9 ± 3.3	44.0 ± 3.2
Level III maximum	55.5 ± 1.1	54.5 ± 1.1	55.3 ± 1.4	54.1 ± 1.4
Level IV mean	53.6 ± 0.5	53.0 ± 0.6	49.4 ± 0.9	49.3 ± 0.8
Level IV minimum	45.2 ± 5.2	43.1 ± 5.0	41.7 ± 5.4	40.9 ± 5.1
Level IV maximum	57.0 ± 1.1	56.3 ± 1.1	52.3 ± 1.1	51.9 ± 0.9
Level V mean	49.7 ± 1.2	49.5 ± 1.0	51.1 ± 0.9	51.1 ± 0.7
Level V minimum	31.0 ± 5.6	30.9 ± 6.2	36.6 ± 7.5	36.5 ± 7.9
Level V maximum	55.5 ± 0.9	55.1 ± 0.9	56.2 ± 1.4	55.1 ± 1.0

All doses are given in Gy (± 1 standard deviation).

nodes were reduced with OF 10 MV (54.8 ± 1.4 to 53.8 ± 1.4 Gy, $p < 0.001$; 55.3 ± 1.4 to 54.1 ± 1.4 Gy, $p < 0.001$; 56.2 ± 1.4 to 55.1 ± 1.0 Gy, $p < 0.001$). OF 10 MV was therefore thought to have a slight benefit over OF 6 MV. Opposed irradiation increased the radiation dose to the posterior neck structures (mainly paraspinal muscles) compared to SF techniques (Fig. 2b).

When SF 10 MV (which represented the better of the SF techniques) was compared to OF 10 MV (which represented the better of the OF techniques), mean doses were closer to the target dose (50 Gy) for lymph node groups II and IV, with OF 10 MV. Minimum doses to the nodes were significantly increased for levels II and V (36.6 ± 2.0 to 41.1 ± 2.4 Gy, $p < 0.001$; 30.9 ± 6.2 to 36.5 ± 7.9 Gy, $p < 0.001$), but reduced for levels Ib and IV (44.7 ± 3.5 to 42.8 ± 5.2 Gy, $p = 0.03$; 43.1 ± 5.0 to 40.9 ± 5.1 Gy, $p = 0.009$, respectively). Maximum doses to levels Ib and IV were reduced with OF 10 MV (56.6 ± 0.8 to 50.6 ± 0.8 Gy, $p < 0.001$; 56.3 ± 1.1 to 51.9 ± 0.9 Gy, $p < 0.001$). The dose to the spinal cord with OFs was slightly higher, but remained within clinical tolerance. It was concluded that, if all nodal groups were to be irradiated using conventional radiotherapy, then the OF 10 MV technique provided the best coverage based on the improvement in dose homogeneity and minimum doses to levels II and V. If the target volume consisted of only levels III and IV, or level IV alone, then these could be adequately treated using a SF technique with either 6 or 10 MV photons.

3.3. Intensity-modulated beams as a method of tissue compensation

The use of SF 6 MV IMRT as a tissue compensator is shown in Table 2 and Fig. 4. When SF 6 MV IMRT was compared to SF 10 MV IMRT, no differences in mean dose to the nodal volumes were found. The minimum dose to

level II was increased with SF 10 MV in a similar way to that observed with conventional radiotherapy (39.8 ± 1.1 to 41.3 ± 1.2 Gy, $p < 0.001$). Maximum doses to levels Ib and II were reduced with SF 10 MV IMRT (62.2 ± 3.1 to 59.4 ± 2.4 Gy, $p < 0.001$; 58.9 ± 2.8 to 57.4 ± 2.1 Gy, $p < 0.001$) suggesting that SF 10 MV IMRT was marginally better.

OF 6 and OF 10 MV IMRT were compared. No differences in mean, minimum or maximum doses were apparent between the techniques. The transaxial dose distribution for OF 6 MV IMRT fields is shown in Fig. 2c.

Finally, SF 10 MV IMRT was compared to OF 10 MV IMRT. The mean doses to all node levels were closer to 50 Gy with the OF techniques, and this was significant for levels Ib and II (52.8 ± 1.2 to 49.8 ± 0.2 Gy, $p < 0.001$; 49.0 ± 0.6 to 50.0 ± 0.0 Gy, $p < 0.001$). Minimum doses improved for levels Ib, II, IV and V (46.3 ± 1.3 to 47.3 ± 1.4 Gy, $p = 0.02$; 41.3 ± 1.2 to 47.2 ± 2.9 Gy, $p < 0.001$; 42.9 ± 4.2 to 45.7 ± 3.0 Gy, $p < 0.001$; 34.2 ± 8.4 to 39.4 ± 7.9 Gy, $p = 0.002$). Maximum doses were reduced for all groups Ib–IV ($p < 0.01$). Mean, minimum and maximum doses for levels II and V are plotted in Fig. 5. For all plans studied, the spinal cord dose remained below tolerance.

3.4. Generation of an algorithm for technique of nodal irradiation

The posterior part of level II and parts of level V were the most likely areas of under-dose in the plans studied. If these levels were within the PTV, then the use of OF was mandatory to avoid significant under-dosage of this part of the PTV. This is shown in the left section of the algorithm in Fig. 6. The use of OF with 6 MV using IMRT as a tissue compensator gave the most homogeneous dose distribution.

Table 2
Mean, minimum and maximum doses to the PTV for each lymph node level using SF and OF IMRT techniques

	SF 6 MV	SF 10 MV	OF 6 MV	OF 10 MV
Level Ib mean	53.6 ± 1.4	52.8 ± 1.2	49.9 ± 0.1	49.8 ± 0.2
Level Ib minimum	45.6 ± 1.6	46.3 ± 1.3	47.3 ± 1.4	47.3 ± 1.4
Level Ib maximum	62.2 ± 3.1	59.4 ± 2.4	50.9 ± 0.3	50.8 ± 0.3
Level II mean	48.7 ± 0.8	49.0 ± 0.6	50.0 ± 0.1	50.0 ± 0.0
Level II minimum	39.8 ± 1.1	41.3 ± 1.2	47.1 ± 3.2	47.2 ± 2.9
Level II maximum	58.9 ± 2.8	57.4 ± 2.1	51.9 ± 1.5	52.1 ± 1.5
Level III mean	50.3 ± 0.2	50.2 ± 0.1	49.9 ± 0.1	49.9 ± 0.1
Level III minimum	44.6 ± 2.3	45.0 ± 3.0	45.7 ± 3.3	45.9 ± 2.8
Level III maximum	54.6 ± 1.2	53.7 ± 1.1	51.4 ± 0.8	52.0 ± 1.2
Level IV mean	50.1 ± 0.2	50.1 ± 0.2	49.9 ± 0.1	50.0 ± 0.1
Level IV minimum	44.2 ± 3.9	42.9 ± 4.2	45.5 ± 3.1	45.7 ± 3.0
Level IV maximum	54.3 ± 2.2	53.3 ± 1.4	52.0 ± 1.6	52.1 ± 1.3
Level V mean	49.4 ± 0.8	49.5 ± 0.7	50.1 ± 0.1	50.1 ± 0.1
Level V minimum	33.9 ± 7.0	34.2 ± 8.4	39.2 ± 7.5	39.4 ± 7.9
Level V maximum	59.3 ± 8.7	57.6 ± 7.6	55.2 ± 4.6	55.0 ± 3.7

All doses are given in Gy (± 1 standard deviation).

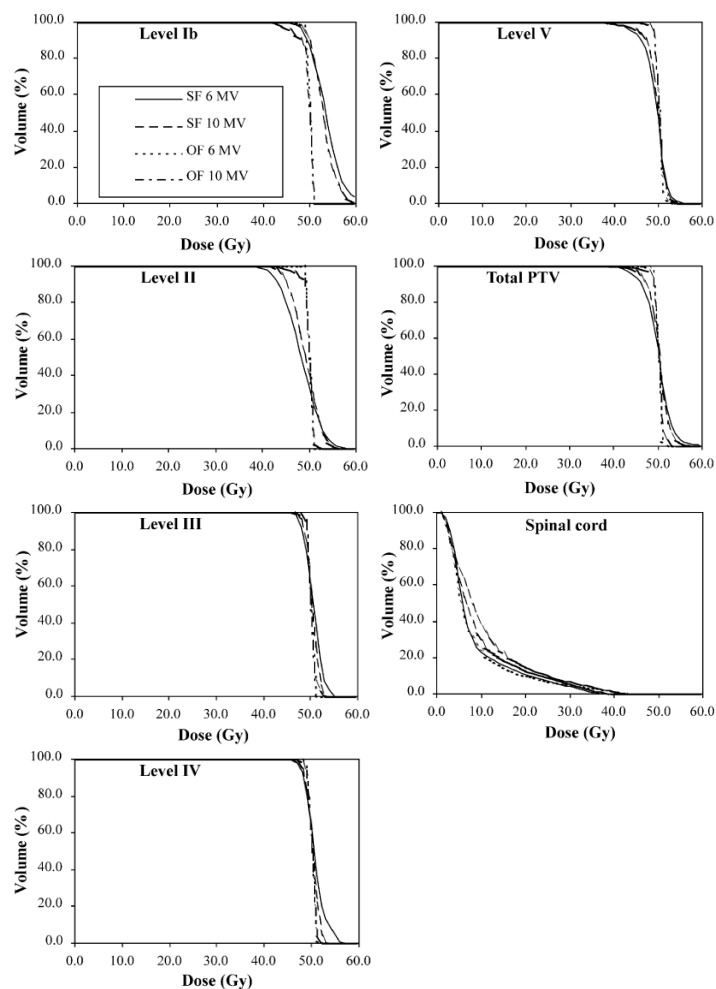


Fig. 4. DVHs for IMRT techniques showing the dose distribution for each nodal PTV, the total PTV and the spinal cord. SF, single field, OF, opposed fields.

If levels II and V were not part of the PTV, then the most common clinical scenario was when levels III and IV were the target volume (the upper neck typically being treated with opposed lateral fields). In this situation, the PTV was adequately covered using SFs (Fig. 6). A single 6 or 10 MV field was the most efficient technique, and is recommended. The use of a single IMRT field had little benefit.

If only level IV was to be irradiated, for example when the upper neck was irradiated using opposed lateral fields, then the use of a single 6 or 10 MV field gave adequate

target coverage; the more complex techniques with OF or IMRT did not confer any significant benefit.

4. Discussion

This study aimed to investigate how well the recently described CT-based target volumes are covered by the CRT, and if target coverage and dose homogeneity can be improved with a simple IMRT technique. Coverage of the retropharyngeal nodes is not assessed, and these techniques

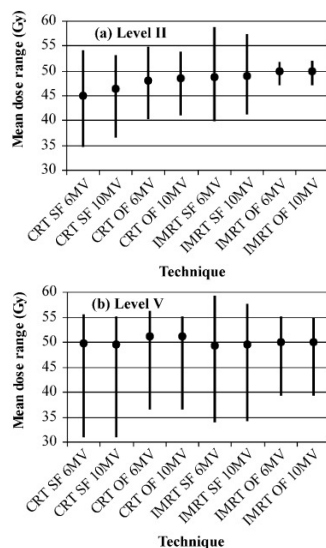


Fig. 5. A plot to show the mean, minimum and maximum doses to the PTV for (a) level II and (b) level V using each RT technique. The circles show the mean dose averaged over the six patients. The bottoms and tops of the bars represent the minimum and maximum doses, respectively, also averaged over the six patients. CRT, conventional radiotherapy, IMRT, intensity-modulated radiotherapy, SF, single field, OF, opposed fields.

are not suitable for patients in whom the lower retropharyngeal nodes are involved or at high risk. We conclude that there are significant areas of potential under-dose especially of level V and the posterior part of level II with conventional SF techniques. This can be partly overcome by using higher energy photons, but better target coverage is obtained using OF. The risk of involvement will determine whether the increased irradiated volume observed with OF is clinically acceptable. IMRT does improve dose homogeneity. OF represent a very inefficient way of delivering IMRT, and it is likely that better dose distributions can be obtained with more complex field arrangements.

The optimal techniques for selective cervical node irradiation have not been comprehensively studied here, but some conclusions can be made. The most common clinical scenarios are shown in the algorithm in Fig. 6. If the aim is irradiation of the whole cervical lymph node chain (levels Ib–V), either unilaterally (e.g. hemi-neck for unknown primary tumour site) or bilaterally (e.g. as part of nasopharyngeal carcinoma treatment), then OF with 6 or 10 MV IMRT gives the best dose distribution. In the absence of IMRT 10 MV OF irradiation may be used. The most common selective nodal irradiation targets are levels III and IV, or IV alone, when the upper neck is included in lateral fields that also irradiate the primary tumour site (e.g. oropharyngeal or laryngeal tumours, respectively). In both clinical scenarios the best dose coverage is with single 6 MV field, and IMRT showed no benefit. Local control following irradiation of the elective neck is very high. This study did not examine doses

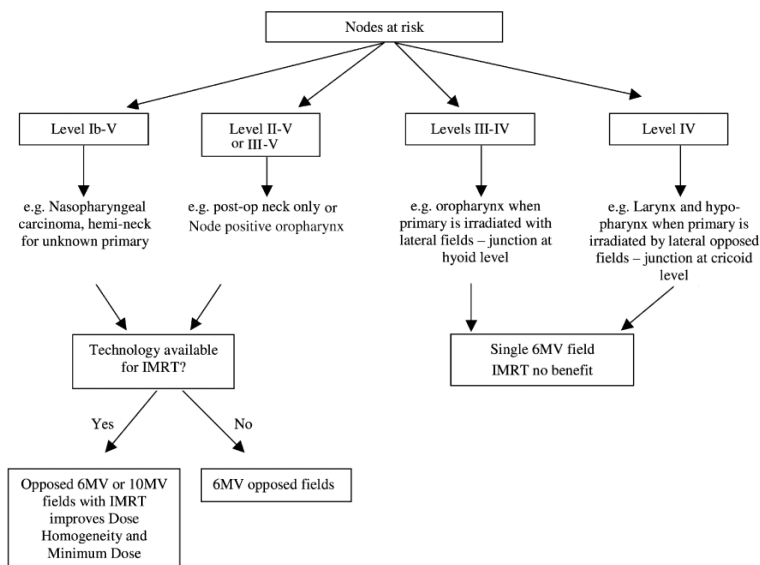


Fig. 6. An algorithm for head and neck nodal irradiation.

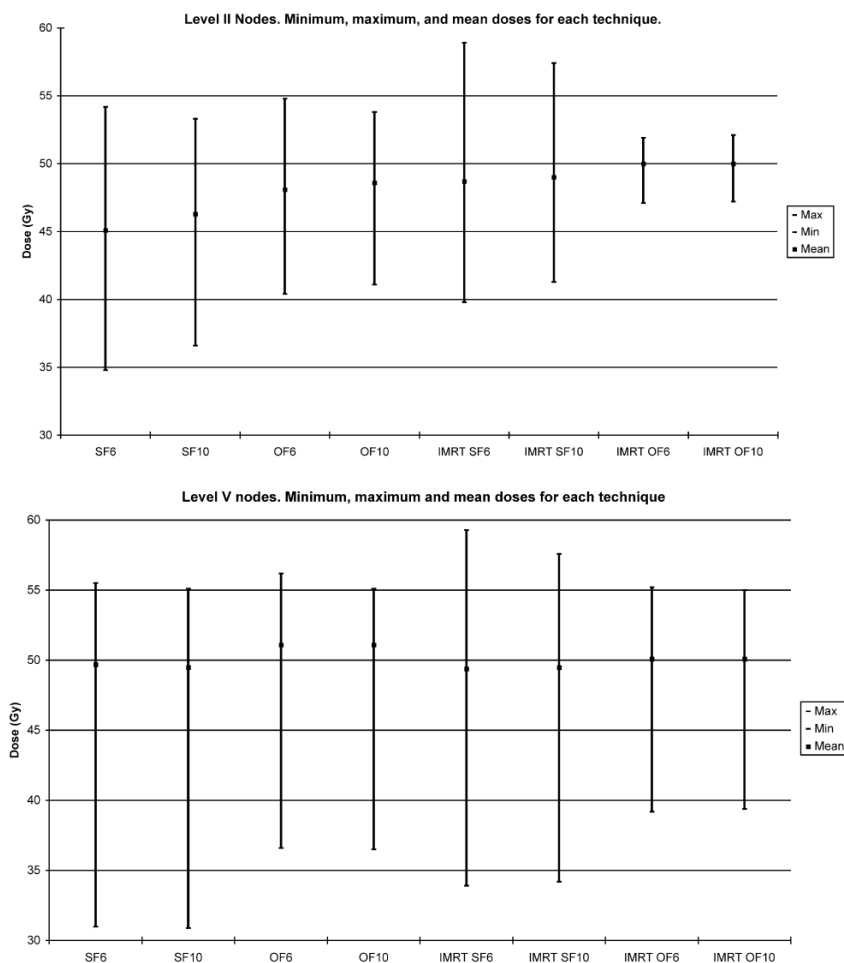


Fig. 6 (continued)

for irradiation of the involved neck, but for small volume lymphadenopathy the target volumes are similar, and if the neck contour is not significantly changed, then we may assume that the techniques described above also hold true. Patients with small volume anterior cervical nodal metastases are at risk of level V node involvement and should also be treated with OF IMRT. There is a risk that acute and late radiation reactions, particularly to the skin may be worse with OF due to the additive effects of exit and entry dose to the skin. Clinicians must accept this toxicity if adequate coverage of levels II and V is required. It is likely in the future that more elaborate combinations of node levels and

head and neck mucosa will form the basis of radiation therapy targets. This is the subject of ongoing study.

Clinical trials are required to verify that tumour control is optimal with these radiotherapy techniques and to test if these improved dose distributions translate into improved local control for head and neck cancer patients.

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Paper 3

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Impact of IMRT

The impact of introducing intensity modulated radiotherapy into routine clinical practice

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Abstract

Background and purpose: Intensity modulated radiotherapy (IMRT) at the Royal Marsden Hospital London was introduced in July 2001. Treatment delivery was dynamic using a single-phase technique. Concerns were raised regarding increased clinical workload due to introduction of new technology. The potential increased use of resources was assessed.

Patients and methods: IMRT patient selection was within guidelines of clinical trials and included patients undergoing prostate plus pelvic lymph node (PPN) irradiation and head and neck cancer (HNC) treatment. Patient planning, quality assurance and treatment times were collected for an initial IMRT patient group. A comparative group of patients with advanced HNC undergoing two- or three-phase conventional radiotherapy, requiring matched photon and electron fields, were also timed.

Results: The median overall total planning time for IMRT was greater for HNC patients compared to the PPN cohort. For HNC the overall IMRT planning time was significantly longer than for conventional. The median treatment time for conventional two- or three-phase HNC treatments, encompassing similar volumes to those treated with IMRT, was greater than that for the IMRT HNC patient cohort. A reduction in radiographer man hours per patient of 4.8 h was recorded whereas physics time was increased by 4.9 h per patient.

Conclusions: IMRT currently increases overall planning time. Additional clinician input is required for target volume localisation. Physics time is increased, a significant component of this being patient specific QA. Radiographer time is decreased. For HNC a single phase IMRT treatment has proven to be more efficient than a multiple phase conventional treatment. IMRT has been integrated smoothly and efficiently into the existing treatment working day. This preliminary study suggests that IMRT could be a routine treatment with efficient use of current radiotherapy resources.

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Keywords: IMRT; Clinical implementation; Planning and treatment times

Intensity modulated radiotherapy (IMRT) represents a significant advance in conformal radiotherapy. It allows radiation dose to be shaped around complex tumours including concave shapes and thus has the potential to reduce the radiation dose to radiosensitive normal tissues. Current applications are conformal avoidance of organs at risk or dose escalation strategies aimed at increasing tumour control.

With the introduction of new technologies often leading to more complex treatments, the justification of a potential increased use of specific resources, such as time and staff, needs to be assessed and justified per patient. An increasing number of radiotherapy departments are aiming for clinical implementation of IMRT and initial experience from other centres is invaluable to achieve this [1,2,18,20,23].

However, increased workload is still a major concern in implementation. Little data is available regarding planning and treatment times. These are important for the acceptance of IMRT from both the patients' perspective and ultimately for integration of a change in clinical practice into the routine clinical workload.

A number of strategies have been proposed to optimise the planning and delivery of IMRT. At the Royal Marsden Hospital IMRT is delivered in a single phase [3,21]. Conventional treatment often requires multiple portals and sequential field reductions. We hypothesised that a single-phase treatment would provide the potential to reduce workload and improve the efficiency of radiotherapy delivery. Major gains were anticipated in patients with advanced head and neck cancer (HNC) eliminating

the complexity of photon and electron field matching and multiple-phase treatments [4].

Method and materials

Trials and patients

IMRT patient selection was within the guidelines of clinical trials. At the London branch the IMRT programme began in July 2001 with a phase I study for prostate plus pelvic lymph node (PPN) irradiation [5]. HNC IMRT protocols were introduced in April 2002 with a phase I/II dose escalation study in advanced cancer of the thyroid [14], larynx and hypopharynx [4] and subsequently several centres in the UK have joined us in a phase III multi centre randomised parotid sparing trial (PARSPORT) [13]. Between July 2001 and July 2005, 53 PPN patients and 48 HNC patients have been entered into IMRT clinical trials.

Study

Initially we were concerned as to the impact this new technique would have on our clinical service. A study was conducted, in parallel with the clinical studies, to collate information regarding time taken for treatment planning (incorporating all planning processes performed by all staff groups to prepare the patient for a course of radiotherapy treatment), patient specific quality assurance (QA) and treatment, for an initial IMRT patient group. A comparative group of patients with advanced HNC undergoing our standard conventional radiotherapy (two- or three-phase treatments requiring matched photon and electron fields) were also timed.

Planning process

The planning stages were grouped into tasks performed by different staff disciplines:

- Target volume and organ at risk (OAR) outlining undertaken by clinicians.
- Beam directional shell preparation and processing, CT scanning and simulation carried out by radiographers.
- Outline editing, plan generation and dosimetry calculation (including full 3D calculation for IMRT) plus

preparation, execution and analysis of patient specific QA performed by physicists.

- Pre treatment checks, data input and checking within the record and verify system by radiographers.
- Overall planning time was defined as the sum of all the above planning stages.
- On couch to off couch times were recorded for all patients during CT, simulator and treatment procedures.

All IMRT patients were planned with a sliding window technique on Cadplan (v.3.6.5) using Helios inverse planning software. Five fields were used, a class solution being implemented for the PPN patients. Treatment was carried out on Varian 2100CD linear accelerators, with Millennium 120 leaf MLC, run at a dose rate of 400 MU/min and networked to Varis/Vision record and verify system. The patient specific QA involved ion chamber measurements of a hybrid phantom plan and individual field portal delivery to film. Planning and QA techniques for both anatomical sites have been detailed elsewhere [4,5]. Conventional HNC treatment employed two-dimensional (2D) planning in comparison to the more complex three-dimensional (3D) CT planning used for IMRT.

Treatment delivery

Conventionally planned HNC patients were routinely designated 20-min treatment times to account for the treatment of multiple modality fields. All IMRT patients were also allocated two time slots, the equivalent of 20 min.

Treatment verification

On treatment verification was adapted for IMRT patients. To overcome the masking of anatomy when using an intensity modulated technique additional orthogonal isocentre check fields were set up [1,5,11]. For conventional patients open treatment fields were used for positional imaging. Standard treatment verification protocols were followed for all patients, imaging on days 1-5 then weekly thereafter.

Staff responsibilities

IMRT planning and patient specific QA, along with developmental work and associated studies have been the responsibility of dedicated research staff. Beam

Table 1
Median planning times (with range) in hours for prostate and pelvic lymph node (PPN) IMRT, head and neck cancer (HNC) IMRT and conventional head and neck cancer (HNC) patients

Planning tasks	IMRT PPN median time (range)	IMRT HNC median time (range)	Conventional HNC median time (range)	Median difference between IMRT and conventional	P value
Clinician outlining	1.4 (0.9-2.2)	2.3 (0.7-3.5)	NA		
Radiographer	2.1 (1.8-2.7)	5.2 (4.33-6.0)	6.8 (5.1-9.2)	-2.0 95% CI (-1.1 to -2.9)	<0.001
Physics					
Dosimetry ^a	5.1 (3.8-11.5)	5.8 (4.3-8.5)	NA		
QA	3.3 (1.9-4.3)	2.50 (1.7-4.2)	NA		
Total	8.4 (6.3-14.0)	8.2 (5.9-11.5)	3.3 (1.5-6.3)	+5.0 95% CI (3.4-6.7)	<0.001
Overall total planning	11.0 (9.6-17.7)	14.8 (12.8-19.0)	10.4 (8.1-15.5)	+4.6 95% CI (2.7-6.5)	<0.001

^a Plan generation and dosimetry calculation.

directional shell preparation, CT, simulation and treatment aspects of the patient pathway have been integrated into the daily workload from the outset.

Statistical analysis

For HNC the IMRT process was compared to conventional in terms of time taken for patient planning, quality assurance and treatment. IMRT and conventional times for different processes were not normally distributed and therefore a Mann-Whitney *U* test was performed to investigate differences between the two techniques. *P* values were calculated at the 95% level.

Results

Data collection

Planning data was recorded on 11 patients in both HNC cohorts and 10 PPN patients. Treatment data

included 16 PPN, 12 HNC IMRT and 11 HNC conventional patients.

Planning

Overall planning time

Total median times in hours (with range) for planning are shown in Table 1. The median times for overall total planning, radiographer tasks and clinician outlining were less for PPN IMRT than for HNC IMRT. The median total physics planning times for the two sites were comparable, however for the PPN patient cohort the patient specific QA was greater and the dosimetry calculation less than the HNC cohort.

Target volume outlining

The range of outlining times for individual IMRT patients are 0.9-2.2 h and 0.7-3.5 h for PPN and HNC patient cohorts, respectively (Table 1). PPN times have remained more constant than HNC times.

Individual patient planning time

Planning time breakdown per patient is shown in Fig. 1. For IMRT patients, radiographer time per patient remains fairly constant. The difference in radiographer time between the two IMRT sites reflects the impact of beam directional shell production, where the median time for patient impression, shell processing and fitting was 2.8 h.

The largest variable in the process was physics dosimetry time. Specific patient examples demonstrated longer times than others. HNC times showed an overall trend towards a decrease in time with increase in patient numbers whereas PPN patients demonstrated an initial decrease followed by an increase coinciding with the introduction of new staff to the physics dosimetry process.

Patient specific QA

When individual patient QA times were plotted the trend indicated an overall decrease in time taken for QA per patient over time (Fig. 2).

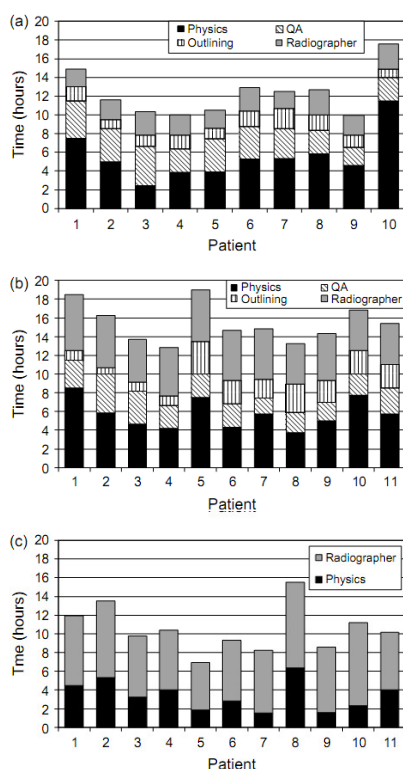


Fig. 1. Total planning times per patient showing staff group breakdown for (a) prostate and pelvic lymph node (b) head and neck cancer IMRT and (c) conventional head and neck cancer, two phase and three phase (patients 1, 2, 4 and 8) treatments. Patients are plotted in order of treatment start date over time.

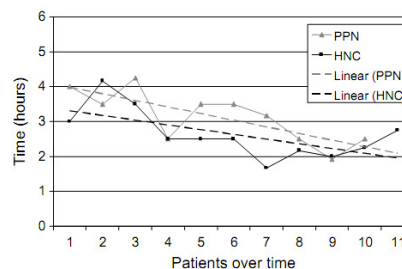


Fig. 2. IMRT patient specific quality assurance for prostate and pelvic lymph node (PPN) and head and neck cancer (HNC) patients plotted according to treatment start date.

Comparison of IMRT and conventional planning processes for HNC

The statistical comparison between HNC IMRT and conventional median planning times is shown in Table 1. Overall total planning time was significantly longer for the IMRT group compared with conventional, median difference 4.6 h. Radiographer time for IMRT showed a significant reduction when compared with conventional, median difference 2 h. Physics IMRT planning time, assessed both with and without the QA component was statistically significantly longer compared to conventional.

Treatment

Overall treatment time

On couch to off couch treatment time incorporated patient set up, imaging and beam on time for all treatment fields. The median treatment time for all IMRT patients was 12.0 min. Site specific times varied as shown in Table 2. Conventional HNC median treatment time was greater than that for the IMRT patients. Phase specific median treatment times for conventional HNC demonstrated increased time taken for the phase 2 matched photon and electron set up in comparison to phase 1 and 3.

Trends in treatment delivery time

Treatment times for PPN IMRT have decreased over time as patient numbers have increased (Fig. 3(a)). IMRT HNC treatment times have remained fairly constant compared to the more erratic nature of the conventional HNC treatments (Fig. 3(b)). The median treatment time for IMRT HNC patient 12 was considerably greater than the values for the previous eleven patients. This patient was difficult to set up for treatment and radiographers, less experienced in IMRT were delivering the treatment.

Treatment delivery time over entire course of radiotherapy

Both PPN and HNC times displayed a similar trend of decreasing over time. Median treatment time for day 1, 22 and 25 min respectively for HNC and PPN cohorts, was greater than that for subsequent treatments. All median treatment times from week 2 onwards were less than 15 min.

Table 2
Site-specific median treatment times (with range) in minutes for prostate and pelvic lymph node (PPN) and head and neck cancer (HNC) IMRT

Site	Treatment phase	Median (range)
IMRT PPN	Single	12.0 (11.0-16.7)
IMRT HNC	Single	11.2 (10.0-18.0)
Conventional HNC	1	10.5 (7.5-15.0)
	2	17.2 (15.0-30.0)
	3	9.5 (6.5-25.0)
	All phases	12.0 (8.0-20.0)

Phase specific median times for conventional head and neck cancer (HNC) are also shown.

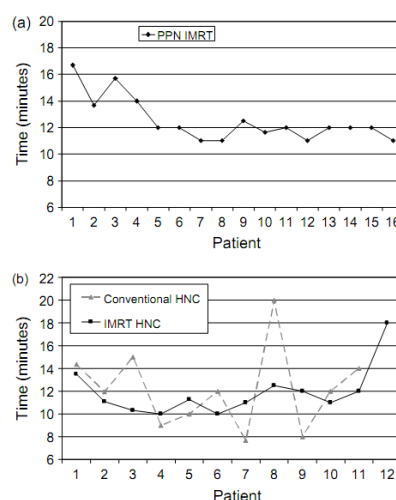


Fig. 3. Median treatment times per patient for prostate and pelvic lymph node (PPN) IMRT (a) and head and neck cancer (HNC), both IMRT and conventional (b). Patients plotted according to treatment start date.

IMRT and conventional HNC comparison in terms of man hours

Using HNC planning and treatment times, the difference in man hours between IMRT and conventional processes was calculated for both radiographers and physicists incorporating the number of staff involved in a particular process and the number of patient attendances.

For the IMRT process there were timesavings for radiographers in both treatment and planning procedures. Total saved man hours for a treatment course was 47 min, based on 28 fractions and two staff members. For the planning component a median 2 h reduction in time per patient equated to a 4 h saving with two staff involved. The overall reduction in radiographer man hours per patient was 4.8 h. Physics time was increased by 4.9 h per patient.

Discussion

Clinical implementation of IMRT has been shown to be a complex process [1,2,4,5,11,17,23]. It is therefore important to be aware of the impact of such a programme and allocate adequate resources to support its introduction. Staff time and effort have previously been shown to be greater than with conventional techniques [1,5,15]. Limited data regarding timing and resources of the complete IMRT planning and treatment process is to be found in the literature. Some of the documented times for clinical cases are shown in Table 3. However, the majority of these papers provide little information on the time required for individual stages of planning and patient specific QA.

The current study indicated that the IMRT process impacts differently on different staff groups. The HNC IMRT

Table 3
Reported treatment and planning times for IMRT

	Planning time (h)	Treatment time (min)	Technique	Treatment site
Boemer et al. [2]	4.25	No data	Dynamic	Prostate only
Adams et al. [1]	3-5	28 (mean)	Dynamic 5-field	Prostate plus pelvic nodes
Adams et al. [1]	3-5	24 (mean)	Step and shoot 5-field	Prostate plus pelvic nodes
Munter et al. [12]	No data	12.6 (mean) ^a	Step and shoot 5-9 field	HNC sites
Clark et al. [5]	10	15-20	Dynamic 5-field	Prostate plus pelvic nodes
Ozyigit and Chau [15]	4	35	MIMiC	HNC sites
Hunt et al. [7]	8	20-25	Dynamic 7-field	Nasopharynx
Xia et al. [22]	4-8 (no QA)	25-30	MIMiC 5-field	Nasopharynx
Butler et al. [3]	Two days (with QA)	20 (mean)	MIMiC 3-5 field	HNC sites
Grant and Woo [6]	No data	15-20	MIMiC 3-field	HNC sites

^a Beam on time only. Additional 5 min for patient positioning and 2-3 min for gantry movement.

and conventional comparison showed an increase in clinician and physicist workload and a decrease in radiographer workload. The planning breakdown (Fig. 1) demonstrated that factors such as anatomical site, case complexity particularly with respect to position and size of target volumes and OARs, protocol changes and staff experience will all affect the time taken for IMRT planning.

For clinicians, the challenge of IMRT is in the selection and delineation of target volumes, in addition to defining organs at risk and non-involved tissue to be spared. The introduction of site-specific outlining protocols enables the process to become more predictable over time. Volume delineation by an experienced clinician using standard guidelines can be completed within 1.5 h per patient.

The HNC group results reflected the impact of a change in staff and introduction of new outlining protocol guidelines. The initial four patients were outlined by an experienced clinician using familiar outlining guidelines; for subsequent patients a new outlining technique following the guidelines set out by Rotterdam/Brussels consensus [9] was adopted and a research fellow performed the outlining.

The most significant increase in the planning workload was seen by physics. The plan design and dosimetry calculation component showed the greatest variation in time on individual patient analysis (Fig. 1); this component of the IMRT process may be less predictable than others. PPN patient 6 was planned by a physicist inexperienced in IMRT and PPN patient 10 was a difficult case requiring a large number of plans to be produced in order to achieve a satisfactory IMRT solution. In the HNC patient cohort the implementation of a new outlining protocol had an impact on the physics planning for patient 5, and patient 10 was the first case introducing a new anatomical site.

Plan design and dosimetry calculation time for the PPN cohort of patients was less than that for the HNC patient group, median time 5.1 h compared with 5.8 h. With increased IMRT experience, we have found that PPN planning lends itself more to the use of a class solution compared to HNC planning.

Initial commitment to patient specific QA for IMRT is considerable. This has been addressed by Van Esch et al. [19] using the experience of five departments having adopted the Varian sliding window solution for IMRT. The mean

physicists' workload per patient for pre-treatment verification for four departments ranged from 3 to 10 h. The fifth recorded a time of 40 h as a result of two or three IMRT plans being verified for each patient.

The initial QA programme at this centre involved individual field portal delivery to film plus four dose point measurements per patient. As confidence increased we reduced the number of individual dose points measured from four to one per patient and also patient bookings were coordinated which enabled the QA for at least two patients to be performed at the same time. This was found to be more efficient in terms of set up and calibration of equipment.

Many lessons in IMRT QA were learnt from the initial PPN patient cohort; the knowledge gained was then applied to the HNC patients explaining the difference in median QA time for the two patient groups, 3.3 h per patient versus 2.5 h. The overall QA trend was a decrease in time taken per patient over time (Fig. 2). PPN QA fell more steeply as this was our first patient cohort. Dose points were reduced from four to one after an initial 10 PPN patients and an initial eight HNC patients. Our current QA time per patient has been reduced to less than 2 h. Other groups have also reported a reduction in QA [1,16]. Further developments to reduce the QA of IMRT fields include the introduction of validated calculation systems for independent check of monitor units [10] and the use of EPID for dosimetric pre-treatment verification [19]. Reduction of time and workload should still be balanced against an evidence base and confidence in technique [2,8].

For all IMRT patients daily treatment was efficiently completed within the 20 min allocated with a median time of 12 min. This is comparable with other complex treatment deliveries within this department and in-line with the IMRT experience of other centres [3,23]. The PPN treatment times have shown a trend for significant reduction over time, 16.7 min for patient 1 reduced to 11 min for patient 16. The small difference in overall median treatment time for the two sites, 12 and 11.2 min for PPN and HNC patients, respectively, can be attributed to the initial IMRT learning curve; longer treatment times were experienced with the first few PPN patients at the outset of the IMRT implementation programme. For HNC cases when using IMRT, rather

than conventional treatment, it was easier to predict how long the treatment delivery will take. During the first week of treatment, times will be influenced by set up and acquisition of additional orthogonal isocentre check fields used for positional verification. The median time taken for treatment in week 1 will be longer than for subsequent weeks. All median treatment times from week 2 onwards are less than 15 min hence, for the majority of IMRT patients, shorter treatment appointment times may be allocated subsequent to week 1.

Conclusions

A number of conclusions can be drawn from the comparison between IMRT and conventional processes for HNC patients:

IMRT currently increases overall planning time. Additional clinician input is required for target volume localisation. Physics time is increased, a significant component of this being patient specific QA. Ultimately physics QA input will reduce with the developments in QA processes. However, radiographer time is decreased.

Use of a single phase in IMRT has proven to be more efficient than a multiple phase conventional treatment. IMRT treatment has been more consistent, with less variation between patients than conventional treatment and times have decreased with training and increased technique familiarity.

IMRT planning and delivery will continue to evolve and efficiency will be improved. It has been possible to integrate IMRT treatment smoothly and efficiently into the existing treatment working day and this preliminary study suggests that IMRT could become a routine treatment with efficient use of current radiotherapy resources.

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Paper 4

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Original Article

Target Volume Definition for Head and Neck Intensity Modulated Radiotherapy: Pre-clinical Evaluation of PARSPORT Trial Guidelines

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ABSTRACT:

Aims: There is considerable controversy surrounding target volume definition for parotid-sparing intensity modulated radiotherapy (IMRT) for head and neck cancer. The aim of this study was to evaluate the dosimetric and radiobiological predictors of outcome anticipated by application of the detailed target volume definition guidelines agreed for the UK multicentre randomised controlled trial of parotid-sparing IMRT (PARSPORT).

Materials and methods: Five patients eligible for the study were delineated using the trial guidelines. Following the protocol, plans were produced to treat these volumes with three-dimensional radiotherapy (control arm) and IMRT aimed to spare dose to the contralateral parotid gland (experimental arm). Dosimetric comparisons were made between plans, and normal tissue complication probability (NTCP) modelling for salivary glands was carried out.

Results: Doses delivered to the planning target volumes (PTV) were similar with each technique, although IMRT produced more homogeneous irradiation of the PTV. Mean doses to the contralateral parotid gland were 22.4 ± 1.7 Gy with the IMRT plans vs 60.0 ± 7.2 Gy with three-dimensional radiotherapy, $P = 0.0003$. Calculated contralateral parotid gland NTCP values for grade 2 xerostomia were 20–22% for IMRT and 98–100% for three-dimensional radiotherapy ($P < 0.0001$).

Conclusion: Pre-clinical evaluation of the PARSPORT trial target volume definition guidelines provides theoretical support for a significant reduction in xerostomia rates. These data await confirmation from the clinical trial results. Guerrero Urbano, M. T. *et al.* (2007). *Clinical Oncology* 19, 604–613

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Key words: Head and neck cancer, IMRT, oropharynx, parotid sparing

Introduction

Xerostomia is the most prevalent long-term complication after radiotherapy for head and neck cancer in patients who require bilateral neck irradiation and is associated with significant deterioration in the patient's quality of life [1–3]. Intensity modulated radiotherapy (IMRT) has been shown to achieve significant reductions in the dose delivered to the parotid glands and several phase II studies have suggested lower xerostomia rates and improvements in quality of life [4–8]. Most of these early clinical reports fail to give clear protocols for target volume definition, making reproducibility difficult. The ability to reduce the radiation dose to the parotid gland is largely determined by its proximity to the planning target volume (PTV) [9] and therefore is significantly affected by differences in target volume definition.

In the UK, a multicentre randomised controlled trial of parotid-sparing IMRT vs conventional radiotherapy is underway (PARSPORT). The trial aims to compare the

incidence of LENT SOM (late effects on normal tissue: subjective, objective, management) grade 2 xerostomia 1 year after treatment between patients treated with parotid-sparing IMRT and conventional radiotherapy. Agreement has been reached among the trial participants as to the methods of target volume definition. The aim of this current study was to calculate the theoretical outcomes of the application of our detailed target volume definition for oropharyngeal tumours in terms of dosimetric and calculated normal tissue complication probability.

Materials and Methods

Patients and Radiotherapy Planning

Five patients with histologically proven locally advanced squamous cell carcinoma of the oropharynx (T1–4, N1–2b M0) who met the entry criteria for the PARSPORT trial were evaluated. All patients were immobilised using a custom-made cabulite head and neck mask in the conventional

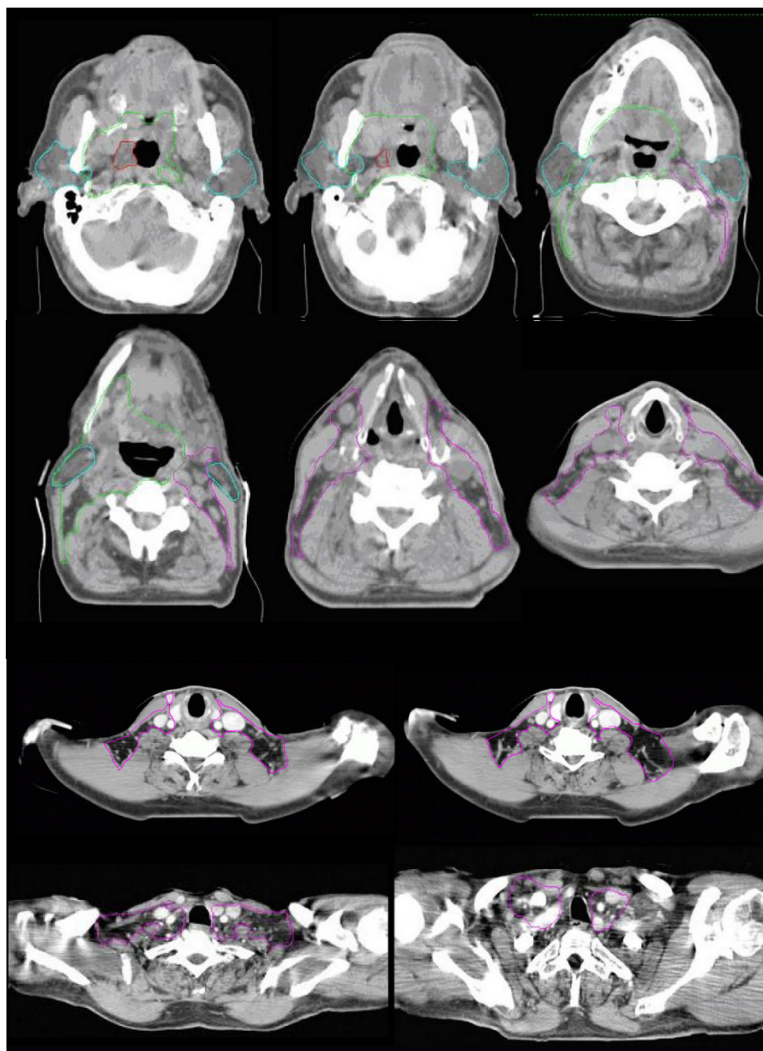


Fig. 1 — Representative outlines for gross tumour volume (GTV), clinical target volumes (CTV) and organs at risk using the PARSPORT trial guidelines (GTV in red, CTV1 in green, CTV2 in pink, parotid glands in blue).

treatment position, i.e. neutral neck with a straight spine. They then underwent radiotherapy planning computed tomography of the head and neck, from the supra-orbital ridge to the carina. Both non-contrast-enhanced and contrast-enhanced scans were obtained to aid target volume definition. All planning computed tomography was

carried out on a GE lightspeed scanner, with the patient immobilised. Images were taken at 3 mm intervals from the hard palate to the hyoid bone and at 5 mm intervals for the rest of the volume. The computed tomography data sets were then transferred to the Eclipse planning system (version 7.3.10). Target volume definition was carried out

according to the PARSPORT trial guidelines on each computed tomography image by a single clinician in order to minimise inter-observer variability. The target volumes defined were a primary clinical target volume (CTV1) and a nodal CTV (CTV2) (Figs. 1, 2). Both CTVs were grown by 3 mm in the antero-posterior, lateral and supero-inferior directions [10] and the resulting volumes edited to ensure that their superficial aspect lay 5 mm from the skin surface, thereby avoiding the PTV impinging on the build-up region, in order to create the primary and elective PTVs (PTV1 and PTV2, respectively). The organs at risk delineated were the spinal cord and the parotid glands. For the IMRT planning process a 3 mm margin was added to the spinal cord to create an expanded volume (SC-Planning Organs at Risk Volumes (PRV)). Several structures were created to aid the inverse optimisation process: planning oral cavity, parotids, midline sparing and posterior sparing volumes. The same volumes were used for both IMRT and conventional planning. The dose to the PTV1 was 65 Gy in 30 daily fractions and that to the PTV2 50 Gy in 25 daily fractions. The latter was calculated to be equivalent to 54 Gy in 30 daily fractions for the parotid-sparing IMRT plans where a single phase technique was used.

PARSPORT Study Target Volume Definition Guidelines

Gross tumour volume

The gross tumour volume (GTV) was defined for both the primary tumour and any involved nodes with the aid of the diagnostic scans, operation notes, clinical examination and nasendoscopy assessment.

Clinical target volumes

Radical clinical target volume (CTV1). This CTV encompassed the GTV and those areas at high risk of spread that

were to be treated to a radical dose. It was obtained by adding a customised margin to the GTV. The entire oropharynx was included, from the superior aspect of the soft palate to the hyoid bone. Laterally, on the involved side, the CTV1 extended to the mandible and included the ipsilateral parapharyngeal space. The contralateral parapharyngeal space was spared. Where no obvious anatomical barrier existed, a minimum 10 mm margin was added to the GTV to account for microscopic spread. Therefore, the anterior extent of the CTV1 into the tongue base was usually a geometric margin (at least 10 mm) and included at least the posterior third of the tongue. Medially and posteriorly the oropharyngeal mucosa was included. In general, barriers to tumour spread, such as bone and fasciae, were excluded, provided they were not breached. Air was not part of CTV1; however, the growing algorithms of some treatment planning systems are such that incorporating the air within an organ is unavoidable. Any neighbouring structures invaded by tumour (parotid gland, medial pterygoid muscle, mandible, etc) were included.

The node-positive neck. This included the nodal GTV with a margin of at least 10 mm to account for extracapsular spread, which was customised around any intact anatomical barriers (bone, fasciae, etc) and included any involved structures (i.e. muscle, soft tissues, bone). Where level 2 was involved, the superior margin was extended superiorly up to the jugular fossa and both levels 2a and 2b included.

The postoperative neck. CTV1 included the preoperative GTV and the surgical bed of the primary tumour and/or involved nodes with a customised margin. This volume was edited to include the entire organ where the tumour arose but to respect anatomical barriers that had not been breached (bone, fasciae, etc.). Where there was no anatomical barrier a 10 mm margin was added. The nodal surgical bed was included in CTV1 if pathologically positive.

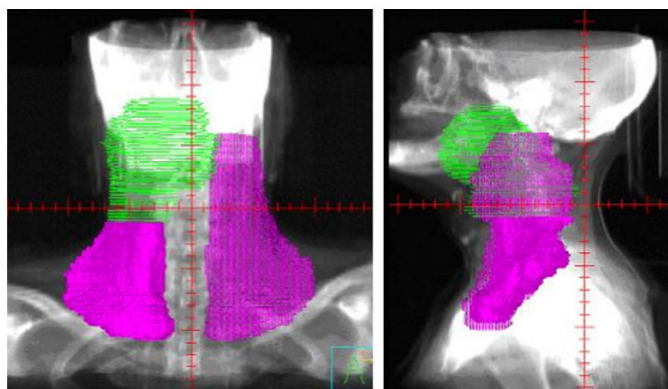


Fig. 2 — Three-dimensional reconstruction of CTV1 (green) and CTV2 (pink) on an antero-posterior (left) and lateral (right). Digitally reconstructed radiograph (DRR).

The posterior and antero-medial margins of this volume were often the same as in the N0 neck, except where these structures were involved. The lateral margin of this volume usually extended to, but did not include, the skin, unless otherwise indicated (i.e. skin infiltration).

Elective clinical target volume (CTV2)

The DAHANCA, EORTC, GORTEC, NCIC, RTOG consensus guidelines [11] were followed for target volume definition of the node-negative neck for levels 1–5. In addition, a supraclavicular fossa nodal volume was defined. This level was in continuity with levels 4 and 5 and encompassed the fatty planes and blood vessels at the root of the neck at the level of or just below the clavicle.

Three-dimensional Radiotherapy Planning using a Conventional Beam Arrangement

A single isocentre technique in two phases, which is used routinely in the UK, was used. Asymmetric parallel-opposed lateral fields were used to treat PTV1 to 40 Gy in 20 fractions and an antero-posterior/postero-anterior (AP/PA) beam arrangement was used to treat the lower neck to 50 Gy in 25 fractions. The lateral fields were matched to the neck fields, using a half-beam technique, at the isocentre plane, placed below the hyoid bone. All beams were shaped to encompass the PTVs using 5–10 mm multileaf collimators viewing Beams eye views (BEVs). A 6 mm margin around the PTVs was used to account for beam penumbra ensuring 95% prescription dose coverage to the periphery of the PTVs. 6 MV beams were selected for all the photon beams. Enhanced dynamic wedges were selected for use on the lateral fields to improve dose homogeneity and beam and wedge weightings were optimised manually to ensure coverage of the PTV with the 95% isodose line and limiting higher isodose levels to below 107% (ICRU50). This first phase was planned to 40 Gy in 20 fractions and the dose normalised to the midline at the field centre. The lower neck fields were planned to 50 Gy in 25 fractions and normalised to a point 3 cm lateral to the central axis 2.5 cm depth from the anterior skin surface and midfield. After 40 Gy, the lateral fields were reduced posteriorly to avoid the spinal cord and the posterior margin moved 5 mm anterior to the posterior aspect of the vertebral bodies. They were planned, using the same technique as for phase 1, to 25 Gy in 10 fractions and the dose normalised to the same point. Posterior electron fields were matched to the photon fields using the field borders (50% isodose line) on the skin for a further 10 Gy in five fractions to the uninvolved neck and 25 Gy in 10 fractions to the involved neck. The energy of the electron fields was chosen such that the total spinal cord dose was less than 45 Gy. 9 MeV electrons were used for all fields in all patients and the dose prescribed to 100% at $D_{\max}$. Separate plans were produced for the lateral photons (phase 1), reduced lateral photons (phase 2), AP/PA photons (lower neck) and individual electron fields.

Doses for all photon plans were calculated on a 2.5 mm dose matrix using a single pencil beam algorithm and the modified Batho inhomogeneity correction for photons. The

algorithm for the electron calculations was based on electron Monte Carlo calculations. These plans were then summed in Eclipse to produce composite dose-volume histograms (DVH) and isodose distributions.

Intensity Modulated Radiotherapy Planning

Plans were produced using a simultaneous integrated boost technique [12,13], which is characterised by the delivery of a different dose-per-fraction to the different targets within the head and neck region. A dose of 2.17 Gy per fraction was delivered to the primary tumour site, and involved the lymph nodes (PTV1) and 1.8 Gy per fraction to elective lymph node groups in 30 daily fractions (nodal PTV or PTV2), i.e. a total dose to the radical volume of 65 and 54 Gy to the elective lymph nodes. This latter dose was used as the radiobiological equivalent of 50 Gy in 25 fractions in the conventional plans. The inverse planning module of Eclipse was used for all IMRT plans for dynamic delivery on linear accelerator (Varian 2100CD) and plans were prescribed to the median volume of PTV1.

The use of IMRT plans with a larger number of equispaced fields has been suggested to provide the best dose distributions [12]. However, previous work at our institution showed that reducing the number of beams to five provided adequate target coverage while maintaining the sparing of the organs at risk in a range of head and neck tumours [14]. Given the complexity of IMRT and the effect it may have on a busy radiotherapy department, we decided on a five-beam arrangement, as a reduction in the number of beams is associated with shorter delivery times and pre-treatment quality assurance [15]. The isocentre was placed at a point equidistant from the superior and inferior margins of combined PTVs, at midline and on the anterior aspect of the vertebral body. A five-field equispaced arrangement (0, 72, 144, 216 and 288°) was set. However, in practical terms, delivery of the posterior oblique fields often involves beam entry through the headboard or couch. Hence, the gantry angles of the posterior oblique fields were manually adjusted to avoid the couch bars by viewing the BEVs.

For each patient, initial dose volume objectives for the target volumes and constraints for the organs at risk were designed for the inverse planning process. The inverse planning module of Eclipse allows the user to adjust the constraints and objectives as the optimisation process is occurring. This was used to produce the best DVH for each patient by tightening the constraints and increasing the priorities for each volume, as the optimisation function progressed. To avoid dose dumping in areas such as the oral cavity, the larynx and the posterior neck, specific planning avoidance volumes were used during the optimisation process. Plans were optimised until the desired objectives to obtain a clinically acceptable plan were met (Table 1).

After the optimisation was finished, the leaf motion calculator was run to provide a dynamic sliding window for delivery and a three-dimensional dose cube was calculated using a single pencil beam algorithm [16]. The dose was then normalised to the median volume of PTV1. Several optimisations were run until an acceptable clinical plan was

Table 1 — Target volumes and organs at risk: objectives and constraints

Target structures	Volume objective	Dose required
Primary planning target volume (PTV1)		
Dose 65 Gy	99% 95% 50% 5% 2%	> 90% (58.5 Gy) > 95% (61.75 Gy) 100% (65.0 Gy) < 105% (68.25 Gy) < 110% (71.5 Gy)
Nodal planning target volume (PTV2)		
Dose 54 Gy	99% 95% 50%	> 90% (48.6 Gy) > 95% (51.3 Gy) 100% (54.0 Gy)
Risk structures	Dose constraint	
Contralateral parotid	24 Gy (mean dose)	
Ipsilateral parotid	N/A	
Spinal cord	Maximum < 45 Gy 1 cm ³ at 3 mm < 48 Gy	
Brainstem	Maximum < 50 Gy 1 cm ³ at 3 mm < 55 Gy	

obtained for each patient and, in general, three to five IMRT plans were required before a satisfactory result was achieved.

Comparison of Treatment Plans

The methods used for plan evaluation in this study were dose statistics, isodose distributions in transverse, sagittal and coronal slices, and DVHs.

The mean PTV1/2 doses were calculated and the minimum and maximum, defined as the dose received by $\geq 99\%$ (D99%) and by $\leq 1\%$ (D1%) of the PTV1/2, were obtained. An inhomogeneity coefficient was calculated ($IC = \text{maximum dose} - \text{minimum dose} / \text{minimum dose}$) to reflect the degree of target homogeneity. This is equal to 0 if no intra-target homogeneity is observed [17]. The doses delivered to 95% of PTV1/2 (D95%) were obtained. As the prescribed doses to the nodal PTV (PTV2) were different for the three-dimensional radiotherapy and IMRT plans, comparisons were made between the achieved doses relative to the prescribed dose, expressed in percentage points. A conformity index (CI95%) defined as the volume encompassed by the 95% isodose ($V_{95\%}$) divided by the PTV volume was calculated for all plans [18]. This measures the degree of conformity and should ideally be equal to 1. The absolute maximum spinal cord dose and maximum dose to 1 cm³ of the spinal cord were obtained, as well as DVHs and the mean doses for the contralateral and ipsilateral whole parotids glands.

Plans were compared using a paired Student's *t* test and the differences were reported as statistically significant if they achieved the $P \leq 0.05$ level (two-tailed). The basis for this study is that large standardised differences will exist between the within-patient PTV parameter comparisons. These parameters are based on physical rather than

Table 2 — Eisbruch *et al.* and Roesink *et al.* parameters

	Eisbruch <i>et al.</i>		Roesink <i>et al.</i>	
Parameter	TD50	m	TD50	m
Mean	28.4	0.18	39	0.45
95% confidence interval	25–34.7	0.1–0.33	34–44	0.33–0.65

biological measurements and therefore will show less variability than biological parameters. A standardised difference of 2 can be detected using a paired *t* test with five pairs (90% power, 5% significance level). A five patient comparison of similar techniques (with significant results) has been undertaken in rectal cancer patients [19], suggesting that the sample size is adequate. Many of the parameters are themselves correlated and significance tests will therefore not be independent. It is therefore not clear what form of correction should be used. This type of problem is recognised in the statistical literature regarding uncorrected *P*-values. We have followed the philosophy of Perneger [20] that stating what significant tests have been

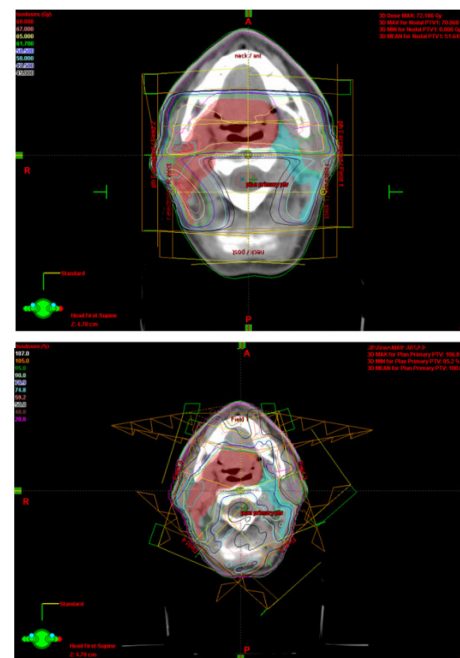


Fig. 3 — Typical dose distributions for the three-dimensional radiotherapy (above) and intensity modulated radiotherapy (below) plans.

carried out and why is an effective way of dealing with multiple comparisons. Readers are able to reach their own conclusions about the overall plausibility of the findings.

NTCP Calculations

The Lyman–Kutcher model was used to calculate NTCP values for all parotid glands for a reduction in flow to $\leq 25\%$ of pre-treatment values. The calculations were carried out using BIOPLAN software [21]. The input data for the Lyman model in BIOPLAN were, for each calculated value, the DVHs, the volume parameter (n), the TD50 and the steepness of the dose–response curve (m), using the parameters obtained by

Eisbruch *et al.* [22] and Roesink *et al.* [23]. The volume parameter (n) was fixed at 1. Given the differences between the parameters obtained in both studies, we calculated NTCP values for both sets of parameters and their confidence interval limit values (Table 2).

Results

Target Volumes

Typical dose distributions for the three-dimensional radiotherapy and IMRT plans are shown in Fig. 3 and typical DVHs in Fig. 4. Plan objectives were achieved for all IMRT plans, but not all three-dimensional radiotherapy plans.

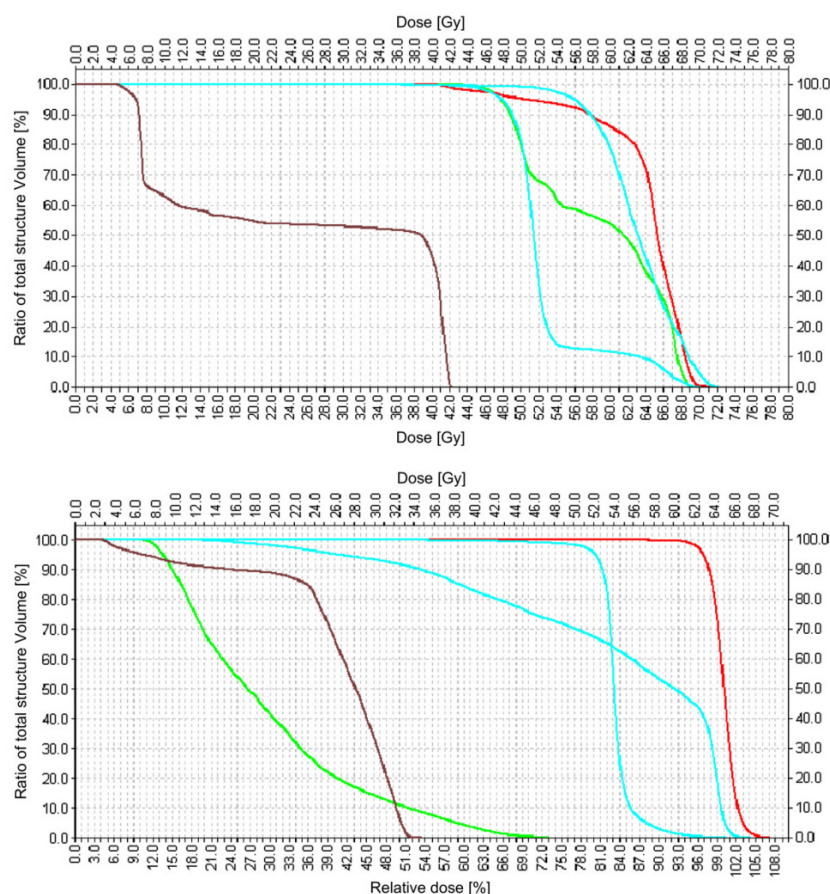


Fig. 4 – Typical dose-volume histograms for the three-dimensional radiotherapy (above) and intensity modulated radiotherapy plans (below): PTV1 in red, PTV2 in light blue, ipsilateral parotid in blue, contralateral parotid in green and spinal cord in brown.

Table 3 – Mean ($\pm$ standard deviation) dose statistics, inhomogeneity coefficient, D95% and conformity indexes

	IMRT (65 Gy)	Three-dimensional radiotherapy (65 Gy)	P value
PTV1			
Minimum (D99%)	61.7 $\pm$ 0.6	51.9 $\pm$ 10.6	0.106
Mean	64.3 $\pm$ 1.5	65.3 $\pm$ 1.3	0.17
Maximum (D1%)	67.6 $\pm$ 0.3	68.9 $\pm$ 0.8	0.02*
Inhomogeneity coefficient	0.09 $\pm$ 0.01	0.37 $\pm$ 0.30	0.10
D95%	63.0 $\pm$ 0.3	58.3 $\pm$ 6.8	0.187
Conformity index	0.99 $\pm$ 0.01	0.93 $\pm$ 0.07	0.15
	IMRT (54 Gy)	Three-dimensional radiotherapy (50 Gy)	P value
PTV2			
Minimum (D99%)	50.7 $\pm$ 1.9	35.2 $\pm$ 17.0	0.20
Mean	54.9 $\pm$ 0.7	52.5 $\pm$ 1.5	0.05*
Maximum (D1%)	62.1 $\pm$ 1.8	69.1 $\pm$ 2.5	0.0009
Inhomogeneity coefficient	0.2 $\pm$ 0.04	2.8 $\pm$ 4.8	0.30
D95%	52.7 $\pm$ 0.7	46.9 $\pm$ 1.2	0.01*
Conformity index	0.98 $\pm$ 0.01	0.93 $\pm$ 0.03	0.01*

IMRT, intensity modulated radiotherapy; PTV, planning target volume. *Statistical significance, $P \leq 0.05$, with Student's *t* test. Many of the parameters are correlated and the significance tests are therefore not independent. We have presented all significant tests carried out, allowing readers to reach their own conclusions about the overall plausibility of the findings [20].

Table 3 shows the mean ($\pm$ standard deviation) dose statistics, inhomogeneity coefficient, D95% and conformity indexes for the three-dimensional radiotherapy and IMRT plans. On average, maximum doses to both PTVs were higher for the three-dimensional radiotherapy plans (Table 3) and were located in the regions of minimal lateral separation of the lateral fields within PTV1. For the IMRT plans they were scattered within the volume with no specific pattern.

Minimum doses were lower for both PTVs with the three-dimensional radiotherapy plans and a wide range of values was found, reflecting the patient's anatomy, deviations from a straight neck position and the shape of the target volumes (Fig. 5). These minimum doses were located at the photon–photon and photon–electron match lines and in the superior and inferior parts of the neck fields. Noticeably, the deep parts of PTV1 behind

the posterior margin of the phase 2 fields and nodal PTV were under-dosed because of the rapid dose fall-off observed with electrons. In this group of patients, using higher energy electrons would have only led to small increases in target coverage, but at the expense of increasing the dose to the spinal cord. In one patient, a mild degree of lower neck rotation led to a small part of the lower nodal PTV to be shielded by the anterior midline multileaf collimators and a minimum nodal PTV dose of 5 Gy (Fig. 5).

The aim of both the IMRT and the three-dimensional radiotherapy plans was to cover 95% of the volume with 95% of the prescribed dose, i.e. 61.75 Gy to PTV1 with both techniques and 51.3 Gy with IMRT and 47.5 Gy with three-dimensional radiotherapy for the nodal PTV. D95% doses for the three-dimensional radiotherapy plans were below the plan objectives, 58.3 $\pm$ 6.8 Gy for PTV1 and 46.9 $\pm$ 1.2 Gy

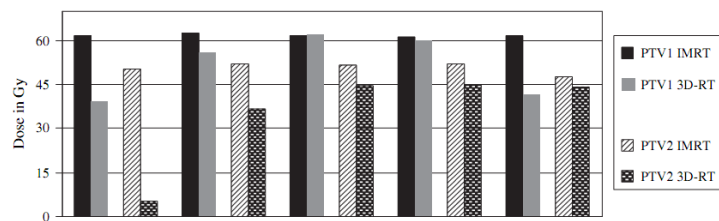


Fig. 5 – Histogram of minimum doses.

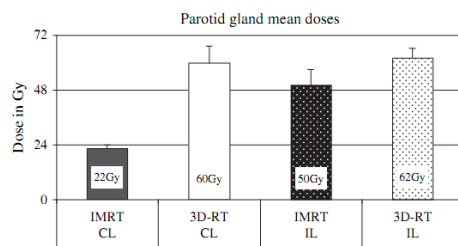


Fig. 6 – Mean (± 1 standard deviation) parotid doses in Gy for the intensity modulated radiotherapy and three-dimensional radiotherapy plans.

for PTV2. For the IMRT plans, they achieved the objectives, 63.0 ± 0.3 Gy for PTV1 and 52.7 ± 0.7 Gy for the nodal PTV, $P=0.2$ and $P=0.01$ compared with three-dimensional radiotherapy. A higher degree of conformity was achieved for both target volumes with the IMRT plans, and this reached statistical significance for the nodal PTV, 0.93 ± 0.03 vs 0.98 ± 0.01 , $P=0.01$.

Organs at Risk

In all plans, the spinal cord was kept within tolerance, with mean absolute maximum doses of 39.9 ± 4.2 Gy for the IMRT plans and 43.3 ± 1.6 Gy for the three-dimensional radiotherapy plans. When considering the dose to 1 cm^3 of the spinal cord, the doses for the IMRT plans were statistically

significantly lower than for the three-dimensional radiotherapy plans (36.5 ± 3.2 Gy vs 42.6 ± 1.0 Gy, $P=0.01$).

As set out in the objectives, the IMRT plans achieved sparing of the contralateral parotid gland, with average mean doses of 22.4 ± 1.7 Gy for the IMRT plans vs 60.0 ± 7.2 Gy for the three-dimensional radiotherapy plans ($P < 0.001$). In addition, analysis of the mean doses to the ipsilateral parotid glands also revealed a significant mean dose reduction with IMRT, 50.1 ± 6.9 Gy vs 61.9 ± 4.4 Gy, $P=0.01$. Figure 6 depicts the average mean doses for the parotid glands.

A significant reduction in the percentage volume of contralateral parotid gland irradiated to 15, 30, 45 and 60 Gy with IMRT was seen (Table 4). The volumes of contralateral parotid irradiated to 30 and 45 Gy were 19.7 ± 2.2 and $4.4 \pm 3.5\%$, well below the threshold suggested by Eisbruch *et al.* [22] (45% to 30 Gy and 25% to 45 Gy). In our study, however, $71.8 \pm 9.7\%$ of the contralateral parotid volume was irradiated to 15 Gy, above the threshold suggested by Eisbruch *et al.* [22] (67%). There was also a significant reduction in the volume of ipsilateral parotid gland irradiated to 45 Gy to $65.2 \pm 20.8\%$ with IMRT, which may potentially allow for a degree of recovery, as suggested by Roesink *et al.* [23].

NTCP Calculations

The mean contralateral parotid NTCP values with the mean Eisbruch parameters [22] were $22.3 \pm 10.3\%$ for IMRT and $100 \pm 0\%$ for three-dimensional radiotherapy ($P=0.00007$); with the mean Roesink parameters [23] they were $20.1 \pm 3.4\%$ for IMRT and $98.7 \pm 2.7\%$ for three-dimensional

Table 4 – Mean (± 1 standard deviation) percentage parotid volume irradiated to 15, 30, 45 and 60 Gy with three-dimensional radiotherapy (3D-RT) and intensity modulated radiotherapy (IMRT)

	15 Gy		30 Gy		45 Gy		60 Gy	
	IMRT	3D-RT	IMRT	3D-RT	IMRT	3D-RT	IMRT	3D-RT
Ipsilateral parotid	98.2 ± 2.0	99.8 ± 0.4 $P=0.1$	91.5 ± 8.1	99.0 ± 1.2 $P=0.1$	65.2 ± 20.8	94.9 ± 7.2 $P=0.03^*$	33.1 ± 21.6	73.3 ± 19.8 $P=0.01^*$
Contralateral parotid	71.8 ± 9.7	99.0 ± 2.2 $P=0.004^*$	19.7 ± 4.4	96.9 ± 6.1 $P < 0.001^*$	4.4 ± 3.5	93.3 ± 11.6 $P < 0.001^*$	0.0 ± 0.0	64.9 ± 27.6 $P=0.006^*$

*Statistical significance ($P < 0.05$) with Student's *t* test comparing the volume irradiated to each dose level with IMRT vs 3D-RT.

Table 5 – Mean (± 1 standard deviation) NTCP values for intensity modulated radiotherapy (IMRT) vs three-dimensional radiotherapy (3D-RT)

	Eisbruch <i>et al.</i> [22]			Roesink <i>et al.</i> [23]		
	IMRT	3D-RT	<i>P</i>	IMRT	3D-RT	<i>P</i>
Contralateral parotid	22.3 ± 10.3	100.0 ± 0.0	0.00007^*	20.1 ± 3.5	98.7 ± 2.7	0.000004^*
Ipsilateral parotid	100.0 ± 0.0	100.0 ± 0.0	NA	92.2 ± 11.0	99.6 ± 0.6	0.2

*Statistical significance ($P < 0.05$) with Student's *t* test.

radiotherapy ($P < 0.001$) (Table 5). There were no statistically significant differences between the NTCP values obtained with either set of parameters.

Analysis of the NTCPs obtained with the confidence interval limits from both studies showed that most values for the three-dimensional radiotherapy plans were $\sim 100\%$, although there was a small number of values between 75 and 100% with the Roesink parameters. For the IMRT plans, with the Eisbruch parameters, the NTCP values obtained ranged from 0 to 60% for the contralateral parotid glands and above 90% for the ipsilateral parotid glands. With the Roesink parameters, the contralateral parotid values ranged from 0 to 40% and for the ipsilateral parotid glands from 60 to 100%.

Discussion

A number of phase II trials of parotid-sparing IMRT have been reported. These studies contained small numbers of patients, but concluded that sparing the parotid gland contralateral to the primary tumour reduces the rates of xerostomia, and increases salivary flow from the spared gland. Patterns of recurrence reported in these trials show that a proportion of tumours recur in the locoregional area, mostly within the areas treated with a high radiation dose [24–26]. These recurrences are thought to be due to primary radioresistance, as seen with conventional radiotherapy, with only one relapse reported in the region of the spared parotid gland [25], although the patient numbers reported do not allow this observation to be conclusive. Furthermore, application of these techniques remains difficult, as most experience is confined to specialist centres and methods of target volume definition, particularly around the primary tumour site, have not been described in detail. The aim of this study was to standardise target volume definition in this patient group for the purposes of testing in the clinical trial setting.

In this study, areas of low minimum dose were found within PTV1 and PTV2 with conventional planning. These were located mostly in areas of photon–photon and photon–electron field matching and only became apparent when full three-dimensional planning was evaluated. Although statistical significance was not reached, these results are highly clinically relevant and both Chao *et al.* [25] and Bussels *et al.* [24] reported recurrences located in or near the match regions. With IMRT, these areas of low minimum dose were improved, as were tumour coverage, dose homogeneity and conformality. These improvements should translate into an improvement in tumour control. It could be argued that further dosimetric improvements could potentially be achieved by increasing the number of fields, but five beam arrangements have previously been shown to provide adequate target coverage while maintaining organ at risk sparing [14].

Parotid-sparing IMRT target definition requires careful consideration of the doses to PTVs close to the spared parotid gland, as under-dosage of these PTVs may lead to local recurrence. The important PTVs are the mucosa of the oropharynx, the parapharyngeal space and the level 2a

lymph nodes. The trial guidelines stipulate that the entire mucosa of the oropharynx should be treated. We feel that this is essential to treat potential sub-mucosal spread, which is not visible with computed tomography [27]. This is in contrast to other groups who simply add a geometric margin to the visualised GTV, and accept partial oropharyngeal irradiation.

Another important factor in parotid-sparing IMRT is the level of the superior limit of level 2 neck nodes with lower levels facilitating sparing of the parotid. The initial anatomical descriptions placed its superior limit at the level of the base of the skull [28] and for level 2 surgical node dissections it is set at the level of the insertion of the posterior belly of the digastric muscle on the mastoid process [29]. Different studies initially proposed different superior borders for the node-negative neck: inferior aspect of C1 [30], superior aspect of C1 [31], bottom of the transverse process of C1 [11], crossing of the posterior belly of the digastric muscle and internal jugular vein [24,26]. Only one recurrence was seen in the spared tissue adjacent to the parotid gland [25]. In an update of the Michigan experience, Eisbruch *et al.* [32] found no recurrences in the contralateral neck, cranial to the sub-digastric nodes and the investigators felt that the crossing of the posterior belly of the digastric muscle and the internal jugular vein was a safe superior margin for the contralateral level [32]. So the consensus is that it seems safe to place the margin at the bottom of the transverse process of C1 [11] in the node-negative neck and where there is no specific clinical indication to include the jugular fossa [33].

In our study, parotid-sparing IMRT achieved reductions in the mean dose to the contralateral parotid gland to 22 Gy, below the threshold suggested by Eisbruch *et al.* [7] for the preservation of function [7]. We also found reductions in the volume of ipsilateral parotid irradiated to 45 and 60 Gy. Roesink *et al.* [23] reported some recovery when 40–80% of the gland was irradiated to 35–45 Gy and it may be that these observed reductions in volume irradiated could possibly translate into a small recovery of function.

NTCP values for the contralateral parotid with parotid-sparing IMRT were 20–22%, suggesting that xerostomia may be significantly reduced, but not eliminated [22,23]. These values are above the 5% reported by Eisbruch *et al.* [22] on spared parotid glands. However, this study had glands that received lower radiation doses.

These pre-clinical and modelling data serve as a theoretical baseline for comparison with clinical data that will be forthcoming from the PARSORT trial.

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Paper 5

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Quality assurance

Dosimetry audit for a multi-centre IMRT head and neck trial

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ABSTRACT

Background and purpose: PARSPORT was a multi-centre randomised trial in the UK which compared Intensity-Modulated Radiotherapy (IMRT) and conventional radiotherapy (CRT) for patients with head and neck cancer. The dosimetry audit goals were to verify the plan delivery in participating centres, ascertain what tolerances were suitable for head and neck IMRT trials and develop an IMRT credentialing program.

Materials and methods: Centres enrolling patients underwent rigorous quality assurance before joining the trial. Following this each centre was visited for a dosimetry audit, which consisted of treatment planning system tests, fluence verification films, combined field films and dose point measurements.

Results: Mean dose point measurements were made at six centres. For the primary planning target volume (PTV) the differences with the planned values for the IMRT and CRT arms were -0.6% (1.8% to -2.4%) and 0.7% (2.0% to -0.9%), respectively. Ninety-four percent of the IMRT fluence films for individual fields passed gamma criterion of $3\%/3$ mm and 75% of the films for combined fields passed gamma criterion $4\%/3$ mm (no significant difference between dynamic delivery and step and shoot delivery).

Conclusions: This audit suggests that a 3% tolerance could be applied for PTV point doses. For dose distributions tolerances of $3\%/3$ mm on individual fields and $4\%/3$ mm for combined fields are proposed for multi-centre head and neck IMRT trials.

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A multi-centre randomised controlled trial of parotid sparing Intensity-Modulated Radiotherapy (IMRT) versus conventional radiotherapy was commenced in the UK in 2003 for patients with oropharyngeal and hypopharyngeal tumours (PARSPORT). The primary endpoint was the incidence of xerostomia of grade 2 or more, assessed by subjective measure on the LENT/SOMA [1] late toxicity scale, one year after treatment. Centres proposing to join PARSPORT underwent rigorous pre-trial exercises [2] in volume delineation and planning. They were also required to complete a questionnaire and produce a document describing the details of their radiotherapy procedures, including IMRT, this document is referred to as 'the process document'. Each centre was visited to discuss the clinical and physical aspects of the trial, including plan-

ning, delivery and verification. The first three patients (at least one in each trial arm) were submitted to the QA centre for assessment before treatment could commence. As PARSPORT [3] was the first multi-centre head and neck IMRT trial to take place in the UK, the requirements of the dosimetry audit were not only to verify the delivery of patient plans, but also to check the commissioning of the treatment planning and delivery systems for IMRT in head and neck. For this reason the audit was designed to evaluate basic IMRT fields as well as to measure the dose delivered on the IMRT and conventional plans used in the pre-trial exercises. The results of these measurements are discussed in this paper. The complete trial QA process (from outlining and planning exercises to the dosimetry audit) took the form of a credentialing program. Credentialing has been used worldwide for IMRT programs and was pioneered by the Image-Guided Therapy QA Center (ITC) and Radiation Therapy Oncology Group (RTOG) in the US [4]. It has been shown that credentialing significantly reduces the deviations on a trial protocol [5].

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Data from radiotherapy trials with quality assurance programs [6–8] have shown that, although a contributing centre may have a proper understanding of a trial protocol, audit visits can identify differences in the dosimetry between the centres which could have an impact on the results of the trial. Pettersen et al. [9] have shown that uncertainties in radiation dose can reduce the steepness of the dose–response curve and that reduced uncertainty leads to a significant reduction in the number of patients required in order to show a difference between the two arms of a trial.

There were three goals of the PARSPORT dosimetry audit. Firstly to verify the delivery of the IMRT plans in participating centres using an in-depth audit, secondly to ascertain and confirm what tolerances might be suitable for head and neck IMRT multi-centre trials and finally to develop an IMRT credentialing service which could be used in collaboration with other IMRT trials in the UK.

Six UK centres were audited: Addenbrookes Hospital (Cambridge), Christie Hospital (Manchester), Ipswich Hospital (Ipswich), North Staffordshire University Hospital, (Stoke) and the Royal Marsden Hospitals (London and Sutton), the latter was also the home of the QA centre. The QA centre consists of one physicist (CHC), and the equipment used for all the QA measurements, based at the Royal Marsden hospital. The QA program was also supported by the RadioTherapy Trials Quality Assurance (RTTQA) group [10] which is a virtual group of QA staff based in several UK hospitals and funded by the trials they support. Each of the participating centres had already run an IMRT program for head and neck or another clinical site and had previously been audited for other trials within the RTTQA group.

Materials and methods

Each centre had previously been asked to undertake a planning exercise on its own treatment planning system (TPS) as part of a dummy run for assessment before entering the trial [2].

The IMRT test case was a T2 N0 M0 SCC (squamous cell carcinoma) of the left tongue base with the primary clinical target volume (CTV) abutting the ipsi-lateral parotid gland. Forward or inverse planning methods could be used with either step and shoot or dynamic delivery, as selected for use in the trial. The use of between 5 and 9 gantry angles was suggested and non-coplanar fields were allowed. CTV1 contained the primary tumour and any macroscopic lymph node metastases, and CTV2 contained elective lymph node sites. Margins were determined by each centre based on its individual setup and immobilization systems. The doses for both the PTV1 (65 Gy in 30 fractions) and PTV2 (54 Gy in 30 fractions; biologically equivalent to 50 Gy in 25 fractions, when $\alpha/\beta = 10$ is used for the tumour, and the overall time increase of a week is taken into account) were prescribed to the median of the respective volume (i.e. the dose is prescribed as 100% to the 50% of the volume on the dose volume histogram) for planning with a single IMRT plan. Patients were scanned and treated in an extended neck position to minimise dose to the oral cavity (see Fig. 1). Dose constraints were given in the protocol for all planning target volumes (PTVs) and organs at risk (OARs) [3].

The conventional plan test case was a T3 N2b SCC of the left tonsil with involved nodes extending below the level of the hyoid. Centres were asked to use their standard local planning technique as far as possible. The planner was asked to create a plan consisting of lateral pharyngeal and anterior neck fields, using a half-beam blocking technique with the isocentre at or close to the level of the hyoid cartilage. In order to avoid exceeding cord tolerance, electron fields could be added in the second phase of the treatment. The neck field consisted of an anterior field with spinal cord shielding; a posterior field could be added if necessary to improve PTV2 homogeneity. Optimisation of the field weights was allowed,

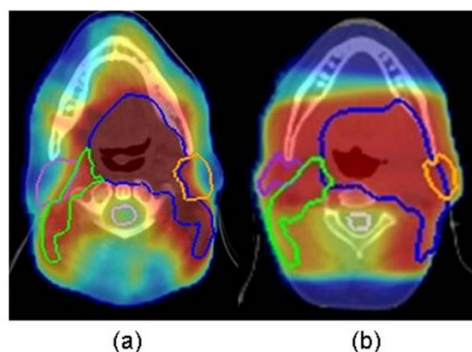


Fig. 1. Examples of the (a) IMRT and (b) conventional plans used for the audit. Primary and elective nodal PTVs, parotid glands and the spinal cord are shown. For the IMRT plan the patient has an extended neck and the conventional plan is for a patient with a straight neck.

as were small top-up fields to boost the dose where needed. The planner was free to choose the energy for all fields. The aim was to cover the PTV1 (65 Gy in 30 fractions) and PTV2 (50 Gy in 25 fractions) by the respective 95% of prescription isodose lines. Where this was not possible, clinical judgment was used. Patients were scanned and treated with a straight neck (see Fig. 1).

These plans were used to make measurements in the dosimetry audit. Documentation was sent in advance to each centre giving an overview of the visit as well as detailed instructions on how to prepare for and carry out each exercise. The measurements took 5–6 h of linac time and for each centre 1.5 days was allocated for each visit. Inevitably with this first IMRT national audit there was a great deal of discussion at each centre. The analysis and report writing generally took 2 days.

Commissioning audit

The aim of these tests was to provide simple shapes to verify the dosimetry of the IMRT treatment planning system (TPS) in order to check the commissioning of the planning system and also that if differences were found between the planned and delivered clinical fields, these more straightforward tests may help to shed light on the causes.

There were three tests in all: 'Dip', 'Steps' and 'Jigsaw'. The first test was designed to test dynamic delivery and the other two tests were designed to test both dynamic delivery and step and shoot delivery. The Dip and Steps tests were based on those described by Van Esch et al. [11]. The Jigsaw test was created to test the accuracy of the TPS modelling of the abutting leaf segments. For each test a set of pre-defined volumes (see Fig. 2), delineated on a CT scan of a cuboidal block of Barts solid water [12] (WT1) phantom, were sent to each centre. The volumes were 5 cm (L-R) 9 cm (S-I) and 0.5 cm (A-P). In each of the tests the volumes were created to abut one another as do the volumes in a PARSPORT plan. The length of each of the segments in the 'Dip' and 'Steps' tests would generally be considerably longer than 9 cm to fully cover the volume.

Each plan was planned as a single field with the isocentre placed at a depth of 5 cm. The Dip test established the goal of a specified dose of 0.7 Gy to each of the outer volumes and of 0.0 Gy to the middle volume. The aim was to verify that the leaves could adequately shield the central volume and that the TPS

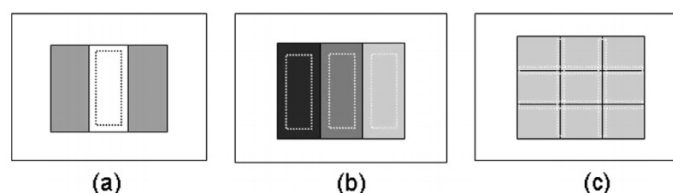


Fig. 2. Coronal view of the three commissioning tests: (a) Dip (b) Steps and (c) Jigsaw. For Dip and Steps tests the areas are of 5×9 cm. For Jigsaw test the segments are of 3×3 cm² or 4×4 cm². The dotted regions (3×7 cm) are the areas used for analysis. The gray scale indicates dose intensity.

modelled the transmission of the leaves correctly thus not over- or under-representing the dose in this region. In the Steps test, the volumes received 0.7, 0.5 and 0.3 Gy, respectively (left to right in Fig. 2). Here the aim was to test the delivered accuracy of the three relative dose levels. Finally the Jigsaw test used 3×3 cm² or 4×4 cm² segments (depending on MLC capability) to create a square shape made up of nine abutting sections. The dose was 0.5 Gy to each segment and the aim was to check whether the TPS correctly modelled the matchlines of the abutting segments.

Kodak X-Omat films were placed in a coronal orientation (see Fig. 3) in the solid water blocks at depths of 3 and 5 cm. A comparison using line profiles and dose difference maps was made between the calculated and delivered profiles for each of the tests. For each centre a single batch of films was used and films were exposed, processed and analysed together, to minimise any differences between films.

IMRT film audit

Each IMRT plan was transferred onto a CT scan of solid water blocks, whilst maintaining the MU from the original plan. The plan dose distribution was then recalculated and the resulting dose cube was exported in either DICOM or RTG format. The dose cubes were with a dose grid spacing of 0.25–0.30 cm, which is also required for an accurate assessment of the plan DVHs. For the individual fields the gantry was reset to 0° (Fig. 3) and each field was calculated in a separate plan. For the combined fields the clinical gantry angles were maintained and the plan was recalculated with all fields (see Fig. 3).

Film calibration was carried out by exposing 10×10 cm fields at 5-cm depth to known doses on individual films. This was repeated for both the Kodak X-Omat film (used for single field measurements, where maximum dose does not exceed 0.80 Gy) and Kodak EDR2 film (used for combined fields or whole treatment, where maximum dose may be up to 2.7 Gy). A calibration curve

was then constructed for each film type from the optical density at the centre of each field plotted against known dose.

Individual field films

The aim of the individual field tests was to ascertain whether the MLC delivery patterns were correctly delivered in each field with gantry set to 0°. This avoids errors due to gravitational effects of the gantry orientation. In addition individual fields may uncover errors being masked by other fields in the combined field films. Each field was delivered to Kodak X-Omat films positioned at 3 and 5 cm depths.

Combined field films

These tests were carried out on the solid water phantom (Fig. 3a) with all fields delivered at their clinical gantry angles to Kodak EDR2 film positioned in the coronal plane at 3 and 5 cm. The coronal plane was chosen to ensure the maximum interrogation of the MLC leaves with a single film. The isocentre of the plan was positioned in such a way that the upper film (3 cm) was in the centre of the high dose volume and parotid glands and the lower film (5 cm) was through the neck nodes and cord. The aim was to ascertain whether the individual fields combine correctly on delivery and whether there are any effects of gantry orientation (e.g. gravitational) or other errors.

Film analysis

Each film was scanned through a Vidar Dosimetry Pro Advantage film digitiser. The calibration curve was created from the five different dose level calibration films taken at each centre. This was repeated for each film type. These curves were then used to convert each of the individual field, combined field and commissioning test films. The digitised film was then transferred into the OmniPro IMRT (v1.5; iba dosimetry) analysis software. The corresponding dose planes from the phantom plan were exported from the TPS

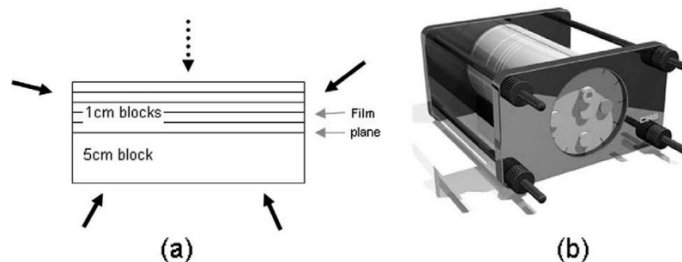


Fig. 3. Phantoms for (a) Film tests: configuration and orientation of the beams and films for the (i) commissioning tests and individual fields (dotted arrow) and (ii) combined fields (all arrows) and (b) Ion chamber tests: the CIRS 002HN Head and Neck phantom.

into OmniPro. The films and TPS planes were normalised to a value of 100% in a region of high dose gradient and low dose gradient. All commissioning tests were analysed as dose difference of film subtracted from TPS. All individual and combined field films were analysed using the gamma index tool for combining dose difference and distance to agreement [13]. In the OmniPro I'mRT software all percentages are of the 100% normalisation and not local percentage differences.

Ion chamber measurements

The phantom used for the dose point measurements was a CIRS 002HN Head and Neck phantom (tissue equivalent epoxy resin cylinder of 16 cm diameter and 30 cm length). The ion chamber was a PTW semiflex thimble chamber of 0.125 cm³ (SN TW31010) and was used with a UNIDOS E universal dosimeter (T10009-90116). Interchangeable rods of the same solid resin drilled to take the ion chamber could be used to locate the chamber in five different positions, see Fig. 3. CT images of the phantom were taken at 2.5 mm slice thickness and spacing.

Prior to making measurements in the head and neck phantom an output measurement was made in solid water blocks using a 10 × 10 cm field at 5 cm depth and 100 cm FSD. This was compared with the depth dose data for this setup from the respective centre.

The IMRT and conventional plans from the pre-trial exercise were transferred onto the images of the head and neck phantom and recalculated. During the planning exercise the centres were allowed to use their usual isocentre placement and therefore there were a variety of positions used. In order that the measurements were always made in the same part of the patient anatomy, the isocentre was positioned on the phantom such that the chamber was in a specified location relative to the original patient volumes. These were the same for the IMRT and conventional plans. These measurement points were in the geometric centre of PTV1, the geometric centre of the section of PTV2 inferior to the primary disease and in the centre of the cord on the same transverse slice as the PTV2 point.

A single fraction of the treatment plan was delivered to the phantom and the dose recorded for each field was delivered. Each field dose and the combined field dose were compared with the calculated point doses from the TPS.

Local QA measurements

Each centre was also asked to make its own measurements of the IMRT plan using its own equipment and analysis techniques. Table 1 lists the equipments which each centre routinely uses to

Table 2

Results from the TPS tests at 5 cm depth. Negative results mean that the measured point was lower than the TPS calculated point.

	Dip test	Steps test	Jigsaw test
Tolerance	3%	3%	20%
Result	Mean –1.0%	High dose mean –0.5%	Low dose mean –0.4%
Range	0.0 to –2.5%	3 to –7.5% ^a	28/40 (70%) [38/40 (95%) for tolerance of 25%] –26.2% to 26.6%

^a One centre failed due to film saturation in the high dose region.

plan, deliver and make IMRT verification measurements. All centres used an inverse planning technique.

Results

Six centres undertook the audit with three using dynamic delivery and three using step and shoot delivery (see Table 1 for details of TPS and linac). All IMRT plans were within the required dose constraints and all conventional plans were acceptable for treatment within the trial.

Commissioning tests by film

Dip test

For the results obtained from gamma map comparison of the dose predicted by the planning system and the dose measured from films, a tolerance of 3% of the normalisation was set for the low dose region, where the peaks at either side were normalised to 100% and the films were normalised to the treatment plans, so this comparison is a relative dosimetric test. A region of 3 cm width (chosen to avoid including the steep gradient on each side, see Fig. 2) and 7 cm length was analysed in the centre of the spared volume. The dose grid was 1 × 1 mm with a total of 2100 points analysed on each film. Three centres (dynamic delivery, see Table 1) carried out this test and all achieved differences of relative dose between measured and calculated data of less than 3%. The mean value in the analysed region was –0.6% (range 0.6% to –2.2%) and –1.0% (0.0% to –2.5%) at 3 cm and 5 cm film depths, respectively. Table 2 lists out data at 5 cm depth.

Steps test

The dose for the middle step was normalised to 100% and a tolerance of 3% was applied to the higher and lower step doses. A region of 3 cm width and 7 cm length was analysed in the centre of the high dose and low dose volumes, thus avoiding the dose level interface region (see Fig. 2). Six centres completed this test and the

Table 1

Equipments used at each centre for planning, delivery and patient-specific QA measurements. If a second phantom is given^a, then the first is for the dose point and the second is for the dose distribution (IC, ion chamber; PX, Perspex; SW, solid water; XV, Kodak X-Omat film; EDR2, Kodak EDR2 film; GC, gafchromic film).

Centre	Treatment planning system	Linac	Delivery technique	Dose point detector	Phantom for dose point and dose distribution ^a	Dose distribution verification	Plane for dose distribution
1	Eclipse 6.1.67	Varian 2100C	Dynamic	0.015 cc IC	Cylindrical PX (25d × 25l) Cuboidal SW (30 × 30 × 15)	EDR2	2 Coronal
2	Pinnacle 6.2b	Elekta SL series	Step and shoot	0.6 cc IC	Cuboidal SW (30 × 30 × 20)	EDR2/GC	2 Coronal
3	Eclipse 7.1.67	Varian 2300EX	Dynamic	0.015 cc IC	Cuboidal PX (15 × 15 × 10) Cuboidal SW (40 × 40 × 15)	XV or Diode array	Each field
4	Pinnacle 6.2	Elekta Precise	Step and shoot	0.125 cc IC	H&N PX (30x15x15or45) Cuboidal SW (15 × 15 × 10)	EDR2/GC	1 coronal
5	Xio 4.2	Siemens Primus, Oncor	Step and shoot	0.125 cc IC	In house SW (24 × 29 × 20) Cubic SW (20 × 20 × 20)	EDR2	Each field & 1 coronal
6	Eclipse 6.5	Varian 2100CD	Dynamic	IC array	IC array (40 × 40 × 5)	IC array	Each field

Table 3

Results from the individual and combined field film tests. (Thresholds applied are 10% for individual beams and 20% for combined beams.)

Gamma parameters/mm	2/2	3/2	3/3	4/3	4/4	5/3	5/4	5/5
% Individual films passing (/31)	48% (15)	84% (26)	94% (29)	100% (31)	100% (31)	–	–	–
Mean	90.9	95.0	97.7	98.7	99.4	–	–	–
% Combined films passing (/12)	–	–	67% (8)	75% (9)	83% (10)	92% (11)	92% (11)	100% (12)
Mean	–	–	94.9	97.4	98.2	98.7	99.1	99.4

mean values were -0.8% (2.0% to -4.6%) and -0.5% (3% to -7.5%) at 3 and 5 cm film depths, respectively, for the high dose volume. For the low dose volume the mean values were 0.4% (2.6% to -2.2%) and -0.4% (1.9% to -3.0%) at 3 and 5 cm, respectively. One centre failed the tolerance value in the high dose step, due to problems with film saturation, which caused high levels of noise.

Jigsaw test

Five of the six centres completed this test. The dose was normalised to 100% at the centre of the middle segment. The aim was to check the modelling of the matchline between segments. The four main axes were analysed at both depths, evaluating an area to 1 mm either side of the junction (210 points in each axis). The maximum difference between TPS and film was recorded, with the tolerance set to 20%. Seventy percent (28 of 40) achieved less than 20% difference on all points throughout the abutting penumbral area (only one centre had all within 20%). Ninety-five percent achieved less than 25% difference between film and TPS, with two centres each having one junction which failed this tolerance.

IMRT film tests

The criterion for the film analysis to pass was set to be that >95% of the analysed film gave a gamma index of <1 tested at a range of gamma parameters [14]. The analysis was done on relative dose distributions, where both the plan and the film were normalised in a high dose region with low gradients. A threshold dose of 10% for the individual fields and of 20% for the combined fields were set for each film, below which the data were not analysed.

Individual field films

For individual fields the gamma tolerance parameters were set at 4%/4 mm, 4%/3 mm, 3%/3 mm, 3%/2 mm and 2%/2 mm and were passed by 100%, 100%, 94%, 84% and 48% of the films analysed, respectively, see Table 3.

Combined field films

For combined fields the gamma tolerance parameters were set at 5%/5 mm, 5%/4 mm, 5%/3 mm, 4%/4 mm, 4%/3 mm and 3%/

3 mm with 100%, 92%, 92%, 83%, 75% and 67% of the films passing, respectively (see Table 3). There was no significant difference between dynamic delivery and step and shoot delivery.

Ion chamber measurements

Table 4 lists out the results of the combined dose points for IMRT and conventional treatment at each centre. The tolerance for the PTV1 and PTV2 dose points was set at 3% and all centres passed this. The tolerance for the cord point was set at 5%, due to difficulties in locating a good measurement point close to a high dose gradient. Five centres passed the cord point for IMRT. One centre failed this, but as the measurement was lower than the TPS and did not exceed cord tolerance dose, this would not change a clinical decision to treat. Two centres failed the cord point tolerance for conventional treatment, but both had measurements lower than calculated. In Centres 4 and 5 the large discrepancy in the cord points was due to the modelling of the low dose penumbral region where a compromise in fit had to be made between the shoulder of the penumbra and the tail. In both cases the tail had been compromised to allow good shoulder fit. This meant that as the measured low dose tail on the penumbra was significantly lower than the modelled tail, the percentage difference between these two values was large, although the absolute difference was in the order of a few centigrays. These findings were reported to both centres.

Local QA measurements

All centres submitted measured verification data on IMRT patients enrolled into the trials. For combined fields the mean dose difference across all centres was -0.6% (range -2.8% to 3.2%). Forty of 41 patients were within 3% tolerance (the patient at 3.2% was accepted by the local clinician as an acceptable plan). For individual fields the mean across all centres was 0.1% (range -11.4% to 12.9% ; large range due to occasional difficulty in finding a good measurement point in each fluence).

Data were also collected from annual UK interdepartmental audits (where a local visitor centre will visit a host centre and make measurements to check the linac output dosimetry). This was done to check the output at a time point different from that of the dosimetry audit visit. Data were collected from these audits for the period during which the centres recruited to the trial. All host data were within 2% of the visitors' measurements (range 0.99–1.017).

Discussion

PARSPORT was one of the first multi-centre IMRT trials in the UK and at the time of starting (2003) there had been no previous IMRT audit or credentialing service available in the UK. However, data from the USA suggested that those centres which have been

Table 4

Combined point dose results for conventional (*italic*) and IMRT (**bold**) plans. Mean and standard deviation (SD) are of the data for the six centres. Negative results for percentage differences mean that the measured point was lower than the TPS calculated point.

CONV IMRT	Average dose (Gy)	Dose range (Gy)	Centre no.						Mean (%)	SD (%)
			1 (%)	2 (%)	3 (%)	4 (%)	5 (%)	6 (%)		
PTV1	<i>1.95</i>	<i>1.83–2.11</i>	<i>1.1</i>	<i>2.0</i>	<i>1.2</i>	<i>–0.9</i>	<i>0.0</i>	<i>0.9</i>	<i>0.7</i>	<i>1.0</i>
	2.24	2.17–2.32	0.1	–0.4	–2.0	1.8	–2.4	–0.5	–0.6	1.5
PTV2	<i>1.89</i>	<i>1.69–2.06</i>	<i>0.9</i>	<i>1.7</i>	<i>0.3</i>	<i>–0.3</i>	<i>–0.7</i>	<i>–2.6</i>	<i>–0.1</i>	<i>1.5</i>
	1.82	1.68–2.02	0.5	2.2	–1.9	–2.7	–2.4	–0.7	–0.8	1.9
Cord	<i>0.46</i>	<i>0.24–1.06</i>	<i>–1.7</i>	<i>0.0</i>	<i>–1.5</i>	<i>–35.8</i>	<i>–32.7</i>	<i>2.9</i>	<i>–11.5</i>	<i>17.8</i>
	1.12	0.55–1.43	–0.5	2.4	–6.4	4.2	–4.9	–2.6	–1.3	4.1

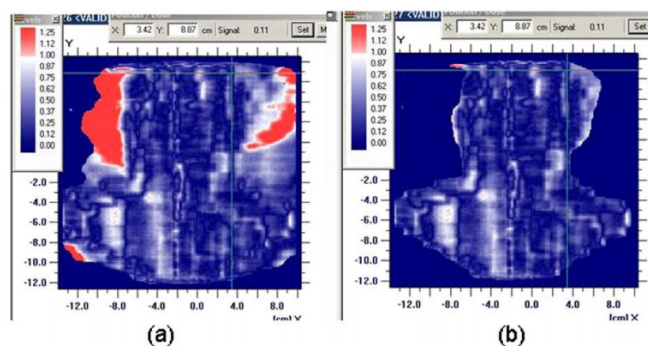


Fig. 4. Examples of gamma maps for combined beam film where the main areas of failure are outside the patient volume (the red colour indicates which areas fail a gamma criterion of 4%/3 mm) (a) has a 20% threshold and (b) has a 40% threshold.

credentialed in a trial are better able to deliver accurate dose distributions [5]. Van Esch et al. had published work on commissioning Varian systems [11], but there was little in the literature on tolerances. As the trial progressed an ongoing review of the literature suggested that tolerances set for multi-centre trials and those set for in-house routine QA differ in that the in-house values are generally lower e.g. QUASIMODO [15] proposed 4%/3 mm for inter-centre verification whereas Budgell et al. [16] suggested that 3%/3 mm was feasible for in-house verification of prostate IMRT. This is probably due to the trials covering different centres using different techniques for verification methods. Previous IMRT audits of head and neck treatments also suggested a range of tolerances for what was acceptable and achievable. Zefkili et al. (GORTEC) [17] collected dosimetry measurement data for 108 patients (of varying head and neck sites and treated under local protocols) in 12 centres and concluded that 4% was an acceptable difference between local measurements and TPS calculations. De Martin et al. [18] used 4%/3 mm as in-house acceptance criterion for head and neck IMRT and van Zijtvelde suggested 3%/3 mm for individual head and neck fields measured in-house with an EPID device [19]. There appears to be a difference between tolerances for local QA [17,18] and those used for multi-centre trials where measurements are made with the same equipment transported between each centre and the results from the different centres are compared with one another in an external audit [20,21], this is particularly so in the larger trials with many centres contributing. There is also a difference between appropriate tolerances for individual field and combined field dose distributions [18,19]. Molineu et al. [20] designed and sent an anthropomorphic head and neck phantom to 10 institutions in the US participating in RTOG trials to verify IMRT. From this study they concluded that when using TLDs they should set an acceptance criterion of $\pm 7\%$ in the primary and secondary PTVs and a distance to agreement criterion of 4 mm in the primary PTV and OARs.

Due to the uncertainty of appropriate tolerances the main goals of the PARSPORT dosimetry audit were to verify the delivery of the IMRT plans in participating centres using an in-depth audit as well as to ascertain and confirm what tolerances might be suitable for head and neck IMRT multi-centre trials. The appropriate tolerances were expected to be tighter than those from the RTOG trials, as the QA centre also provided advice and feedback on the process of setting up head and neck IMRT. Initial tolerances were set, but it was expected that these would need to be reviewed following data collection and analysis. The ion chamber point measurement tolerance was to be within $\pm 3\%$ for PTV measurements (as this is

what has been previously set for complex conformal trials [22]) and all centres achieved this. Combined with information from the literature, this was therefore considered to be an acceptable tolerance for future trials. Our experience in this trial was that point dose measurements sometimes fail due to poor selection of measurement point. In these cases, review of the point generally showed that although the combined dose distribution surrounding the point appears to have a low gradient, the individual field gradients are considerably higher. We recommend that both combined and individual dose gradients should be checked when selecting a point to measure.

For the film tests a 4%/4 mm tolerance was initially set, however following analysis it was clear that different values were suitable for individual fields and combined fields. We suggest that 3%/3 mm with a 10% threshold is suitable for individual field films when applying a tolerance of 95% giving a gamma index of less than 1. However for combined films, where gravity can affect both the gantry rotation and the leaf motion, we recommend that 4%/3 mm with a 20% threshold is appropriate. Furthermore we suggest that each film be analysed for where the failure regions are in terms of where they fall in the patient anatomy. If the film measurements suggest a lower dose in an organ of risk it is clinically not a problem. However, particular attention should be paid to fail regions in the targets and measured overdose in the organs-at-risk. Regions outside the body are irrelevant and can be ignored. Fig. 4 shows the effect of increasing the threshold to 40% which effectively removes the dose outside the body. However a 40% threshold can also mean some low dose within the body may be removed and therefore this threshold should not be used as a routine first analysis. This 40% threshold would have meant that 12/12 combined films would have passed the criterion of 4%/3 mm (Table 3).

The commissioning tests were found to be useful to confirm the accuracy of the planning system to create deliverable fluences. In Centre 3 (see Table 4) a profile taken from the Dip test film helped to verify whether the cord point dose measured out of tolerance was due to the modelling of the penumbra within the TPS for IMRT fields. In Centres 4 and 5 the penumbral modelling problems were for the conventional plans, but did not occur in the IMRT plans where the beam was modelled differently.

The complete PARSPORT QA process, including both the dosimetry audit and pre-trial exercises [23], led to an IMRT credentialing program for UK IMRT trials in collaboration with the CHHiP [24], IMPT High [25] and COSTAR [26] IMRT trials (coordinated by the Radiotherapy Trials QA group (RTTQA) [10]). This includes an in-depth program of pre-trial outlining and planning exercises,

process documents and questionnaires as well as the commissioning, film and ion chamber tests described in this paper. Following successful achievement of these exercises the centre can then join one of the other UK IMRT trials listed, with a significantly reduced trial QA audit.

The IPEM IMRT report 96 [27] states that audit and external review of IMRT programme are strongly recommended and following our experiences with the PARSPORT trial we recommend that for a first IMRT trial at any centre an in-depth external audit is undertaken.

Conclusions

These dosimetry audit measurements suggest that a tolerance of 3% for target point doses could be applied for future IMRT multi-centre head and neck trials. For dose distributions tolerances using the gamma index of 3%/3 mm on individual films and 4%/3 mm for combined films are proposed. The authors also recommend that centres joining an IMRT trial undertake an external audit in the form of a credentialing program to ensure adherence to the protocol and as a benchmark for their IMRT program.

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Paper 6

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Pre-trial quality assurance processes for an intensity-modulated radiation therapy (IMRT) trial: PARSPORT, a UK multicentre Phase III trial comparing conventional radiotherapy and parotid-sparing IMRT for locally advanced head and neck cancer

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ABSTRACT. The purpose of this study was to compare conventional radiotherapy with parotid gland-sparing intensity-modulated radiation therapy (IMRT) using the PARSPORT trial. The validity of such a trial depends on the radiotherapy planning and delivery meeting a defined standard across all centres. At the outset, many of the centres had little or no experience of delivering IMRT; therefore, quality assurance processes were devised to ensure consistency and standardisation of all processes for comparison within the trial. The pre-trial quality assurance (QA) programme and results are described. Each centre undertook exercises in target volume definition and treatment planning, completed a resource questionnaire and produced a process document. Additionally, the QA team visited each participating centre. Each exercise had to be accepted before patients could be recruited into the trial. 10 centres successfully completed the quality assurance exercises. A range of treatment planning systems, linear accelerators and delivery methods were used for the planning exercises, and all the plans created reached the standard required for participation in this multicentre trial. All 10 participating centres achieved implementation of a comprehensive and robust IMRT programme for treatment of head and neck cancer.

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Irradiation of parotid glands is known to carry a high risk of permanent xerostomia, which occurs in most patients with head and neck cancer treated with conventional parallel opposed-field arrangements. Intensity-modulated radiation therapy (IMRT) has the ability to produce shaped dose distributions that allow preservation of parotid salivary tissue, leading to a reduction in xerostomia, as shown in several phase II clinical studies [1–4].

In the UK, a multicentre randomised controlled trial of parotid-sparing IMRT (PS-IMRT) *vs* conventional radiotherapy (CRT) was commenced in 2003 in patients with oropharyngeal and hypopharyngeal tumours (PARSPORT) [5]. The primary endpoint was the incidence of xerostomia of grade 2 or more, assessed by subjective measure on the LENT/SOMA late toxicity scale, 1 year after treatment.

At the start of PARSPORT, detailed procedures for the implementation of IMRT had not yet been established in the UK and, although some centres in the UK had started IMRT programmes [6–9], most centres joining the study had not yet implemented head and neck IMRT. In addition, only some early recommendations in general implementation had been published in the USA [10, 11],

as well as some initial quality assurance recommendations for IMRT in the head and neck [12, 13]. Prior to opening the trial, the PARSPORT Trial Management Group (TMG) agreed on the protocol, which included the voluming guidelines and quality assurance (QA) requirements. The TMG consisted of the principal investigator (PI) from each centre as well as physicists, radiographers, statisticians and trial managers.

A rigorous QA programme to cover all aspects of the patient pathway, from target volume definition to verification, was designed for participating centres to ensure parity of treatment planning, pre-treatment verification and delivery across the different institutions [14–17]. The programme also served to give the centres a structure on which to base their IMRT protocol and provided guidance and support for clinical implementation. As many centres were starting IMRT there was also an element of teaching required in the set-up process. A dosimetry audit was carried out after the centres had joined the trial and patients had been entered. This study relates to the pre-entry QA: the dosimetry QA was studied later [18].

Methods and materials

A set of quality assurance exercises was designed for completion prior to a centre being deemed eligible to

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enter patients into the study. These exercises assessed both understanding of the trial protocol guidelines and compliance, and consisted of a questionnaire, a planning exercise, an outlining exercise and a process document. Evaluation of these took place at the QA centre and was followed by a preliminary visit to each institution. A report was then sent to each centre.

Questionnaire

The questionnaire was designed to obtain information on which equipment, protocols and tolerances were used in each centre. It was intended to complement the process document, and to provide information on the salient aspects of the IMRT process. The questionnaire was divided into sections on equipment, patient-specific quality assurance, immobilisation and margins.

Process document

Previous trials [19] which have led to an upgrade of treatment technique have found that a process document was central to discussion of implementing the new technique. Each centre was asked to provide information about the procedures that would take place for the production and verification of each patient plan, from randomisation to treatment. A detailed description was requested for the following steps: CT scanning, delineation, planning, pre-treatment QA, transfer to record and verification of the system, treatment delivery, verification and back-up processes. Centres were also asked to give details of the time required for each process as well as the interval between each step. An example process document from the Royal Marsden Hospital was available as a template.

Outlining exercise

In each centre the PI and any other clinicians proposing to enter patients into the trial were asked to undertake an outlining exercise to ensure adherence to the trial outlining protocol. The outlining exercise was performed on a software package (SimpleViewer, Nederlands Kanker Instituut (NKI), Amsterdam [20]). Use of this software meant that all the data were in the same format for analysis. An added advantage was that the clinicians did not need to use a treatment planning system (TPS) for the exercise as it could be done on any PC. Each clinician was sent a CD containing the software to view and delineate an oropharynx and a hypopharynx example of PARSPORT patients, a copy of the target volume definition protocol which had been agreed and accepted by the TMG [5, 21, 22] and a clinical history. The participating clinician was asked to define a gross tumour volume (GTV), a primary clinical target volume (CTV1) and a nodal clinical target volume (CTV2) as well as the parotid glands, while adhering to the trial guidelines. The delineated volumes were submitted to the QA centre for review and comparison with a reference set which had previously been created by the trial PI and two other lead trial clinicians.

Case reviews of the first three patients were employed to check that the outlining guidelines continued to be followed.

Planning exercises

Pre-delineated CT scans containing the CTV1/2 and the organs at risk (OARs: spinal cord, brainstem, both parotid glands) were sent in DICOM (Digital Imaging and Communications in Medicine) format to each centre, one for IMRT and one for conventional planning. Different scan positions were used for each arm of the trial as the IMRT arm required the neck to be extended and thus the spinal cord is usually curved. This neck position is not suitable for conventional planning, as a straight spine is required to match the electron fields to photon fields. Planners were required to create the corresponding primary and nodal planning target volumes (PTV1/2) using their institutional standard margins. No modification of the CTVs or OARs was permitted. For the conventional plans, the dose to the PTV1 was 65 Gy in 30 daily fractions and to PTV2 was 50 Gy in 25 daily fractions. The IMRT plans were created using a simultaneous integrated boost technique (SIB) [23, 24]. The PTV1 received 65 Gy in 30 fractions and the dose to the PTV2 was adjusted to 54 Gy in 30 fractions, which is equivalent to 50 Gy in 25 daily fractions [21]. Each centre was asked to submit a DICOM or RTOG (Radiation Therapy Oncology Group) export of each of the plans as well as hard copies of dose-volume histograms (DVHs) and dose distributions. A plan assessment sheet showing the dose-volume constraints and achieved plan values was also required. Table 1 shows these constraints with a compilation of the results from the 10 centres.

IMRT plan

The IMRT test case was a T2N0M0 squamous cell carcinoma (SCC) of the left lateral tongue base with relatively small parotid glands (24.8 and 24.3 cm³) and with the primary CTV abutting the ipsilateral parotid gland. Forward or inverse planning methods could be used with either step and shoot or dynamic delivery. The use of between five and nine gantry angles was suggested and non-coplanar fields were allowed. The doses for both the PTV1 and PTV2 were prescribed to the median of the corresponding volume. Dose constraints were given in the protocol for all PTVs and OARs (Table 1). This typical example of a PARSPORT patient was chosen in order to highlight the importance of prioritising target coverage over parotid sparing, while not exceeding spinal cord and brainstem tolerance, as the small volume and proximity to PTV1/2 of the contralateral parotid gland made complete sparing quite complex.

Conventional plan

The conventional plan test case was a T3N2b SCC of the left tonsil with involved nodes extending below the

Pre-trial quality assurance for an IMRT trial

Table 1. IMRT dose and volume constraints for the planning exercise shown with a compilation of the results for both the conventional and IMRT planning exercises from the 10 centres

Structure	Volume	Dose constraint (Gy)	IMRT dose range achieved (Gy)		Conventional dose range achieved (Gy)
			Edited volume	Original volume	Original volume
Primary PTV (PTV1)	99%	> 58.5	57.7–62.2	54.8–61.7	26.2–55.0
	95%	> 61.75	61.2–63.2	60.0–63.2	36.0–60.5
	50%	= 65.0	65.0–65.3	64.8–65.6	63.2–66.6
	5%	< 68.25	66.1–68.4	67.1–68.3	67.1–70.2
	2%	< 71.5	66.3–70.7	67.3–70.0	67.7–71.1
Nodal PTV (PTV2)	99%	> 48.6	44.8–51.6	2.2–41.0	17.9–39.0
	95%	> 51.3	50.5–52.7	46.0–52.7	22.1–44.0
	50%	= 54.0	53.9–55.8	53.9–54.5	47.7–51.2
	Maximum	< 48.0	39.4–48.0		42.6–46.9
Spinal cord	1 cm ³	< 46.0	33.0–46.2		42.2–45.0
Brainstem	Maximum	< 55.0	38.9–53.8		26.0–43.5
Contralateral parotid	Mean	< 24.0	22.0–29.4		56.1–65.9
Ipsilateral parotid	Mean	< 24.0	34.3–63.9		61.3–65.4

The data illustrate the dose ranges achieved with the two planning techniques.

IMRT, intensity-modulated radiation therapy; PTV, planning target volume; PTV1, primary PTV; PTV2, nodal PTV.

level of the hyoid. Centres were asked to use their standard planning technique as far as possible, and shielding could be either conventional or conformal. However, all conventional planning was required to be carried out on CT and with three-dimensional (3D) dose calculations, such that DVHs could be submitted for the plans.

The planner was asked to create a plan consisting of lateral pharyngeal and anterior neck fields, using a half-blocking technique with the isocentre at or close to the level of the hyoid. The neck field consisted of an anterior field with spinal cord shielding; a posterior field could be added if necessary to improve PTV2 homogeneity. Optimisation of the field weights was allowed, as were small top-up fields to boost the dose where needed. The planner was free to choose the energy for all of the fields. The aim was to cover the PTV1 and PTV2 by the corresponding 95% isodose lines. Where this was not possible, clinical judgement was used.

The lower neck field(s) was prescribed to a point termed the 'neck reference point', located 3 cm lateral to midline and at a depth of 2.5 cm. The weighting of the neck field(s) was such that the 100% isodose line passed through the neck reference point. The upper lateral fields were prescribed at 100% of the prescription dose to the midline/midfield point. Plans had to be calculated using inhomogeneity corrections and included all fields so as to include cross-scatter from other fields.

In the second phase of treatment, the posterior border of the lateral photon fields were moved 5 mm anterior to the spinal cord and electron fields were matched at the posterior and inferior borders to the photon fields. The superior border of the electron field could be varied according to volume coverage. Appropriate electron energy was determined from cord depth at field centre and 3D calculations were used. The total cord dose from the combined phases was required to stay below 48 Gy.

Nine of the 10 centres did not use the electron calculation algorithms available in their TPS clinically, and had hand calculation or measurement procedures in place. A preliminary investigation of eligible patients showed that in two-thirds of patients part of the parotid

gland was in the electron field, and in these patients the use of bilateral electrons made a difference of approximately 2 Gy to the mean parotid dose. As the primary endpoint of the trial was to measure the effect of sparing the parotid gland using the IMRT technique, it was decided that the omission of electron data in the DVH calculation for each patient would be less accurate than the inclusion, albeit with an algorithm that was generally unused clinically. Therefore, all centres were asked to commission the electron calculation algorithm for relevant energies and field sizes to provide dose cubes for the analysis of the conventional treatments. Centres were allowed to continue with their existing practice for monitor unit (MU) calculation and then transfer the electron field data into the planning system to provide the dose cubes for DVH calculation.

Preliminary visits and meetings

One of the goals of PARSORT, as an early IMRT trial, was to help centres set up an IMRT programme. To facilitate this, a visit was made to each centre by the trial QA physicist before the centre was approved to start trial recruitment. The purpose of this visit was to discuss any discrepancies which had arisen in the pre-trial exercises or documentation and to provide a forum for discussion of the implementation of the PARSORT trial in the individual centres.

Annual trial management and progress meetings were held throughout the recruitment period to bring participants up to date with the data and provide guidance for new centres joining the trial. Pre-trial workshops were also held, including physics planning, QA and clinical target definition training.

Results

In total, 10 centres completed the entire pre-trial QA process, of which two had no prior clinical experience of IMRT planning or delivery. Four centres had used IMRT

in non-head and neck sites, and four other centres had established a head and neck IMRT delivery protocol, but with limited patient numbers.

Questionnaire

Equipment

Table 2 gives the equipment for the 10 centres that completed the pre-trial exercises. All but two centres used the same TPS for both arms of the trial. Photons at 6 MV for IMRT and at 6 MV and/or 10 MV for conventional treatment were always used and a range of electron energies was available in each centre. All linear accelerators (Linacs) were calibrated with the UK Institute of Physics and Engineering in Medicine (IPeM) 1990 code of practice for photons [25] and either the 1996 or 2003 code of practice for electrons [26, 27].

Patient-specific quality assurance

Six centres used a commercial independent calculation programme to verify their conventional plan calculations and four used programmes developed locally. All centres set a tolerance of 2–3% between the two calculations. Nine centres made manual calculations for electrons and one centre made routine measurements. Only two of the centres already had electron calculations commissioned in their TPS, but all centres commissioned at least a small range of low-energy electrons at appropriate field sizes for use in the trial.

All TPSs used for IMRT had the capability of plan transfer onto a phantom for recalculation and verification measurements. A range of phantoms were used, including blocks of solid water (typically 30 × 30 cm at differing depths), cylinders of solid water or Perspex, or “head and neck-shaped” blocks of Perspex (Table 3). Only one centre used a phantom with heterogeneities. Six centres used the same phantom for fluency or dose distribution verification as was used for dose point verification.

Nine centres used an ion chamber to make measurements of dose points. All centres applied a 2–3% tolerance on dose points measured chosen in high-dose, low-gradient regions for all fields combined. Four centres used an independent MU calculation to verify

their IMRT, but all were using this as a secondary check supplementary to their measurements. Two centres were in the process of commissioning programmes and four centres were not using any independent calculation but were using measurements only.

All centres used a gamma index method of combining dose difference (%dd; percentage dose difference) and distance to agreement (DTA) [28] to analyse the combined beam or individual beam dose distributions. Tolerances of between 3% and 5% (%dd) and 3 mm and 5 mm (DTA) were reported, but at the time of questioning most said they did not have sufficient experience to set a definitive tolerance value. All centres used the gamma index as an action level to undertake further investigation into why an area of dose had failed and what effect it might have on a patient plan. Commonly, this was carried out if less than 95% of the field achieved 4% per 4 mm. Typically, dose thresholds of 10–20% were used to remove very low-dose regions.

At the onset of the trial most centres performed a comprehensive set of measurements for all trial patients with at least one-point dose measured with an ion chamber and typically either each field individually measured and/or multiple planes of combined fields delivered to processed film. By 2007, 7 of the 10 centres had moved to ion chamber or diode array, Gafchromic film or supplementary independent calculations. However, at the time of writing no centre has replaced measurements completely, although several were in the process of collecting data to compare measurements and independent calculations.

Immobilisation and margins

All centres used five-point fixation immobilisation systems both for conventional and IMRT treatments [29]. Seven centres used vacuum-formed pETG (polyethylene terephthalate and modified glycol copolyester) shells, which were then cut out during treatment to maximise skin sparing; of these seven centres using PETG in 2003, three switched to thermoplastic (TP) shells during the trial and three used TP throughout. Patient positioning was different for the two arms of the study, with a straight spine required in the conventional arm to allow the use of phase 2 electrons, whereas in the IMRT arm the neck could be comfortably extended to reduce the

Table 2. Equipment for the 10 centres that completed the pre-trial exercises

Centre	TPS	Linac	MLC	IMRT delivery
1	Eclipse	Varian 2100CD	120 leaf (5 mm/10 mm)	DMLC
2	Pinnacle	Elekta SL Series	80 leaf (10 mm)	SMLC
3	Eclipse	Varian 2300EX	120 leaf (5 mm/10 mm)	DMLC
4	Eclipse	Varian 600CD	120 leaf (5 mm/10 mm)	DMLC
5	Pinnacle	Elekta Precise	80 leaf (10 mm)	SMLC
6	Xio/ARPS	Siemens Primus	82 leaf (10 mm)	SMLC
7	Eclipse/Oncentra	Varian 2100EX	120 leaf (5 mm/10 mm)	DMLC
8	Xio	Elekta Precise	80 leaf (10 mm)	SMLC
9	Eclipse	Varian 2100/600CD	120 leaf (5 mm/10 mm)	DMLC
10	Eclipse	Varian 2100EX	120 leaf (5 mm 10 mm)	DMLC

TPS version not given as most centres had at least one upgrade during the period of the trial.

ARPS, Addenbrookes Radiotherapy Planning System; DMLC, dynamic multileaf collimator; IMRT, intensity-modulated radiation therapy; MLC, multileaf collimator; SMLC, step and shoot multileaf collimator; TPS, treatment planning system; Linac, linear accelerator.

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Table 3. Equipment and set-up for measurements of IMRT dose points and dose distributions in 2007

Centre	Dose point detector	Phantom for dose point and dose distribution ^a	Independent calculation for MU	Dose distribution verification	Plane for dose distribution
1	0.015 cc IC	Cylindrical PX (25 d × 25 l) Cuboidal SW (30 × 30 × 15)	No	EDR2	Two coronal
2	0.6 cc IC	Cuboidal SW (30 × 30 × 20)	Yes — RadCalc	EDR2/GC	Two coronal
3	0.015 cc IC	Cuboidal PX (15 × 15 × 10) Cuboidal SW (40 × 40 × 15)	Yes — RadCalc	XV or diode array	Each field
4	0.016 cc IC	Cylindrical SW (16 d × 30 l)	Yes — MU check	PDIP	Each field
5	0.125 cc IC	Head and neck PX (30 × 15 × 15 or 45) Cuboidal SW (15 × 15 × 10) In house SW (24 × 29 × 20)	No	EDR2/GC	One coronal
6	0.6 cc IC	Cubic SW (20 × 20 × 20) Cuboidal SW (30 × 30 × 21)	Yes — transfer to second TPS	EDR2	Each field and one coronal
7	0.6 cc IC	Cuboidal SW (30 × 30 × 23)	Evaluating — Diamond	XV and EDR2 (valid. PDIP)	Each field and one coronal
8	0.6 cc IC	IC array (40 × 40 × 5)	Yes — Diamond	EDR2	Three axial
9	IC array	Cuboidal SW (30 × 30 × 10)	No	IC array	Each field
10	0.015 cc IC		No	XV	Each field

All dimensions are given in centimetres (cm).

d, diameter; EDR2, high-dose Kodak film; GC, gafchromic film; IC, ion chamber; l, length; MU, monitor unit; PDIP, Portal Dose Image Prediction package from Varian; PX, Perspex; SW, solid water; TPS, treatment planning system; XV, low-dose Kodak film.

^aIf a second phantom is given, then the first is for the dose point and the second for the dose distribution.

dose to the oral cavity. All centres had previously undertaken a study of their immobilisation system [30] to ascertain the appropriate margins to be used based on evaluation of set-up accuracy. Seven centres used a 3 mm margin to grow the primary and nodal CTVs to create PTVs, one centre used a 4 mm margin and the remaining two centres used a 5 mm margin.

Outlining exercise

All volumes were reviewed centrally. A report containing a description of any discrepancies with the reference volume and an indication to re-do the exercise where necessary was prepared for each participating clinician. In addition, password access to the reference volumes contained in the CD was given. Further discussion was undertaken, as necessary, via email or telephone.

For three submissions, there were no significant differences between the submitted and reference volumes. Small discrepancies relating to some of the finer details of target volume definition were described for four submissions. These were attributed to a 'learning curve effect' as well as to a degree of interobserver variability. These were anticipated to reduce with increasing clinician experience and hence a discussion took place, but resubmissions were not required. Large differences, mostly derived from lack of adherence to the trial target volume definition guidelines, were found for three submissions. These were mostly represented by inclusion (or lack of inclusion) of anatomical areas or specific nodal levels (in particular levels IIb and V) in either CTV1 or CTV2, and reflected areas of controversy in head and neck radiotherapy. The centres involved were asked to resubmit the exercise. Figure 1 shows examples of some of the submissions, with an example of an incorrect inclusion of a nodal group.

The review of the first three cases from each centre showed that all but one centre had followed the guidelines. Following further discussions, the single centre also adjusted their delineation to follow the guidelines. In total, 2 out of 18 review cases required replanning.

Planning exercise

IMRT plan

All IMRT plans used 6 MV photons. Seven centres used five beams and three centres used seven beams for the IMRT plan. Beam numbers were chosen by the planner based on experience and not according to which TPS was used. All centres chose an odd number of beams as this has been shown to provide the best range of beam angles with non-opposed fields [31]. All centres used an anterior field; five used equispaced fields and five adapted the beam directions. One centre used a non-coplanar beam with an inferior tilt to avoid the chin. All centres using custom beam directions did so in order to avoid beam direction restrictions of couch or immobilisation systems [32–34].

The position that was chosen for the isocentre varied between centres, including positioning on the set-up tattoos, at the geometric centre of the primary PTV or at the geometric centre of the combined PTVs. Some had continued local practice used for conformal treatments, others had chosen to minimise the shift from the scanning set-up marks or had chosen a position which was easy to set up. As the IMRT plans were not normalised to the isocentre, the position could be chosen to minimise set-up difficulties rather than for dosimetric reasons.

Four centres used collimator rotations ranging from a few degrees to a large range of angles. This was done to

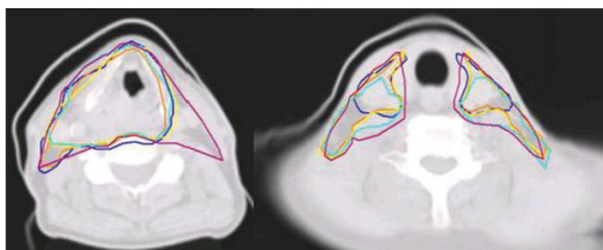


Figure 1. Examples of the volumes submitted for the delineation exercise, T2N0 squamous cell carcinoma of the right pyriform fossa. The left image shows a cross-section through the primary clinical target volume (CTV) and an example of an incorrect inclusion of level III nodes on the contralateral side. The right image is of the nodal CTV and shows an example of an incorrect exclusion of level V nodes on both sides.

achieve optimal multileaf collimator (MLC) fit to the volumes and also to smear out any tongue-and-groove leakage. The effects of this are leaf sequencer dependent, but MLC fit depends on leaf [35].

Although different patients were used for the IMRT and conventional planning exercises they were similar in terms of tumour size and depth and it is interesting to compare the average total MU used for each technique. For dynamic MLC (DMLC), the average total was 1222 (range 929–1975), and for step and shoot MLC (SMLC) it was 740 (570–985). Overall, the dynamically delivered plans used 65% more monitor units than the step and shoot techniques to deliver the same dose per fraction. The IMRT plans required a factor of 1.6 more MU for SMLC and 2.6 more MU for DMLC than the conventional plan (average of 470 MU per fraction for the phase 1 photon treatment). For SMLC the number of segments per beam ranged from 5 to 25. All plans were calculated on a 2.5 mm or 3 mm grid and normalised to either the mean or median PTV1.

Eight centres achieved the required dose constraints, with the remaining two being acceptably close (within 2% for the 95% isodose level) (Table 1). All centres achieved satisfactory plans with good coverage, with no correlation between beam angle, isocentre position or collimator rotation and dose compliance. IMRT plans were primarily assessed on “edited target volumes” which were brought 5 mm back from the skin. These were the volumes used for planning to avoid attempts by the optimiser to put too much dose into the build-up region. Original volumes were also checked to ensure that there were no hotspots in the skin-sparing region.

The cord and brainstem tolerance were set at 48 Gy and 55 Gy maximum doses, respectively [5], and these were not exceeded in all plans. Both absolute maximum dose and dose to 1 cm³ of the spinal cord were documented, as some planning systems calculated a very small high-dose “tail” which is not representative of the maximum dose received. This can be seen by the difference between the dose ranges achieved for the maximum and 1 cm³ (Table 1). One centre exceeded the 1 cm³ spinal cord tolerance by 0.2 Gy, but the maximum dose was acceptable. In cases in which the 1 cm³ tolerance was exceeded the positions of the 46 and 48 Gy isodose lines relative to the spinal cord would be checked. The brainstem dose range was wide as the acceptable maximum dose varied across centres. Five centres achieved between 22 and 24 Gy to the contralateral parotid gland, three centres achieved 26–28 Gy and two centres achieved 28–30 Gy. The average mean contralateral parotid dose achieved was 25.5 Gy, suggesting that, even for more difficult

planning scenarios, most centres would be able to achieve some level of sparing.

All contralateral doses under 24 Gy were delivered with dynamic IMRT using 5 mm leaves. All the centres using the SMLC technique had 1 cm MLC. It is likely that the differences in parotid sparing achieved are due to the leaf width rather than the delivery technique, and, as the volume of the contralateral parotid gland volume was 24.3 cm³, a 1 cm leaf is significant in size when conforming to this. The large range of ipsilateral parotid doses depended on whether or not the planner had attempted sparing as the protocol required sparing only of the contralateral gland.

Conventional plan

Five different TPSs were used for the conventional planning exercise. All centres used 6 MV for all fields, except one centre which used a 10 MV posterior neck field. The lateral fields utilised 10–15° wedges and three centres also used small lightly weighted supplementary boosts in the lateral fields. Neck nodes were treated using anterior and posterior fields (six centres) or anterior fields only (four centres). All fields were conformally shielded where appropriate. Five centres used a boost field to cover the primary PTV below the matchline, and three centres moved the matchline inferiorly to completely cover the primary volume by the lateral fields.

All centres added electron fields for the second phase at 40 Gy, delivering 10 Gy in five fractions to the contralateral nodes. For the ipsilateral nodes, seven centres delivered the remaining 25 Gy in 10 fractions (for both photons and electrons). The remaining three centres used 10 Gy in five fractions and then added a final phase of 15 Gy in five fractions. A range of electron energies, from 6 to 10 MeV were used, with the mode (50%) being 9 MeV.

Table 1 shows the range of doses achieved with the conventional plans. The data shown are of the PTV with no editing, and therefore some of these volumes came very close to the skin, in the dose build-up region. There was a large range of achieved doses on both the primary and nodal PTVs (particularly for the 99% volume, which included some low dose close to the skin) due to the variation in margins used by different centres, differences in planning system modelling of the build-up region of the beam, the dose grid used and how it was applied to the data set. This is particularly seen in the nodal PTV, where much of the volume is superficial. In no plan was it possible to treat the PTV and keep the

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parotid gland below tolerance, as the beam orientation required by the protocol was parallel opposed laterals to treat both PTVs. All the submitted exercises contained plans that were considered acceptable for inclusion within the trial.

Preliminary visits and meetings

A pre-trial QA visit was made to each centre. In the case of those centres that already had experience in IMRT, this took place after all the exercises had been submitted. In the case of the centres that had not yet started an IMRT programme, the visit tended to take place earlier to serve as a focal point for the multi-disciplinary members of the local implementation team to discuss the work which was needed to proceed.

The QA and planning meetings served to bring together groups of people using the same software and hardware for discussion as to how to achieve the best results from their equipment. In addition, several groups comprising the users of the different planning systems met separately to discuss commissioning and planning techniques for their systems.

Discussion

PARSPORT was the first randomised controlled trial comparing IMRT and conventional techniques in the UK. At the time, although few centres in the UK were routinely treating patients with IMRT, many were interested, in particular, in the opportunity to use this technique within a clinical trial setting. For those who had already started, it was also a means to audit and assess their service and discuss techniques and systems between different centres. Several groups were created within the trial to bring together centres with the same equipment and create forums for specific discussion points. Most were of the opinion that starting their IMRT programme within the robust framework of a clinical trial would speed up their implementation process and give them greater confidence. Data from the USA have shown that centres going through a QA accreditation process are better prepared to comply with the requirements of a trial protocol [36]. The visits, meetings and subgroups associated with the trial facilitated a forum for dissemination of skills and allowed learning in a structured environment.

The questionnaire highlighted the fact that, with no guidelines yet in place in the UK for IMRT verification, a large range of techniques and phantoms were being used for QA measurements. Although the majority reported that they aimed to achieve 3% per 3 mm (dose difference/distance to agreement) for gamma index parameters, at the start of the trial most stated that they did not yet have the volume of data to ascertain whether this was realistic in this anatomical location. It is in this area of pre-treatment verification where most changes have taken place over the period of the trial. This has been due to both the development of equipment and software as well as the increase in confidence and data. Most centres started with a heavy QA load of individual field films as well as combined field films and several dose points measured. It is now more common to measure at one dose point and to use an array or one

or two films for combined dose distributions or a portal dosimetry system. The dosimetry audit, which followed entry into the trial, also gave centres confidence that their IMRT QA programme was accurate and robust [18]. Since 2004, the national radiotherapy trials group [37] has streamlined its QA processes by launching the "National Baseline Questionnaire", which is used by all trials run within the group, and both the questionnaire and the information gathered are available to any other UK radiotherapy trials group.

The process document produced in each centre, which detailed all sections of the patient pathway, was found to be very useful in terms of structuring the pre-trial visit for discussion of all aspects of the trial. The main discussion points were based on issues that had arisen during the exercises, and primarily were an interpretation of the protocol and planning technique issues. The visiting QA physicist often reported on how other centres with similar equipment or experience had approached a task. The process document also served as an aid for centres new to IMRT to see which processes needed to be set up and evaluated, and as a template for documentation. A key part of the process document listed the time and intervals required for each part of the planning and treatment process. This allowed the multi-disciplinary team to assess realistically how quickly a patient could be treated after randomisation. Miles et al [38] showed that conventional head and neck treatment required more radiographer time due to the multiple-phase treatment and the repeat visits to the simulation suite, but that IMRT needed more physics time for planning and QA. However, it was expected that this would eventually reduce because a significant proportion of the time needed for IMRT was contributed by quality assurance measurements, which it is envisaged will be considerably reduced in the future.

The outlining exercise highlighted the importance of ensuring that guidelines are agreed upon and followed as there will always be an unavoidable degree of inter- and intraobserver variability. At the time of joining the study, 3D target volume definition was not routinely performed in all centres. With the increased use of 3D conformal techniques in head and neck cancer and the need to delineate targets to obtain DVHs, 3D delineation will become more routine and this is likely to become less of a learning issue. This exercise showed that the use of written instructions only can sometimes create quite an extended learning process and that discussion of specific examples is more productive and creates a steeper learning curve. We would also recommend that outlining exercises are undertaken in a centre's own planning system as the use of all the familiar delineation tools would smooth the transition from exercise to clinical practice.

Most centres found that by moving their conventional technique onto a 3D planning system with CT data they were able to make small adaptations to the technique which improved the dosimetry. Some centres chose to add small boost fields to improve the homogeneity of the dose in the target volumes, which was allowed within the protocol. Other changes included adapting the field sizes to fit the volume in 3D, changing to a single isocentre technique and reviewing all the phases summed together. Most centres are not currently in a

position to treat all their head and neck patients with an inverse planned IMRT technique; however, by altering their conventional technique to be CT planned many have improved the planning for other patients. During the period of the trial, most centres updated their electron code of practice to use the UK 2003 version [27], and several also upgraded their TPS to include more advanced Monte Carlo-based electron calculation algorithms. This prompted a review of their electron planning techniques and 3 out of the 10 centres now regularly use their TPS to check the dose distributions of electron fields.

The aim of the trial was to compare IMRT with conventional head and neck planning. The introduction of IMRT meant there was a need for intensive training to ensure all centres were standardised in their planning. This level of training is unusual for a trial, but necessary when implementation of a new technique is required. During each 1-day pre-trial visit, the majority of the time was spent on the planning system, discussing techniques for achieving the best plan. Hence, for this early IMRT trial, the need for training was an integral part of the QA process.

Learning to use an inverse planning optimisation module of a treatment planning system takes experience, but within the structure of a trial the planning goals are clear and an understanding can be gained of what it is possible to obtain from the system. Comparisons with other centres using the same system can also be made. Overall, the centres achieved steep learning curves when starting out with head and neck IMRT planning. Planning skills, such as use of collimator angles to avoid tongue-and-groove effects and to reduce MU and the use of beam angles to optimise avoidance of immobilisation and minimise unnecessary tissue irradiation, were used. Each centre was required to submit their first three patient plans for review, and several of these included planning discussions, typically regarding a return to local methods. Following this, all centres complied very well with the protocol as assessed by regular data collection, suggesting that the planning exercise and plan reviews were sufficient exercises to reach the required standard in learning the planning technique.

Since the PARSPORT trial started, the Radiotherapy Trials QA Group (RTTQA) has developed an IMRT accreditation programme (including a dosimetry audit) in collaboration with the Conventional or Hypofractionated High Dose IMRT for Prostate Cancer (CHHiP) and "IMPORT high" (Intensity Modulated and Partial Organ Radiotherapy) trials [37]. The aim is that for the first IMRT trial a full QA programme and audit, including outlining, planning, processes and techniques and a dosimetry audit, will be undertaken by each centre. Following this, the QA and audit for subsequent trials will be streamlined and reduced. The accreditation programme would also serve to provide audit for the implementation of a new technique in a radiotherapy centre.

Our experience in PARSPORT has shown that an early trial which includes the implementation of a new high-level technique requires a significant amount of training and an intensive QA programme. Subsequent trials can benefit from this by using the results from the first trial. However, we would recommend that outlining and

planning exercises form an integral part of all IMRT trial QA because volume delineation and dose distribution are fundamental to the aims of IMRT. We also recommend that the local TPS be used for all exercises so that techniques and skills learned are easily transferred into clinical use.

The implementation of a new radiotherapy technique within the quality assurance protocol of a multicentre trial can help to initialise consistent practice in that technique and improve the communication between different centres regarding the optimal manner to move forward and expand its use.

Conclusions

Before recruiting patients into the PARSPORT trial, all centres were required to undertake a comprehensive set of QA exercises to confirm that the volume delineation, planning techniques, pre-treatment verification and treatment would be of a consistent standard. After completing this process, all centres could create and verify sufficiently similar head and neck radiotherapy plans, in both arms of the trial, such that the data from all the centres could be analysed within this multicentre trial. All centres have achieved implementation of a comprehensive IMRT programme and all are now treating patients both within PARSPORT and on other head and neck radiotherapy protocols. The confidence in the IMRT process which the external audit provided also facilitated the participating centres in implementing IMRT in different sites.

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Paper 7

Articles

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial



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Summary

Background Xerostomia is the most common late side-effect of radiotherapy to the head and neck. Compared with conventional radiotherapy, intensity-modulated radiotherapy (IMRT) can reduce irradiation of the parotid glands. We assessed the hypothesis that parotid-sparing IMRT reduces the incidence of severe xerostomia.

Methods We undertook a randomised controlled trial between Jan 21, 2003, and Dec 7, 2007, that compared conventional radiotherapy (control) with parotid-sparing IMRT. We randomly assigned patients with histologically confirmed pharyngeal squamous-cell carcinoma (T1–4, N0–3, M0) at six UK radiotherapy centres between the two radiotherapy techniques (1:1 ratio). A dose of 60 or 65 Gy was prescribed in 30 daily fractions given Monday to Friday. Treatment was not masked. Randomisation was by computer-generated permuted blocks and was stratified by centre and tumour site. Our primary endpoint was the proportion of patients with grade 2 or worse xerostomia at 12 months, as assessed by the Late Effects of Normal Tissue (LENT SOMA) scale. Analyses were done on an intention-to-treat basis, with all patients who had assessments included. Long-term follow-up of patients is ongoing. This study is registered with the International Standard Randomised Controlled Trial register, number ISRCTN48243537.

Findings 47 patients were assigned to each treatment arm. Median follow-up was 44·0 months (IQR 30·0–59·7). Six patients from each group died before 12 months and seven patients from the conventional radiotherapy and two from the IMRT group were not assessed at 12 months. At 12 months xerostomia side-effects were reported in 73 of 82 alive patients; grade 2 or worse xerostomia at 12 months was significantly lower in the IMRT group than in the conventional radiotherapy group (25 [74%; 95% CI 56–87] of 34 patients given conventional radiotherapy vs 15 [38%; 23–55] of 39 given IMRT, $p=0\cdot0027$). The only recorded acute adverse event of grade 2 or worse that differed significantly between the treatment groups was fatigue, which was more prevalent in the IMRT group (18 [41%; 99% CI 23–61] of 44 patients given conventional radiotherapy vs 35 [74%; 55–89] of 47 given IMRT, $p=0\cdot0015$). At 24 months, grade 2 or worse xerostomia was significantly less common with IMRT than with conventional radiotherapy (20 [83%; 95% CI 63–95] of 24 patients given conventional radiotherapy vs nine [29%; 14–48] of 31 given IMRT; $p<0\cdot0001$). At 12 and 24 months, significant benefits were seen in recovery of saliva secretion with IMRT compared with conventional radiotherapy, as were clinically significant improvements in dry-mouth-specific and global quality of life scores. At 24 months, no significant differences were seen between randomised groups in non-xerostomia late toxicities, locoregional control, or overall survival.

Interpretation Sparing the parotid glands with IMRT significantly reduces the incidence of xerostomia and leads to recovery of saliva secretion and improvements in associated quality of life, and thus strongly supports a role for IMRT in squamous-cell carcinoma of the head and neck.

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Introduction

Radiotherapy is the main non-surgical treatment for squamous-cell carcinoma of the head and neck (HNSCC).¹ High rates of local tumour control can be achieved with 5-year survival greater than 80% for stage 1 and 2 and 60–70% for stage 3 and 4 tumours;² however, long-term late sequelae of radiotherapy are highly prevalent and have severe adverse effects on quality of life (QoL).^{3,4} Radiation-induced xerostomia is the most commonly reported late side-effect of radiotherapy to the head and

neck. Lack of saliva affects speech and swallowing and can accelerate dental caries.⁵

Intensity-modulated radiotherapy (IMRT) is a conformal radiotherapy technique that can spare the major salivary glands. Small phase 2 studies have shown that a reduction in radiation to the parotid glands (to 24–26 Gy) through parotid-sparing IMRT aids recovery of saliva flow.^{6–8} We report results of the first multicentre randomised controlled trial to assess parotid-sparing IMRT in patients with HNSCC.

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*Details given in the webappendix (p 2)

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Methods

Participants

We undertook a phase 3 randomised controlled trial at six UK radiotherapy centres (recruitment between Jan 21, 2003, and Dec 7, 2007). Eligible patients had histologically confirmed HNSCC that arose from the oropharynx or hypopharynx and were to be treated by radiotherapy either primarily or postoperatively without concomitant chemotherapy. These patients were at high risk of radiation-induced xerostomia—ie, if they were treated with conventional radiotherapy the estimated mean dose to both parotid glands would be greater than 24 Gy. Patients had WHO performance status 0 or 1 and any stage of disease except M1. Patients were required to attend regular follow-up, undergo salivary flow measurements, and complete self-assessed QoL questionnaires.

Exclusion criteria included previous head or neck radiotherapy; previous malignancy except non-melanoma skin cancer; pre-existing salivary gland disease; tumour involvement of the parotid glands; or previous or concurrent illness that would compromise completion of treatment or follow-up. Prophylactic amifostine or pilocarpine was not permitted. Patients who had received neoadjuvant chemotherapy were eligible.

All patients provided written informed consent. PARSPORT (CRUK/03/005) was approved by the national South-West Multicentre Research Ethics Committee (MREC 03/6/79) and the local ethics committees of all participating centres. Our trial was sponsored by the Royal Marsden NHS Foundation Trust and undertaken in accordance with the principles of Good Clinical Practice.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to parotid-sparing IMRT or conventional radiotherapy (control). Independent randomisation was via telephone to the Clinical Trials and Statistics Unit at the Institute of Cancer Research (ICR-CTSU). Computer-generated random permuted blocks were used; stratification was by treatment centre and tumour site. Treatment allocation was not masked; however, the patient was not informed of the treatment until they had completed the baseline QoL questionnaires.

Procedures

Staging investigations included examination under anaesthetic, tumour biopsy, diagnostic CT or MRI of head and neck, chest radiograph, full blood count, and biochemistry. In postoperative patients, histology reports that documented the extent of surgical resection were required.

The protocol for target volume definition and treatment planning has been previously described.⁹ All patients underwent CT-planned radiotherapy with either three-dimensional conformal radiotherapy with parallel opposed lateral fields (conventional radiotherapy) or parotid-sparing IMRT. The conventional radiotherapy regimen was the national standard of care in the UK and most other countries at the time our trial was designed. In both treatment groups, the primary tumour and involved lymph nodes were treated with 65 Gy in 30 daily fractions given Monday to Friday. 60 Gy in 30 fractions was delivered to postoperative patients unless there was macroscopic residual disease in which case 65 Gy in 30 fractions was given. Nodal groups at risk of harbouring occult metastatic disease received a biologically equivalent dose of either 50 Gy in 25 daily fractions (conventional radiotherapy) or 54 Gy in 30 fractions (IMRT). For IMRT patients a planning constraint of less than 24 Gy to the whole contralateral parotid gland was used.^{8,10} For quality assurance, plans were assessed from all centres for protocol compliance and dosimetric consistency.^{10,11}

Acute side-effects were graded weekly with National Cancer Institute Common Toxicity Criteria (version 3)¹² during radiotherapy and until 8 weeks after treatment. Late radiotherapy side-effects were assessed with the Late Effects of Normal Tissues Subjective-Objective Management Analytic (LENT SOMA)^{13,14} and the Radiation Therapy Oncology Group (RTOG)¹⁵ scoring systems at 3, 6, 12, 18, and 24 months after radiotherapy. Salivary flow

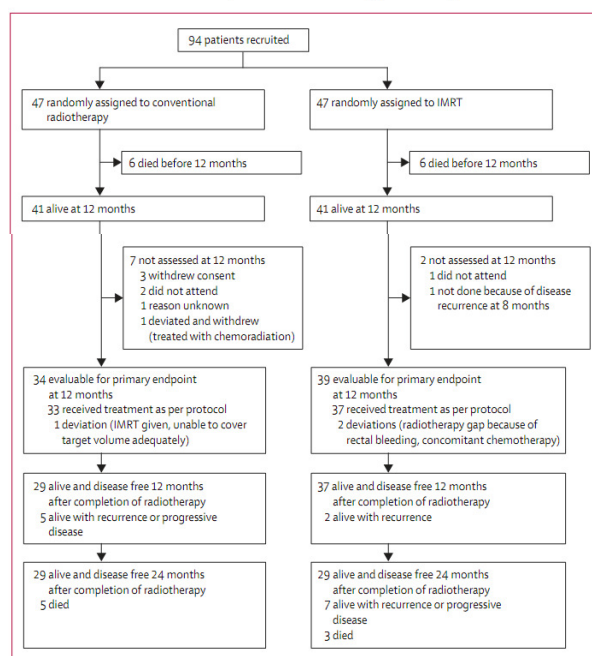


Figure 1: Study profile

IMRT=intensity-modulated radiotherapy.

measurements were done before radiotherapy, at week 4 of radiotherapy, and at 2 weeks, 3, 6, 12, 18, and 24 months after radiotherapy. Unstimulated and sodium-citrate-stimulated parotid saliva from each parotid duct orifice and floor of mouth saliva were collected by standard methods.^{7,8} After treatment, clinical follow-up was monthly in year 1, every 8 weeks in year 2, then every 3–6 months until the end of year 5. Assessments were not blinded to treatment allocation.

Patient-reported QoL was collected with questionnaire booklets that contained the European Organization for Research and Treatment of Cancer (EORTC) QLQC30 quality-of-life instrument¹⁶ (which measures generic cancer-related QoL), the associated head and neck specific module HN35,¹⁷ and the modified xerostomia questionnaire.⁸ Patients completed the baseline booklet in the clinic before randomisation. Follow-up booklets were sent directly to the patients' homes at 2 weeks, 3, 6, 12, 18, and 24 months after radiotherapy.

Our primary objective was to assess late side-effects. Our primary endpoint, agreed in discussion with the independent trial steering committee, was the proportion of patients with xerostomia of grade 2 or worse by the LENT SOMA subjective side-effect scale 1 year after treatment. This endpoint was chosen because it assesses an abnormal symptom (ie, "partial but persistent or complete dryness" or worse) measured by a reliable and sensitive method for scoring late side-effects in HNSCC.¹⁸ We decided on 12 months *a priori* as a clinically appropriate time at which to make a valid assessment of late effects.

Secondary endpoints were the proportion of patients with any measurable salivary flow after radiotherapy, acute and other late radiation side-effects, QoL that included xerostomia-related QoL as measured by the modified xerostomia questionnaire, locoregional progression-free survival (PFS), and overall survival. We defined locoregional PFS as time from randomisation to locoregional recurrence or progressive disease as defined by Response Evaluation Criteria in Solid Tumours.¹⁹ We defined overall survival as time from randomisation to death from any cause.

Statistical analysis

Phase 2 studies had reported reduction in salivary flow rates of 90% at 1–3 months compared with preradiotherapy rates with conventional therapy and of 40% with IMRT.^{7,20–22} If we assume a 1-year xerostomia rate of 90% in the conventional radiotherapy group²³ a sample size of 84 patients is needed to detect a 30% absolute difference in LENT SOMA of grade 2 or worse xerostomia between the study groups (90% power, 5% two-sided significance). In March, 2007, the independent data monitoring committee and the trial steering committee approved an increase in the target sample size to 84 evaluable patients (ie, alive 1 year after the end of radiotherapy) that was anticipated to be achievable with 100 randomly assigned patients. In

December, 2007, both committees approved closure of recruitment after 94 patients had been randomly assigned to the study groups with the expectation that this would provide sufficient evaluable patients to allow robust statistical analysis. Our trial was not powered to reliably assess small differences in locoregional PFS or overall survival, although these are reported for completeness.

Our analysis was done on an intention-to-treat basis, with all patients who had a 12-month xerostomia assessment included. We compared the proportion of patients with grade 2 or worse xerostomia between groups with a χ^2 test. We assessed the sensitivity of results by repeating analyses of the primary endpoint with patients

	Conventional radiotherapy (n=47)	IMRT (n=47)
Mean age at randomisation (years)	57.3 (10.2; 37.5–82.8)	59.5 (9.2; 44.1–77.1)
Number of women	12 (26%)	14 (30%)
WHO performance status		
0	42 (89%)	41 (87%)
1	5 (11%)	6 (13%)
Tumour site		
Oropharynx	40 (85%)	40 (85%)
Hypopharynx	7 (15%)	7 (15%)
Tumour stage		
T1	6 (13%)	6 (13%)
T2	27 (57%)	22 (47%)
T3	11 (23%)	16 (34%)
T4	3 (6%)	3 (6%)
Nodal stage		
N0	16 (34%)	23 (49%)
N1	9 (19%)	15 (32%)
N2a	7 (15%)	2 (4%)
N2b	10 (21%)	6 (13%)
N2c	1 (2%)	0
N2 (unknown)	1 (2%)	1 (2%)
N3	3 (6%)	0
AJCC* stage		
1 and 2	8 (17%)	15 (32%)
3 and 4	39 (83%)	32 (68%)
Neoadjuvant chemotherapy		
Yes	19 (40%)	20 (43%)
No	28 (60%)	27 (57%)
Type of radiotherapy		
Primary	32 (68%)	39 (83%)
Postoperative	15 (32%)	8 (17%)
Radiotherapy dose (Gy)		
Median dose to primary tumour and involved nodes	65.0 (65.0–65.0; 44)	65.0 (65.0–65.0; 47)
Median dose to elective nodes	50.0 (50.0–50.1; 43)	54.0 (54.0–54.1; 47)
Mean contralateral parotid dose†	61.0 (54.6–63.8; 43)	25.4 (23.2–28.0; 46)
Mean ipsilateral parotid dose†	61.0 (57.0–64.4; 43)	47.6 (39.9–54.5; 46)

Data are mean (SD; range), n (%), or median (IQR; n). IMRT=intensity-modulated radiotherapy. *American Joint Committee on Cancer—groupings based on TNM staging data collected. †Mann-Whitney test $p < 0.0001$.

Table 1: Baseline characteristics and treatment details

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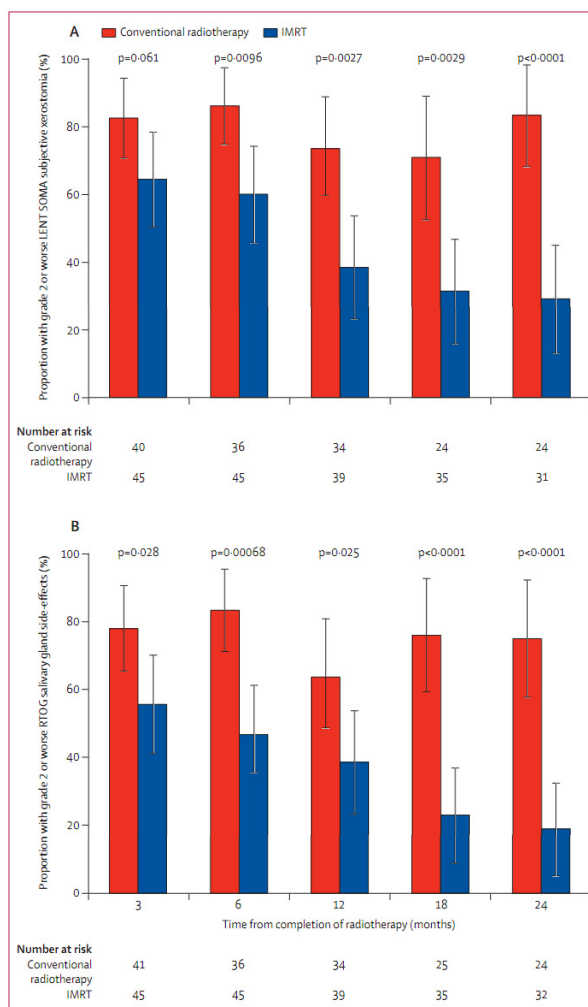


Figure 2: Proportion of patients reporting grade 2 or worse LENT SOMA subjective xerostomia and RTOG salivary gland side-effects

p values quoted compare proportions with grade 2 or worse side-effects in each group with a χ^2 test. Error bars represent 95% CIs. IMRT=intensity-modulated radiotherapy. LENT SOMA=Late Effects of Normal Tissues Subjective-Objective Management Analytic. RTOG=Radiation Therapy Oncology Group.

censored 1 month before any disease recurrence, in case recurrence could adversely affect salivary flow, and by excluding patients whose side-effect assessment was not within 2 months either side of its expected date. We have

not presented these sensitivity analyses because they gave similar results to the main analysis. Odds of grade 2 or worse xerostomia at 12 and 24 months were calculated with a logistic-regression model. We present unadjusted odds ratios (ORs) and ORs adjusted for tumour site (oropharynx or hypopharynx), stage of disease (1 and 2 or 3 and 4), and radiotherapy indication (radical or postoperative). All other analyses are unadjusted.

We compared the proportions of patients with any measurable saliva flow and proportions ever reporting grade 2 or worse acute and late side-effects between treatment groups with Fisher's exact tests. For LENT SOMA scales, we used the maximum of the subjective, objective, management, and analytic component scores. We calculated CIs for differences in proportion between groups with a normal approximation. To make some adjustment for multiple testing we used a significance level of 1% for all secondary side-effects, sialometry, and QoL endpoints and accordingly we provide 99% CIs. Acute and late side-effects in our report were those where side-effects of grade 2 or worse were experienced by at least 20% of patients in either group or those where proportions were significantly different between treatment groups.

We calculated QoL scores with standard algorithms with a higher score suggesting poorer QoL on all scales except EORTC global health status, where a higher score suggests better QoL.²⁴ We deemed differences in EORTC QoL scores of 10 points or more clinically significant in line with EORTC guidelines.²⁵ The primary QoL analysis included all completed questionnaires. We did a sensitivity analysis after censoring at 1 month before disease recurrence or progressive disease. We compared mean changes in EORTC QoL and xerostomia questionnaire item scores from baseline between groups by two-sample *t* tests.

We used generalised estimating equations (GEE), adjusting for the correlations in multiple measurements from the same patient (with an exchangeable correlation matrix) to account for the longitudinal nature of the xerostomia and QoL data. A pragmatic approach to modelling was taken, with treatment-by-time interaction terms included if they were identified in advance as clinically relevant or they were statistically significant. A GEE logistic regression model was fitted with xerostomia (grades 0 and 1 vs grades 2–4) as the response and allocated treatment, days since the completion of radiotherapy, and the interaction between the two as covariates. QoL GEE models also included terms for baseline score for the item of interest.

For survival-related endpoints, alive and disease-free patients were censored at date of last follow-up. We compared treatment groups with the log-rank test. Hazard ratios (HRs) with 95% CIs were obtained from Cox proportional hazards regression models with HRs of less than one favouring IMRT. The proportionality assumption of the Cox model held when tested with Schoenfeld residuals.

Our analyses were based on a database snapshot frozen on May 14, 2010, and were done in STATA version 10. ICR-CTSU had overall responsibility for trial coordination. Data collation, central statistical monitoring of data, and all interim and final analyses were performed at ICR-CTSU. The trial management group was responsible for the day to day running of the trial. The trial was overseen by an independent trial steering committee. The independent data monitoring committee regularly reviewed emerging safety and efficacy data in confidence. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN48243537.

Role of the funding source

The funding source provided peer-reviewed approval for the trial but had no other role in study design, collection, analysis, interpretation of data, or writing of the report.

The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. JPM, RPA'H, and EH also had full access to all the data.

Results

Figure 1 shows the trial profile. We randomly allocated 94 patients from six UK radiotherapy centres to treatment with either IMRT or conventional radiotherapy—47 patients to each group. One patient assigned to the conventional radiotherapy group was deemed ineligible because they were due to be treated with chemoradiation (no follow-up data are available for this patient). Table 1 shows the patient and tumour characteristics at baseline and treatment details. 39 patients (41%) received neoadjuvant chemotherapy (details of specific chemotherapy drugs and doses were not collected). Mean dose to the whole

	Conventional radiotherapy						IMRT					
	N	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	N	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Acute side-effects*												
Mucositis/stomatitis (clinical)	44	0	1 (2%)	16 (36%)	27 (61%)	0	46	1 (2%)	2 (4%)	14 (30%)	29 (63%)	0
Rash (dermatitis)†	44	0	3 (7%)	17 (39%)	24 (55%)	0	47	1 (2%)	9 (19%)	21 (45%)	15 (32%)	1 (2%)
Mucositis/stomatitis (functional/symptomatic)	39	1 (3%)	0	21 (54%)	17 (44%)	0	40	2 (5%)	3 (8%)	11 (28%)	24 (60%)	0
Dysphagia	44	0	1 (2%)	26 (59%)	17 (39%)	0	47	1 (2%)	6 (13%)	17 (36%)	23 (49%)	0
Pain	44	0	5 (11%)	23 (52%)	16 (36%)	0	47	1 (2%)	10 (21%)	19 (40%)	16 (34%)	1 (2%)
Fatigue‡	44	0	26 (59%)	12 (27%)	6 (14%)	0	47	2 (4%)	10 (21%)	23 (49%)	12 (26%)	0
Xerostomia	44	0	4 (9%)	35 (80%)	5 (11%)	..	47	0	14 (30%)	20 (43%)	13 (28%)	..
Salivary gland changes	44	0	2 (5%)	40 (91%)	2 (5%)	0	47	0	11 (23%)	30 (64%)	6 (13%)	0
Weight loss	40	2 (5%)	23 (58%)	14 (35%)	1 (3%)	..	44	9 (20%)	14 (32%)	19 (43%)	2 (5%)	..
Hair loss/alopecia	44	14 (32%)	22 (50%)	8 (18%)	0	..	47	7 (15%)	12 (26%)	12 (26%)	1 (2%)	..
RTOG late side-effects§												
Salivary gland¶	42	1 (2%)	3 (7%)	26 (62%)	12 (29%)	0	46	0	12 (26%)	32 (70%)	2 (4%)	0
Mucous membranes	42	1 (2%)	23 (55%)	17 (40%)	1 (2%)	0	46	4 (9%)	29 (63%)	12 (26%)	1 (2%)	0
Oesophagus	42	22 (52%)	11 (26%)	8 (19%)	1 (2%)	0	46	19 (41%)	17 (37%)	8 (17%)	2 (4%)	0
Joint (temporomandibular joint disorder)	42	22 (52%)	11 (26%)	9 (21%)	0	0	46	31 (67%)	11 (24%)	3 (7%)	1 (2%)	0
LENT SOMA late side-effects§												
Salivary gland‡	41	0	3 (7%)	12 (29%)	14 (34%)	12 (29%)	46	0	8 (17%)	19 (41%)	15 (33%)	4 (9%)
(xerostomia)‡		0	3 (7%)	19 (46%)	14 (34%)	5 (12%)		0	8 (17%)	31 (67%)	4 (9%)	3 (7%)
Mucosa**	41	1 (2%)	9 (22%)	17 (41%)	9 (22%)	5 (12%)	46	1 (2%)	19 (41%)	11 (24%)	11 (24%)	4 (9%)
Oesophagus††	41	15 (37%)	15 (37%)	4 (10%)	5 (12%)	2 (5%)	46	20 (43%)	16 (35%)	4 (9%)	4 (9%)	2 (4%)
(dysphagia)		20 (49%)	16 (39%)	3 (7%)	2 (5%)	0		21 (46%)	16 (35%)	5 (11%)	3 (7%)	1 (2%)
Skin‡‡	41	5 (12%)	19 (46%)	11 (27%)	5 (12%)	1 (2%)	46	10 (22%)	24 (52%)	10 (22%)	2 (4%)	0
Larynx§§	41	16 (39%)	15 (37%)	7 (17%)	2 (5%)	1 (2%)	46	16 (35%)	22 (48%)	8 (17%)	0	0
Mandible¶¶	41	13 (32%)	16 (39%)	9 (22%)	3 (7%)	0	46	19 (41%)	11 (24%)	12 (26%)	3 (7%)	1 (2%)
Ear	41	19 (46%)	12 (29%)	7 (17%)	3 (7%)	0	46	27 (59%)	13 (28%)	6 (13%)	0	0

Data are n (%). IMRT=intensity-modulated radiotherapy. RTOG=Radiotherapy Oncology Group. LENT SOMA=Late Effects of Normal Tissues Subjective-Objective Management Analytic. *Maximum Common Toxicity Criteria score during and up to 8 weeks post radiotherapy. †p for trend 0.01<ps0.05. ‡p for trend 0.001<ps0.01. §Maximum score between 3 and 24 months post radiotherapy. ¶p for trend ps0.001. ||Worst of subjective (xerostomia), objective (saliva flow), and management (xerostomia) grades. **Worst of subjective (pain, dysphagia, taste alteration), objective (mucosal integrity, weight), and management (pain, ulcer, dysphagia, taste alteration) grades. ††Worst of subjective (dysphagia, pain), objective (weight loss, stricture, ulceration, bleeding, anaemia), and management (dysphagia/stricture, weight loss, pain/ulceration, bleeding) grades. ‡‡Worst of subjective (roughness, sensation), objective (oedema, alopecia, pigmentation change, ulcer/necrosis, telangiectasia, fibrosis/scar, atrophy/contraction), and management (dryness, sensation, ulcer, oedema, fibrosis/scar) grades. §§Worst of subjective (pain, voice hoarseness, breathing), objective (oedema, mucosal integrity, respiration), and management (pain, hoarseness, respiration) grades. ¶¶Worst of subjective (pain, mastication, denture use, trismus), objective (exposed bone, trismus), and management (pain, bone, trismus/mastication) grades. |||Worst of subjective (pain, tinnitus, hearing), objective (skin, hearing), and management (pain, skin, hearing loss) grades.

Table 2: Maximum acute and late side-effect grades by treatment group

	Conventional radiotherapy		IMRT	
	No measurable salivary flow* (n=25)	Measurable salivary flow (n=0)	No measurable salivary flow (n=18)	Measurable salivary flow (n=16)
Subjective xerostomia better than grade 2	6 (24%)	0	10 (56%)	12 (75%)
Subjective xerostomia grade 2 or worse	19 (76%)	0	8 (44%)	4 (25%)

Fisher's exact test for association (treatment groups combined) $p=0.018$. LENT SOMA=Late Effects of Normal Tissues Subjective-Objective Management Analytic. IMRT=intensity-modulated radiotherapy. *Measurable salivary flow was defined as any saliva collected from the Lashley cup apparatus.

Table 3: Concordance between unstimulated contralateral saliva flow and LENT SOMA subjective xerostomia at 12 months

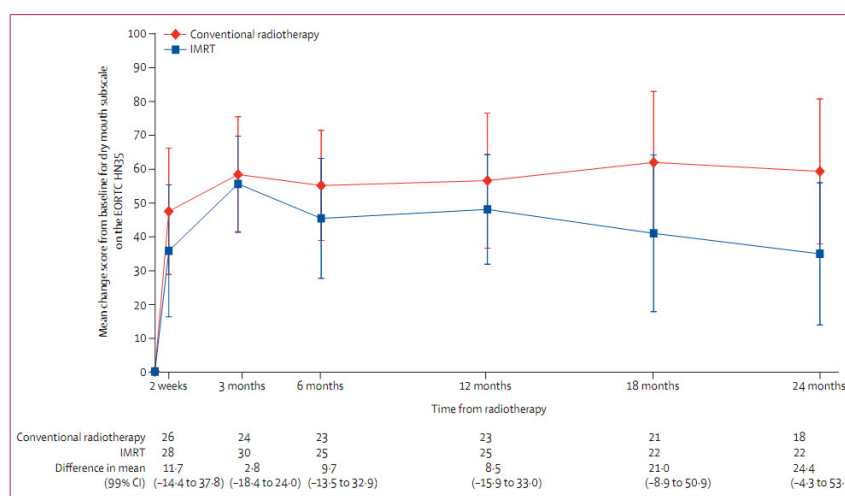


Figure 3: Mean EORTC HN35 dry mouth subscale score changes from baseline

IMRT=intensity-modulated radiotherapy. EORTC HN35=European Organization for Research and Treatment of Cancer head and neck specific module HN35.

contralateral parotid was significantly less in the IMRT group ($p<0.0001$; table 1). 45 of 47 patients randomly allocated to receive conventional radiotherapy and 45 of 47 randomly assigned to receive IMRT completed radiotherapy as per protocol; 33 of the 34 patients evaluable for the primary outcome in the conventional radiotherapy group and 37 of 39 patients evaluable for the primary endpoint in the IMRT group completed radiotherapy as per protocol (figure 1). Median follow-up in alive patients was 44.0 months (IQR 30.0–59.7).

At each timepoint from 3 to 24 months, a smaller proportion of IMRT patients reported grade 2 or worse LENT SOMA subjective xerostomia compared with conventional radiotherapy (figure 2).

Of the 76 patients who had grade 2 or worse xerostomia during their follow-up, 62 (82%) first reported symptoms at 3 months: 33 (87%) of 38 patients in the conventional radiotherapy group versus 29 (76%) of 38 in the IMRT group. At 12 months, there were significantly fewer cases of xerostomia in the IMRT group (25 [74%, 95% CI

56 to 87] of 34 in the conventional radiotherapy group vs 15 [38%, 23 to 55] of 39 in the IMRT group), and the absolute reduction was 35% (95% CI 14 to 56; $p=0.0027$). At 24 months, 20 (83%, 63 to 95) of 24 patients in the conventional radiotherapy group reported xerostomia versus nine (29%, 14 to 48) of 31 in the IMRT group, and the absolute reduction was 54% (32 to 76; $p<0.0001$). These differences equate to ORs of 0.23 (0.08 to 0.61) at 12 months and 0.08 (0.02 to 0.31) at 24 months. Adjusted ORs were 0.23 (0.08 to 0.65) at 12 months and 0.05 (0.01 to 0.26) at 24 months. Exploratory GEE analyses showed similar patterns to other analyses presented here (data not shown). The proportion of patients that reported grade 2 or worse xerostomia at 12 months did not differ by tumour site, radiotherapy indication (primary vs postoperative), stage of disease, or use of neoadjuvant chemotherapy (data not shown). A similar pattern was seen over time and between treatment groups when xerostomia was scored with the RTOG scale (figure 2).

The only recorded acute adverse event of grade 2 or worse to differ between treatment groups (at the 1% significance level) was fatigue (table 2): 18 (41%; 95% CI 23 to 61) of 44 patients in the conventional radiotherapy group versus 35 (74%; 55 to 89) of 47 in the IMRT group ($p=0.0015$). Of note, at 12 months, grade 3 or worse dysphagia was reported by two (5%) of 40 patients in the conventional radiotherapy group and four (9%) of 46 in the IMRT group.

We recorded baseline sialometry in 80 patients, all of whom had measurable salivary flow. At 12 months unstimulated saliva flow from the contralateral parotid gland was noted in 16 (47%) of 34 patients in the IMRT group compared with none of 25 in the conventional radiotherapy group ($p<0.0001$). Corresponding data at 24 months were seven (44%) of 16 in the IMRT group versus none of 15 in the conventional radiotherapy group ($p=0.0068$). Significant differences were also noted in stimulated saliva flow from the contralateral parotid at 12 months ($p<0.0001$). No significant differences between the random assigned groups were seen in proportions with unstimulated or stimulated flow from either the ipsilateral parotid or floor of mouth. Strong concordance was noted between measurable contralateral saliva flow and grade 2 or worse xerostomia (table 3).

Mean changes in global health status from baseline to 12 months were 1.1 (95% CI -9.9 to 12.1) for conventional radiotherapy versus 3.0 (-11.9 to 17.9; $p=0.78$) for IMRT. Changes at 24 months were -2.8 (-17.1 to 11.6) for conventional radiotherapy versus 8.3 (-6.6 to 23.2) for IMRT, corresponding to a between group difference in change scores of 11.1 (-9.0 to 31.2; $p=0.14$). No statistically significant differences in change from baseline between groups were noted for any QLQC30 subscale scores (data not shown).

In both study groups, HN35 subscale scores for dry mouth, senses, and sticky saliva were significantly worse than baseline at 12 months. Figure 3 shows mean increases from baseline from 2 weeks to 24 months in dry mouth subscale score, by treatment group. Mean increases from baseline at 12 months in the dry mouth subscale were 56.5 (95% CI 36.5 to 76.5; $p<0.0001$) for conventional radiotherapy and 48.0 (31.8 to 64.2; $p<0.0001$) for IMRT. Mean increases at 24 months were 59.3 (37.8 to 80.7; $p<0.0001$) for conventional radiotherapy and 34.8 (13.8 to 55.9; $p<0.0001$) for IMRT. At both time points, smaller score changes were noted in the IMRT group than in the conventional radiotherapy group, although these were not significant at the 1% level.

In the GEE model for dry mouth the main treatment coefficient was -6.6 (95% CI -21.5 to 8.3; $p=0.25$) with a treatment-by-time interaction term of -0.03 (-0.06 to 0.00; $p=0.017$), suggesting the difference in dry mouth between treatment groups increases over time. Censoring at recurrence had a negligible effect on QoL results, although the interaction term from the GEE analysis

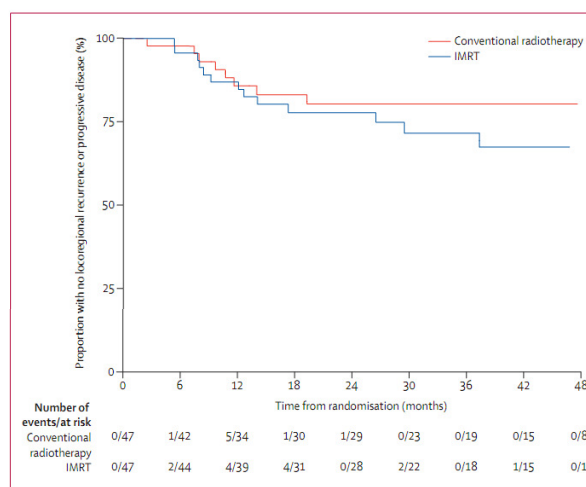


Figure 4: Kaplan-Meier plot of locoregional progression-free survival by treatment group. Hazard ratio 1.53 (95% CI 0.63 to 3.70). Log-rank test $p=0.34$. 2-year locoregional progression-free survival estimates for conventional radiotherapy 80% (95% CI 65 to 90) and for IMRT 78% (62 to 87); absolute difference 3% (-15 to 20). IMRT=intensity-modulated radiotherapy.

became less statistically significant (coefficient -0.02; $p=0.080$).

The xerostomia questionnaire was only completed by 39 patients at baseline and 12 months and by 33 patients at baseline and 24 months (compared with 73 reporting the primary endpoint at 12 months and 55 at 24 months). In both treatment groups all eight xerostomia questionnaire items were significantly worse at 12 and 24 months than at baseline and although the changes were smaller in the IMRT group, no statistically significant differences between group changes were noted (webappendix p 1).

Overall, there were seven locoregional recurrences in the conventional radiotherapy group: five in the high-dose volume and two in both the high-dose volume and electively irradiated neck. In the IMRT group there were 12 locoregional recurrences: 11 in the high-dose volume and one in the electively irradiated neck. No patients had a recurrence in the spared parotid tissue. 2-year locoregional PFS was 80% (95% CI 65 to 90) in the conventional radiotherapy group and 78% (62 to 87) in the IMRT group (absolute difference 3%, 95% CI -15 to 20; HR 1.53, 95% CI 0.63 to 3.70; log-rank $p=0.34$; figure 4).

32 deaths have been reported so far (18 in the conventional radiotherapy group vs 14 in the IMRT group; HR for overall survival 0.68, 95% CI 0.34 to 1.37). Of these deaths, 20 were due to head and neck cancer (ten in the conventional radiotherapy group vs ten in the IMRT

See Online for webappendix

group). Other causes of death in the conventional radiotherapy group were second (non-head-and-neck) primary cancer (four patients), cardiac (two), gastrointestinal complications (one), and suicide (one); and in the IMRT group were infection (two), second primary cancer (one), and gastrointestinal complications (one). Estimated 2-year overall survival was 76% (95% CI 60 to 86) with conventional radiotherapy and 78% (63 to 88) with IMRT (absolute difference 2%, 95% CI -20 to 16).

Discussion

Our trial showed a significant reduction of radiation-induced xerostomia for patients treated with IMRT compared with conventional radiotherapy by use of both LENT SOMA and RTOG scales. Furthermore, we showed recovery of saliva flow by quantitative measurements, and improvements on QoL measures associated with xerostomia. To our knowledge our trial is the first to show that parotid-sparing IMRT reduces xerostomia in HNSCC (panel). A consistently higher QLQC30 Global and HN35 dry mouth QoL score was reported in patients who received IMRT; between group differences at 24 months were clinically but not statistically significant. Xerostomia questionnaire results showed changes in favour of IMRT in all eight questions but these differences were not large enough to reach statistical significance, probably because of the small number of patients that completed this questionnaire. Although an association between measurable saliva flow and presence of grade 2 or worse xerostomia was recorded, there was not perfect concordance. We postulate that this could be because of differences in patient perception of the xerostomia symptom or because of other factors such as submandibular gland or oral cavity dose or comorbidity.

Panel: Research in context

Systematic review

Intensity modulated radiotherapy (IMRT) allows focused radiation delivery to tumours. In patients with head and neck cancer it has been used to reduce the irradiation of salivary tissue to prevent radiation-induced xerostomia. Before the design of our randomised trial, a few small single centre experiences had been published and a review of the published work on IMRT had been done.²⁶ No randomised trials were identified. During the recruitment period of the PARSPORT trial two smaller randomised trials were reported in nasopharyngeal cancer from centres in Asia, and several other single institutional experiences were reported.^{27,28}

Interpretation

Our trial is the largest randomised trial of IMRT in head and neck cancer, and the only trial addressing squamous-cell carcinoma, the predominant form seen worldwide. Our trial shows that IMRT reduces patient-reported xerostomia, allows recovery of salivary flow, and improves quality of life after treatment compared with conventional radiotherapy.

Detailed analyses of the distribution of dose to the salivary tissue including parotid glands and other minor salivary glands, and its correlation with clinical outcomes are ongoing. Initial results suggest that there is no correlation between submandibular gland dose and xerostomia.

A limitation of our trial was that it was not possible to mask the treatments from patients or clinicians because of differences in treatment delivery. However, results that relate to multiple secondary endpoints support the primary analysis and the size of the observed effect is unlikely to be due entirely to assessment or reporting bias. After our trial was designed, several small non-randomised studies^{29–31} and one case-control study³² of parotid-sparing IMRT have been published with a range of endpoints including saliva flow rate, patient-reported symptoms, and QoL. These studies reported apparent improvements for IMRT over conventional radiotherapy. Two small single-institution randomised phase 3 trials of IMRT in nasopharyngeal cancer have also reported benefits of IMRT over conventional radiotherapy. Pow and colleagues²⁷ reported an increase in stimulated whole saliva flow rate in patients receiving IMRT in a randomised trial of 51 patients with early-stage nasopharynx cancer. QoL was assessed with EORTC QLQC30, HN35, and the SF36 health survey and although QoL scores for some domains were better for IMRT patients, no improvements in patient-reported dry mouth symptoms on the HN35 questionnaire were noted. Kam and colleagues²⁸ reported a reduction in observer-rated severe xerostomia (RTOG grade 2 or worse) with IMRT (39% vs 82%; $p=0.001$) in 60 patients with early-stage nasopharyngeal cancer. The results of the PARSPORT trial are thus likely to be generalisable to all head and neck tumours for which conventional radiotherapy is used.

In our study, fewer cases of acute dermatitis were recorded in patients treated with IMRT than in those treated with conventional radiotherapy, although differences were not statistically significant at the 1% level, probably because of reduced dose to skin. The proportions of patients that reported grade 2 or worse acute xerostomia and grade 2 or worse salivary gland changes also showed reductions, albeit not statistically significant (table 2). Late xerostomia side-effects thus accord with acute side-effects; this suggests that late radiation-induced xerostomia is a consequential effect. We did not attempt to spare the submandibular or mucosal minor salivary glands within the planning target volume in our trial. It is possible that further reductions in severe xerostomia can be achieved by sparing these tissues, but this might risk underdosing crucial target tissues. Unexpectedly, acute fatigue was greater in patients treated with IMRT, which could be due to the greater radiation dose to non-tumour tissues. In an unplanned dosimetry review in a subset of patients, mean radiation doses to the posterior fossa were 20–30 Gy in the patients treated with IMRT compared with about 6 Gy in patients treated with conventional

radiotherapy, which could account for the recorded difference in acute radiation fatigue. Late fatigue data were not collected because lethargy is not a recognised long-term side-effect of radiotherapy. There was no significant association between the giving of neoadjuvant chemotherapy and either acute fatigue or xerostomia (data not shown). The addition of concurrent chemotherapy to altered fractionation radiotherapy remains experimental and was not used in our study. Further research is needed to establish the effect of concurrent chemotherapy on xerostomia. Apart from salivary gland changes and radiation-induced xerostomia, other late side-effects of conventional radiotherapy were not altered by IMRT.

Our trial was too small to detect small differences in, or conclude non-inferiority of, locoregional PFS or overall survival. Although patients continue to be followed up for long-term survival, to show non-inferiority in overall survival to no more than 5% at 2 years (80% power, one-sided 5% significance) would need a randomised controlled trial of more than 900 patients. In this, and other, head and neck IMRT studies most tumour recurrences happen within the high-dose volume. Recurrences have not been noted in the spared parotid tissue in patients treated with IMRT or surgery,^{21,39} suggesting that a large study to show non-inferiority in this tumour type is probably both impractical and inappropriate. Our trial has shown a clinically and statistically significant reduction in xerostomia, improved salivary flow, and improved QoL, and thus strongly supports a role for IMRT in HNSCC.

Contributors

CMN and EH were responsible for the trial design, trial management, data interpretation, and writing of the report. CMN was chief investigator of the trial and contributed to trial recruitment. EH oversaw all statistical analyses. JPM did the main analyses and contributed to data interpretation and writing of the report. RPAH contributed statistical support, trial management, data interpretation, and writing of the report. MAS, ME, and MT were responsible for the trial coordination and data collection and contributed to data interpretation and writing of the report. CC and EAM were responsible for the design and conduct of the quality assurance programme and contributed to the trial management, data interpretation, and writing of the report. KJH, KN, CS, SJ, FA, and BKJ all contributed to trial recruitment, trial management, data interpretation, and writing of the report. TGU, SAB, and ABM were clinical coordinators for the trial, contributed to trial management, data collection, data interpretation, and writing of the report. All authors reviewed and approved the final version of the paper.

Conflicts of interest

The authors declared no conflicts of interest.

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Paper 8



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Intensity-modulated radiotherapy improves target coverage, spinal cord sparing and allows dose escalation in patients with locally advanced cancer of the larynx

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Abstract

Background and purpose: An investigation has been carried out into the potential of intensity-modulated radiotherapy (IMRT) to improve the coverage of the targets and the sparing of the spinal cord (SC) in radiotherapy treatment of the larynx and bilateral cervical lymph nodes, in patients with advanced larynx cancer.

Patients and methods: Conventional radiotherapy (CRT) and IMRT plans were produced for six patients to treat the larynx (PTV1) and lymph nodes (PTV2) to 50 Gy (phase 1). A second plan was created to treat the PTV1 to 65 Gy and PTV2 to 50 Gy (phases 1 and 2). The potential to escalate the dose to both the larynx (to 67 Gy) and the nodes (to 56 Gy) was investigated for the IMRT plans.

Results: The phase 1 treatment gave average minimum doses (dose received by 99% volume) of 38.1 (± 8.2) and 48.5 (± 0.2) Gy for PTV1, treated by CRT and IMRT, respectively, and 35.9 (± 2.9) and 46.2 (± 1.8) Gy for PTV2. For the two phase treatment the average minimum doses to PTV1 were 51.6 (± 8.2) (CRT) and 62.1 (± 0.7) Gy (IMRT) ($P = 0.028$) and for PTV2 were 36.2 (± 2.9) (CRT) and 46.8 (± 0.5) Gy (IMRT) ($P = 0.0004$). The average maximum doses (dose received by 1% volume) to the SC were 42.5 (± 1.9) (CRT) and 37.9 (± 1.4) Gy (IMRT) ($P = 0.01$). For the dose escalated IMRT plans the minimum dose to PTV1 was 64.6 (± 0.5) and 50.8 (± 1.8) Gy to PTV2. The average SC maximum was 41.5 (± 1.6) Gy.

Conclusions: IMRT offers improved target homogeneity and reduces irradiation of the SC. This sparing of normal tissue structures is sufficient that significant dose escalation of both the larynx and lymph nodes may be possible.

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Keywords: Larynx carcinoma; Intensity-modulated radiotherapy; Dose escalation

1. Introduction

External beam radiotherapy for advanced cancer of the larynx represents a difficult challenge for treatment planning because the planning target volume (PTV), which includes the larynx and bilateral cervical lymph nodes, is wrapped around the spinal cord (SC).

Typically in the UK, lateral-opposed photon portals are used to treat the PTV up to cord tolerance and then reduced photon fields are matched to high-energy electrons bilaterally to treat the posterior cervical lymph nodes [7,24]. This produces a concave dose distribution surrounding the

SC, but there are areas of potential under-dose in the photon–electron match line that may account for a proportion of patients who relapse in the cervical nodes. Additionally the dose inhomogeneity in the PTV is high due to changes in contour of the head and neck region. These problems cannot be resolved entirely, simply by the use of 3D planning approaches. Dose inhomogeneity can be reduced using customised tissue compensation, but this is rarely used in routine clinical practice because of the complications of design and manufacture.

A radiation dose of 65–75 Gy is required to eradicate macroscopic tumour in the larynx and involved lymph nodes, and 50 Gy elective irradiation to the cervical lymph nodes [9]. These doses are in excess of SC tolerance

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(absolute maximum of 44 Gy in 2 Gy fractions), and without careful treatment planning the patient is at risk of radiation-induced myelopathy due to the proximity of the target volume to the SC.

Intensity-modulated radiotherapy (IMRT) allows complex dose distributions to be produced. The benefits are greatest for concave volumes where the PTV surrounds an organ at risk (OAR) [6,23]. In treatment of carcinoma of the larynx, IMRT may offer the potential to improve target coverage and increase the sparing of the OAR. The primary aim of this study was to investigate whether IMRT could improve coverage of the larynx and nodal PTVs compared to conventional techniques whilst maintaining SC sparing. The magnitudes of these benefits were quantified. This study also addresses some of the practical aspects of planning for implementation in the clinic.

Other studies in the treatment of head and neck cancer have shown that IMRT plans with seven and five fields produced similar dose distributions to nine fields, but that three fields were significantly worse [1,21]. An initial study on one patient confirmed that this is also the case for larynx and involved lymph nodes. However, the use of equispaced fields is not always practical on the linear accelerator. In particular we have found that the design of our head and neck immobilisation system using a pETG copolyester shell (in-house made) and headboard does not always allow access for certain posterior oblique beam angles. Additionally, some anterior oblique fields may enter the patient through the anterior part of the shoulder, thus irradiating more normal tissue than may be necessary and requiring increased tissue compensation. Therefore the second aim of the study was to compare equispaced five-field plans with optimised plans where the anterior and posterior oblique fields had been adjusted to avoid shoulder irradiation and treating through dense parts of the couch and immobilisation system.

The third aim of the study was to investigate if dose escalation is technically possible within SC tolerance. Squamous cell carcinoma of the head and neck is known to have a steep dose–response relationship, and strategies such as accelerated radiotherapy have been shown to increase local control [10]. Dose escalation using conventional radiotherapy (CRT) techniques is possible, but may be associated with increased doses to the OAR. We investigated the potential of IMRT to deliver escalated doses of 67 Gy to the larynx and 56 Gy to the nodes above our current protocol of 65 Gy (larynx) and 50 Gy (nodes) without exceeding the tolerance of the SC.

2. Methods

2.1. Patients and radiotherapy planning

Six patients who had been treated with CT-planned radical external beam radiotherapy for larynx carcinoma

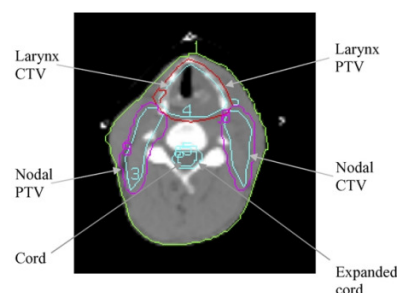


Fig. 1. Outlines of the larynx CTV, larynx PTV (grown by 3 mm from the CTV), bilateral nodal CTVs, nodal PTVs (created using 3 mm margins from the CTVs), spinal cord and expanded cord volume.

(T1-3 N1-2b M0) were studied. All patients had the neck extended and had undergone a supine planning CT scan of the head and neck. Images were taken at 5 mm intervals (one patient was scanned at 10 mm intervals) from skull-base to upper mediastinum. The CT images were imported into CadPlan (version 6.3.5, Varian Medical Systems, Palo Alto, CA).

The clinical target volume (CTV), lungs, oesophagus and SC were outlined on each CT image (Fig. 1) according to ICRU 50 and 62 [14,15]. The larynx CTV included the primary tumour assessed from imaging and clinical findings, and also the whole larynx extending from the inferior border of the hyoid bone to the inferior border of the cricoid cartilage. The lymph nodes were localised as a CTV using the guidelines of Gregoire [11]. These included levels II–V bilaterally extending from the mid-vertebra at the level of C1 to the sterno-clavicular joint. Both CTVs were grown to create the larynx and nodal PTVs. The margin applied was 3 mm in the anterior–posterior (AP) and lateral directions and 5 mm in the cranial–caudal direction, as this was the minimum possible for 5 mm slice thickness. These margins were based on a study of set-up data from our portal imaging system [13]. Special care was taken to ensure that the nodal PTV did not come within 5 mm of the skin to avoid PTV in the build-up region. The nodal PTV was also edited out of the larynx PTV to avoid overlapping structures and thus conflicting dose constraints. A 3 mm margin was also added to the SC to create an expanded volume, which served to guide the planning system to spare the cord volume. The same volumes were used for both IMRT and conventional planning.

2.2. Irradiation of nodal and larynx volumes to 50 Gy

For each patient, CRT and IMRT plans were produced for homogeneous irradiation of the cervical nodes and larynx to 50 Gy in 25 fractions. This was done to allow accurate comparison of the nodal dose–volume relationship between CRT and IMRT plans. A second plan was made for

irradiation of the larynx to 65 Gy and the cervical nodes to 50 Gy (these doses are standard in our centre). For CRT planning the boost plan was a separate plan. For the IMRT planning the boost was incorporated into a single phase plan.

2.2.1. Conventional radiotherapy technique

A single isocentre technique, which is used routinely in our centre, was employed. Asymmetric parallel-opposed lateral fields were used to treat the larynx and upper neck to 40 Gy in 20 fractions. Wedges were employed if necessary to improve dose homogeneity and both beam weights and wedge angle were optimised manually. The dose was normalised to the mid-line at the field centre. The lateral fields were matched using the 50% isodose lines, at the isocentre plane, to an anterior field with a mid-line SC shield and sub-apical lung shielding. Field asymmetry, with one jaw set to the central axis, was used to produce a non-divergent match line and was positioned above the shoulders. The field apertures were obtained using virtual simulation obtained from the delineation, for both the CRT and IMRT, on the CT scans. The anterior field was prescribed to 50 Gy in 25 fractions at a depth of 2.5 cm to a point 3 cm lateral to the central axis and at mid field. After 40 Gy, the lateral fields were reduced posteriorly to avoid the SC and electron fields were matched using the light field borders (50% isodose line) on the skin to the photon fields for a further 10 Gy in 5 fractions to treat the posterior cervical lymph nodes. The energy of the electron fields was chosen such that the total SC dose was <44 Gy. Separate plans were made for the lateral photons, reduced lateral photons, anterior photons and individual electron fields. These plans were then summed in Cadplan to produce composite dose–volume histograms (DVHs) and isodose distributions. For the purposes of this study of a comparison with IMRT, the CRT plans have been calculated in 3D on CT slices. However, in normal clinical practice in our centre these CRT plans are calculated in 2D on a single central field slice. We did not alter our planning practice for this study and hence did not undertake any plan adjustment to ensure PTV coverage, other than ensuring that the field size covered the volumes in the beam's eye view (BEV).

2.2.2. IMRT technique

The Helios inverse planning module in CadPlan was used for all IMRT planning. For each patient, initial dose–volume constraints were designed for the inverse planning process. For uniform irradiation of the larynx and nodal volumes the aim was to deliver 50 Gy in 25 fractions. The initial dose constraints were a median dose of 50 Gy to the lymph node PTV and to the larynx PTV. This produced intensity patterns which, following sequencing, slightly increased the dose to the nodal PTV by approximately 2 Gy relative to the larynx PTV. It was thus necessary to use a median constraint of 48 Gy to the nodal PTV to account for this. The initial weightings used are shown in Table 1. The Helios inverse-planning module allows the user to adjust the constraints as the optimisation process is occurring. This was used to produce the best DVH for each patient by tightening the constraints and increasing the priorities for each volume, as the optimisation function progressed. The SC dose was required to be <40 Gy, a constraint of a maximum of 32 Gy to the expanded cord volume was needed to ensure this. After the optimisation was finished the leaf motion calculator was run to provide a dynamic sliding window for delivery and a 3D dose cube was calculated using these resulting delivery leaf motions. The dose for the IMRT plan was normalised to the median of the larynx PTV. On average 2–3 IMRT plans were required before a satisfactory result was achieved. Each plan took approximately 30–45 min to carry out inverse planning, leaf sequencing and plan calculation [5,20].

2.3. Irradiation of the larynx to 65 Gy and of 50 Gy to the cervical lymph nodes

2.3.1. Conventional radiotherapy technique

These plans were produced as described previously but included a third phase to the larynx PTV alone using parallel opposed photon fields with the isocentre at the geometric centre of the larynx PTV volume. Manually optimised wedges were used if necessary. This boost phase was prescribed as 15 Gy in 5 fractions normalised to a point on the central axis at midline and summed with the 50 Gy (phase 1) plan to produce a composite 65 Gy plan (phases 1 and 2). The total SC dose was maintained at under 44 Gy.

Table 1

The initial dose constraints used in Helios for 50 Gy uniform coverage, with the larynx boosted to 65 Gy and for the doses escalated to 67 Gy to the larynx PTV (L) and 56 Gy to the nodal PTV (N)

Dose prescription	Larynx PTV min		Larynx PTV max		Nodes PTV min		Nodes PTV max		Cord PRV max	
	Dose	Priority	Dose	Priority	Dose	Priority	Dose	Priority	Dose	Priority
50(L)/50(N)	49.8	75	50.2	75	47.5	60	48.5	60	32	50
65(L)/50(N)	64.8	75	65.2	75	47.5	60	48.5	60	32	50
67(L)/56(N)	66.8	75	67.2	75	53.5	60	54.2	60	32	50

DVHs and isodose distributions for plan assessment were produced from this final summed plan.

2.3.2. IMRT technique

The boost dose to the larynx was given as a single-phase simultaneous modulated accelerated radiotherapy (SMART) boost [3] using 28 fractions. The dose per fraction to the larynx was 2.3 Gy (total 65 Gy) and the dose to the lymph nodes was 1.8 Gy (total 50 Gy). The initial planning constraints to treat the larynx to 65 Gy are given in Table 1.

2.4. Beam direction optimisation

The IMRT plans with equispaced fields used beams covering the PTV and nodes at gantry angles of 0 (anterior), 72, 144, 216 and 288°. Use of the Helios inverse planning module produced satisfactory dose distributions, but it would not always be possible to deliver the posterior oblique fields without irradiating through our headboard or couch. The position of the isocentre in the AP direction for individual patients will determine the exact angles available. A range of posterior oblique beam angles for different patients were investigated between 135–145 and 215–225°. The BEV of the field was used to ensure coverage of the target volumes whilst avoiding the headboard and couch. The anterior oblique beams were also optimised at 60 and 300°, to reduce irradiation of the shoulder. The optimised beam angle plans were compared with the plans with equispaced beam arrangements to ascertain whether there was any significant difference between them.

2.5. Dose escalation plans

The escalated dose prescription was 2.4 Gy per fraction to the larynx PTV, to a total of 67 Gy in 28 fractions. The lymph node PTV received 56 Gy in 28 fractions (2.0 Gy per fraction). This schedule was chosen as it was felt it would represent a significant level of dose escalation for a future clinical study. In the UK we have extensive experience of doses to the larynx of over 2.0 Gy per fraction. Plans for dose escalation were carried out using the non-equispaced optimised beam angles as described in Section 2.4. The initial dose–volume constraints for these plans are given in Table 1.

2.6. Comparison of treatment plans

All doses were calculated on a 2.5 mm dose matrix using a single pencil beam algorithm [27] and using the modified Batho inhomogeneity correction for photons. The algorithm for the electron calculations was a generalised Gaussian pencil beam model based on electron multiple scattering theory [2,17,18]. DVHs were calculated for each type of plan and the minimum and maximum doses extracted. The minimum dose was defined as the dose received by 99% of

the volume and the maximum dose as that received by 1% [4,8,16,22]. A dose range (indicating the inhomogeneity in the PTV) was defined as the difference in dose between the 99 and 1% volumes (i.e. the minimum and maximum doses). The maximum SC dose was also recorded in the same way. The results from the different techniques were compared using a two-tailed paired Student's *t*-test as the data exhibited normal distribution.

3. Results

3.1. Irradiation of nodal and larynx volumes to 50 Gy

3.1.1. Conventional radiotherapy technique

Typical conventional dose distributions are shown in Fig. 2. The average dose range to the larynx PTV was 14.1 (± 8.8) Gy and to the nodal PTV was 18.2 (± 3.1) Gy (see Table 2). The average SC maximum dose was 42.4 (± 1.7) Gy (range of values 40.50–44.2 Gy). The areas of minimum dose were at the junction between the electron and photon fields and at the junction between the lateral and anterior photon fields. Areas of minimum dose were not seen close to the skin, which was purposefully excluded from the PTV. There were also areas of underdosage seen in the superior neck where the separation for the lateral fields was greater than on the calculation plane (see Fig. 2b). The areas of maximum dose were in the regions treated by the lateral fields at the sites of minimal lateral separation and in the anterior build-up region in the inferior nodes (see Fig. 2).

3.1.2. IMRT

Examples of IMRT dose distributions, for the same patient as in Fig. 2 and non-equispaced plans, are shown in Fig. 3. The average dose range to the larynx PTV was 2.9 (± 0.5) Gy ($P = 0.03$ compared to CRT), see Table 2. The average dose range to the nodal PTV was 6.3 (± 1.9) Gy ($P = 0.001$). A graphical representation of this data, shown in Fig. 4, shows a comparison of the two techniques for both the larynx and nodal PTVs. The average SC maximum dose was 37.2 (± 2.7) Gy ($P < 0.01$), (range of values 34.6–41.8 Gy). The areas of maximum dose seen with IMRT plans were different from with conventional plans and were situated in small areas near the edges of the larynx PTV. The maximum doses in the nodes were on the anterior border of the inferior nodes and on the posterior/lateral borders of the superior nodes. These maximum doses were lower ($P = 0.05$ for the larynx PTV and $P = 0.1$ for the nodal PTV) than for the CRT plans. The minimum doses to the larynx PTV were greater for the IMRT technique (48.5 ± 0.02 Gy) than for the CRT technique (38.1 ± 8.2 Gy) with $P = 0.03$. A statistically significant difference of $P < 0.01$ was found for the difference in minimum dose to the nodal PTV for the IMRT (46.2 ± 1.8 Gy) compared with the CRT (35.9 ± 2.9 Gy).

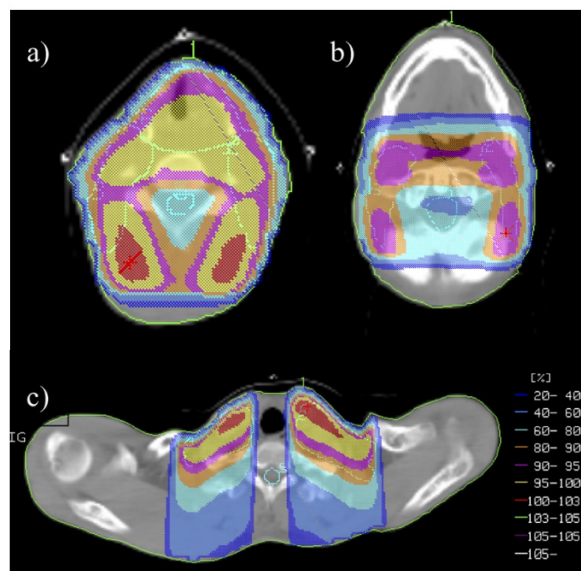


Fig. 2. Dose distributions for phase 1 treatment of the larynx and nodes to 50 Gy using the conventional technique, at transverse cross-sections through (a) the central larynx showing the larynx PTV, the nodal PTVs and the spinal cord (SC), (b) the superior nodes showing the nodal PTVs and the SC and (c) the inferior nodes showing the nodal PTVs and the SC. The shading shows regions of 95–100, 100–103, 103–105, and regions greater than 105%. The cord tolerance is shown as the 90% isodose line.

3.2. Irradiation of the larynx to 65 Gy and lymph nodes to 50 Gy

3.2.1. Conventional radiotherapy technique

A typical conventional dose distribution is shown in Fig. 5. For the larynx PTV the average dose range was 15.5 (± 8.7) Gy. The average dose range was 29.4 (± 3.0) Gy for the nodal PTV (see Table 2). The average SC maximum dose was 42.5 (± 1.9) Gy (range of values 40.6–44.5 Gy). The areas of minimum dose were also at the junction

between the electron and photon fields, and at the junction between the lateral and anterior photon fields. The areas of maximum dose were again in the anterior larynx PTV at site of minimal lateral separation and in the anterior build-up region in the inferior nodes.

3.2.2. IMRT

An example of an IMRT dose distribution for non-equispaced beams is shown in Fig. 6. The average dose range to the larynx PTV was 4.6 (± 1.0) Gy ($P = 0.03$

Table 2
PTV and spinal cord statistics for the phase 1 and with the second phase 15 Gy boost to the larynx PTV for conventional and non-equispaced five-field IMRT techniques

		Conventional 50 Gy	IMRT 50 Gy	<i>P</i> value	Conventional 65/50 Gy	IMRT 65/50 Gy	<i>P</i> value
Larynx PTV	Minimum	38.1 (± 8.2)	48.5 (± 0.2)	0.03	51.6 (± 8.2)	62.1 (± 0.7)	0.03
	Mean	49.5 (± 0.7)	49.9 (± 0.1)	0.25	64.1 (± 0.6)	64.8 (± 0.1)	0.05
	Maximum	52.2 (± 0.7)	51.4 (± 0.3)	0.05	67.1 (± 0.7)	66.7 (± 0.6)	0.4
	Dose range	14.1 (± 8.8)	2.9 (± 0.5)	0.03	15.5 (± 8.7)	4.6 (± 1.0)	0.03
Nodes PTV	Minimum	35.9 (± 2.9)	46.2 (± 1.8)	<0.01	36.2 (± 2.9)	46.8 (± 0.5)	<0.01
	Mean	48.7 (± 0.6)	49.7 (± 0.6)	0.09	51.2 (± 0.8)	50.7 (± 0.5)	0.12
	Maximum	54.1 (± 0.9)	52.5 (± 1.3)	0.1	65.6 (± 0.1)	57.8 (± 2.8)	<0.01
	Dose range	18.2 (± 3.1)	6.3 (± 1.9)	<0.01	29.4 (± 3.0)	11.0 (± 2.7)	<0.01
Spinal cord	Maximum	42.4 (± 1.7)	37.2 (± 2.7)	<0.01	42.5 (± 1.9)	37.9 (± 1.4)	0.01

All doses in Gy (± 1 SD) are the mean of all patients. The *P* value refers to the comparison of the two values to the left of it.

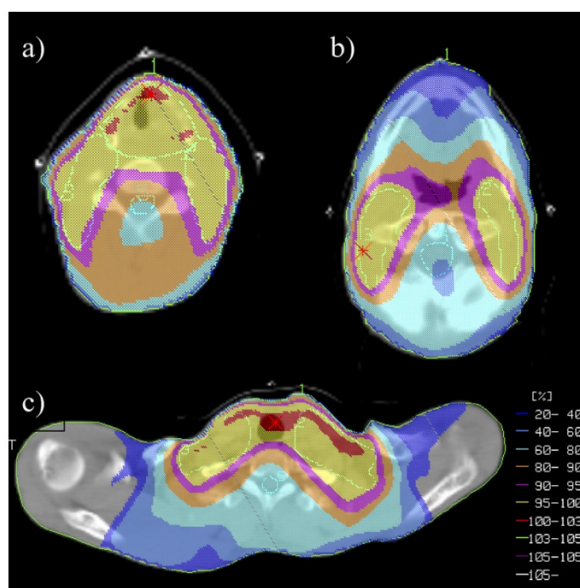


Fig. 3. Dose distributions for phase 1 treatment of the larynx and nodes to 50 Gy using the IMRT technique. The transverse cross-sections and isodoses are the same as shown in Fig. 2.

compared to conventional treatment) and to the nodal PTV dose range was $11.0 (\pm 2.7)$ Gy ($P = 0.0004$), see Table 2. A graphical representation of this data, shown in Fig. 7, shows a comparison of the two techniques for both the larynx and nodal PTVs and the reduced inhomogeneity of the dose for the IMRT technique. The average SC maximum dose was $37.9 (\pm 1.4)$ Gy ($P = 0.01$) (range of values 35.8 – 39.7 Gy). The areas of maximum dose seen with IMRT plans were different from that with conventional plans and were situated in small areas near the edges of the larynx PTV. The maximum doses in the nodes were adjacent to the larynx in the penumbra of the simultaneous boost. The minimum doses to the nodal PTV had a statistical difference of $P < 0.01$ for the IMRT (46.8 ± 0.5) when compared with the CRT (36.2 ± 2.9). For the larynx PTV the minimum dose for the IMRT plan was 62.1 ± 0.7 Gy whereas for the CRT plan this was 51.6 ± 8.2 Gy.

3.3. IMRT beam direction optimisation

No significant difference was found between using the equispaced and customised five-field plans (see Table 3). The average dose range to the larynx was $2.6 (\pm 0.5)$ Gy ($P = 0.24$ compared to customised beam angle IMRT). The average dose range to the lymph nodes was $6.7 (\pm 2.3)$ Gy

($P = 0.44$). The mean SC dose across the six patients was $36.1 (\pm 2.7)$ Gy for the equispaced fields and $37.2 (\pm 2.7)$ Gy for the customised beam angles ($P = 0.07$).

3.4. Dose escalation

The average mean dose to the larynx for all patients was $67.0 (\pm 0.06)$ Gy (see Table 4). The average minimum dose was $64.6 (\pm 0.5)$ Gy and the dose range was $4.2 (\pm 1.1)$ Gy. The average mean dose to the lymph nodes was 55.8

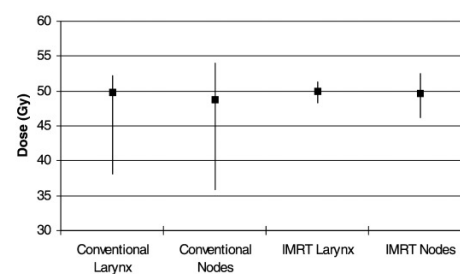


Fig. 4. The mean doses and dose ranges for the larynx PTV and nodal PTV treated by IMRT and conventional techniques for the phase 1 of uniform irradiation of 50 Gy.

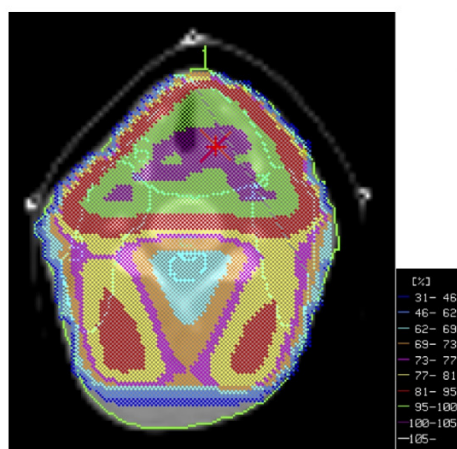


Fig. 5. Dose distributions for the phase 1 and 2 treatment of the larynx to 65 Gy and nodes to 50 Gy, using the conventional technique. The transverse cross-section is shown through the central larynx and shows the larynx PTV, the nodal PTVs and the spinal cord. The regions of 95–100, 100–105 and greater than 105% of the nodal dose respectively are shown. Also shown are regions of 95–100 and 100–105% of the larynx dose, respectively.

(± 0.3) Gy. The average minimum dose was 50.8 (± 1.8) Gy and the dose range was 10.3 (± 2.8) Gy. The average SC maximum dose was 41.5 (± 1.6) Gy (range 39.5–43.6 Gy).

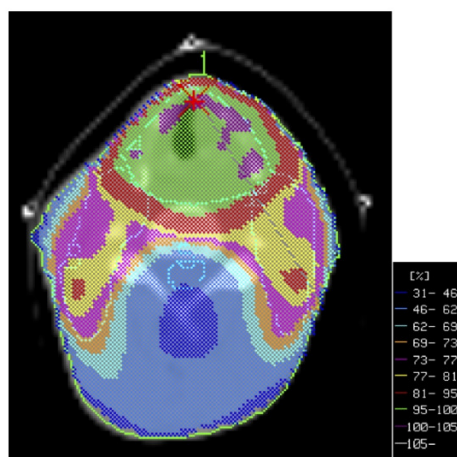


Fig. 6. Dose distributions for the phase 1 and 2 treatment of the larynx to 65 Gy and nodes to 50 Gy, using the IMRT technique. The transverse cross-section and isodoses are the same as those shown in Fig. 5.

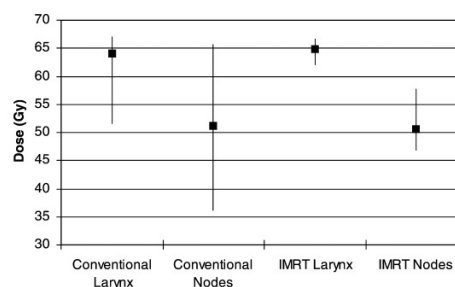


Fig. 7. The mean doses and dose ranges for phases 1 and 2 for the larynx PTV and nodal PTV treated to 65 and 50 Gy, respectively, by IMRT and conventional techniques.

4. Discussion

The goals of radiotherapy for locally advanced (T3–4, N+) carcinoma of the larynx are local control, survival and quality of life—specifically voice/larynx preservation. For T3N0 cases the local control and survival rates with radiotherapy alone are 50–60 and 60–70%, respectively. Two-thirds of patients will survive with a functional larynx [28]. Other larynx preserving approaches include the use of induction and/or concomitant chemoradiation [19,28], and radiotherapy dose escalation. Dose escalation strategies have employed accelerated, hyperfractionated, and CHART schedules which show increase in local control and support the hypothesis of a steep dose–response relationship for squamous cell carcinoma of the head and neck [10].

Radiotherapy techniques have important implications for dose escalation strategies. The likelihood of tumour control is related to minimum dose delivered to the PTV [29]. With CRT techniques for larynx cancer this study suggests that in phase 1 plans there are areas of minimum dose within the nodal PTV of 38 Gy (76% of prescription dose), which is considerably less than those required to achieve tumour cell kill. For a prescribed dose of 65/50 Gy the minimum dose to the larynx was 51.6 Gy (79%). The position of the minimum dose areas suggests that, although small, they are related to the radiation technique employed. These low dose areas are not detectable using conventional 2D planning techniques, and only become apparent when full 3D planning is evaluated. Additionally there were high dose areas within the PTV, which may account for unnecessary normal tissue damage, such as cartilage necrosis and persistent oedema.

The use of IMRT increased the minimum dose within the PTV for both the larynx and cervical lymph nodes. This should translate into an improvement in likelihood of tumour control. The dose inhomogeneity was also reduced (as shown in the DVH in Fig. 8) and may result in a reduction in this cartilage necrosis and persistent oedema and improve the cosmetic outcome of neck irradiation. The SC dose tolerance, as measured using the 1% volume value

Table 3
PTV and spinal cord statistics for the equispaced and non-equispaced five-field phase 1 (50 Gy) IMRT techniques

	Larynx PTV			Nodes PTV			Spinal cord Maximum
	Minimum	Mean	Dose range	Minimum	Mean	Dose range	
Equispaced	48.7 (± 0.4)	49.9 (± 0.06)	2.6 (± 0.5)	46.2 (± 2.1)	49.9 (± 0.5)	6.7 (± 2.3)	36.1 (± 2.7)
Non-equispaced	48.5 (± 0.2)	49.9 (± 0.1)	2.9 (± 0.5)	46.2 (± 1.8)	49.7 (± 0.6)	6.3 (± 1.9)	37.2 (± 2.7)
<i>P</i> value	0.27	0.30	0.24	0.95	0.13	0.44	0.07

All doses in Gy (± 1 SD) are the mean of all patients. The *P* value refers to the comparison of the two values above it.

Table 4
PTV and spinal cord statistics for the boost and dose escalated five-field IMRT techniques

	Larynx PTV			Nodes PTV			Spinal cord Maximum
	Minimum	Mean	Dose range	Minimum	Mean	Dose range	
65/50	62.1 (± 0.2)	64.8 (± 0.1)	4.6 (± 0.5)	46.8 (± 1.8)	50.7 (± 0.6)	11.0 (± 1.9)	37.2 (± 2.7)
67/56	64.6 (± 0.5)	67.0 (± 0.1)	4.2 (± 1.1)	50.8 (± 1.8)	55.8 (± 0.3)	10.3 (± 2.8)	41.5 (± 1.6)

All doses in Gy (± 1 SD) are the mean of all patients.

from the DVH, was always respected with IMRT. The 1% volume gives a more clinically useful estimate of the maximum cord dose than the absolute maximum which may show a hotspot to an irrelevantly small volume.

Concomitant chemo-radiation strategies are becoming increasingly frequent in head and neck cancer. In a large meta-analysis concomitant chemo-radiation had a 9% advantage over radiotherapy alone [25]. Such strategies may carry increased normal tissue toxicity, and there is uncertainty as to the net effect on the therapeutic ratio [12].

Customisation of beam angles to allow delivery of the calculated beams and to avoid irradiation of the shoulder was possible without any detrimental effects on the dose distribution. These considerations are an important part of clinical implementation of a treatment programme in head and neck cancer [26].

This study has also investigated dose escalation, and has shown that a significant nodal dose escalation is possible within SC tolerance. At higher dose levels other normal tissues such as the oesophagus, skin and other soft tissue structures may become dose limiting. We are currently

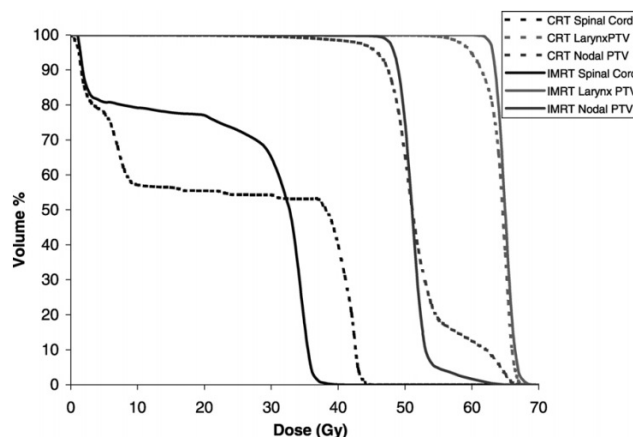


Fig. 8. A dose–volume histogram showing data for a conventional and IMRT plan for a typical patient. The CRT plan data are shown as dotted lines and the IMRT is in solid lines. The IMRT data show a significant improvement in target coverage and dose inhomogeneity as well as improved cord sparing.

investigating this in a dose escalation trial in larynx cancer patients. The dose levels to be studied are accelerated schedules of 67 Gy to the larynx and 56 Gy to the nodes in 28 fractions.

In addition to the dosimetric advantages of IMRT over CRT, there are also likely to be savings in efficiency particularly on the treatment unit. These are the subjects of ongoing time-and-motion studies [5,20].

5. Conclusions

IMRT offers improved target homogeneity in patients with larynx carcinoma and reduces high dose irradiation of the SC. This sparing of normal tissue structures is sufficient that significant dose escalation of both the larynx and lymph nodes may be possible without any predicted increase in likelihood of normal tissue complication. We have undertaken a planning study to investigate whether IMRT can improve target coverage, SC sparing and allow dose escalation, within the practical constraints in the clinic, in patients with locally advanced cancer of the larynx. We have found that both target coverage is improved and SC dose is reduced. We have also carried out a preliminary dose escalation study and have found that target coverage and SC sparing are maintained and therefore could be feasibly planned.

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Paper 9

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Phase I trial

A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer

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Abstract

Background and purpose: Intensity modulated radiotherapy (IMRT) allows the delivery of higher and more homogeneous radiation dose to head and neck tumours. This study aims to determine the safety of dose-escalated chemo-IMRT for larynx preservation in locally advanced head and neck cancer.

Methods: Patients with T2–4, N1–3, M0 squamous cell carcinoma of the larynx or hypopharynx were treated with a simultaneous-boost IMRT. Two radiation dose levels (DL) were tested: In DL 1, 63 Gy/28F was delivered to primary tumour and involved nodes and 51.8 Gy/28F to elective nodes. In DL 2, the doses were 67.2 Gy/28F and 56 Gy/28F, respectively, representing a 9% dose escalation for the primary. All patients received 2 cycles of neoadjuvant cisplatin and 5-fluorouracil, and concomitant cisplatin. Acute (NCICTCv.2.0) and late toxicity (RTOG and modified LENTSUM) were collected.

Results: Thirty patients were entered, 15 in each dose level. All patients completed the treatment schedule. In DL 1, the incidences of acute G3 toxicities were 27% (pain), 20% (radiation dermatitis), 0% (xerostomia) and 67% required gastrostomy tubes. For DL 2 the corresponding incidences were 40%, 20%, 7%, and 87%. G3 dysphagia and pain persisted longer in DL 2. With regard to mucositis, a prolonged healing time for DL 2 was found, with prevalence of G2 of 58% in week 10. No acute grade 4 toxicity was observed. At 6 months, 1 patient in DL 2 had G3 late toxicity (dysphagia). No dose limiting toxicity was found. Complete response rates were 80% in DL 1, and 87% in DL 2.

Conclusion: Moderately accelerated chemo-IMRT is safe and feasible with good compliance and acceptable acute toxicity. Dose escalation was possible without a significant difference in acute toxicity. Longer follow-up is required to determine the incidence of late radiation toxicities, and tumour control rates.

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Keywords: Head and neck cancer; IMRT; Toxicity

Most tumours arising in the larynx and hypopharynx are squamous cell carcinomas (SCC) that display a clear radiation dose–response relationship. In locally advanced tumours survival rates are still poor, with most patients dying of loco-regional rather than systemic failure. The addition of concomitant chemotherapy to radical radiotherapy (RT) schedules in locally advanced head and neck cancer (HNC) has been shown to achieve absolute improvements in 5-year survival rates of 8% compared to RT alone [1] and absolute reductions in laryngectomy rates of 43% [2]. Significant improvements in loco-regional control have been shown with altered fractionation schedules [3], but both approaches are, however, associated with significant morbidity [2,4–6]. At-

tempts to combine both concomitant chemotherapy and altered fractionation schedules using conventional RT techniques have been associated with significant morbidity, with rates of long term dependence on enteral feeding as high as 25–30% [7,8]. In addition, significant acute toxicity can lead to treatment breaks and prolongation of the overall treatment time, which is associated with reduced loco-regional disease-free survival [9] due to accelerated repopulation of tumour clonogens [10]. Although neoadjuvant chemotherapy has not been associated with significant improvements in overall survival [1], it merits further investigation.

Intensity modulated radiotherapy (IMRT) allows improved shaping of dose distributions and hence increased sparing of

normal tissues. This could potentially abrogate the increased acute and late toxicity associated with concomitant chemoradiotherapy and accelerated RT. In addition, dose inhomogeneities within the tumour that are seen with conventional radiation delivery can also be reduced, which should theoretically be associated with a lower risk of loco-regional recurrence [11].

We present here the results of a phase 1 dose escalation study of neoadjuvant chemotherapy followed by concomitant chemotherapy and moderately accelerated IMRT.

Patients and methods

Patients with histologically proven locally advanced laryngeal and hypopharyngeal SCC (T1–T4, N0–N3, M0) suitable for treatment with primary chemo-radiotherapy with curative intent were eligible. Ethics approval was obtained and all patients gave written informed consent. All patients received neoadjuvant chemotherapy: 2 courses of cisplatin (75 mg/m² on day 1) and 5-fluorouracil (5-FU) (1000 mg/m² D1–4) on a 3-weekly basis. Concomitant chemotherapy with cisplatin 100 mg/m² was given in weeks 1 and 5 of IMRT.

A standard phase 1 dose escalation trial design was used, with 15 patients enrolled in each dose level (DL) (Table 1). DL 1 was chosen based on our centre's experience of a standard dose of 65 Gy in 30 fractions, a wish to keep the treatment time between 5 and 6 weeks to reduce the effects of accelerated repopulation, and a calculated BED equivalent to 70 Gy in 35 fractions. Calculations were performed using the formulae $EQD2 = D(d + \alpha/\beta)/2 + \alpha/\beta$ and $EQD2, T = EQD2, t - (T - t) \times D_{prolif}$ [12], where EQD2 represents the equivalent dose in 2 Gy fractions, D and d are the total dose and dose per fraction, T and t take into account changes in the overall treatment time and D_{prolif} is a proliferation factor (0.74 Gy d⁻¹) [13]. Calculations were performed using a tumour α/β of 10 Gy and late effects α/β of 3 Gy. For DL 1, for the primary, $EQD2_{(63Gy, \alpha/\beta=10Gy)}$ was calculated as 64.3 Gy and $EQD2_{(63Gy, \alpha/\beta=3Gy)}$ as 66.15 Gy, which corrected for the reduction in overall treatment time resulted in $EQD2$ of 70 Gy. The nodal $EQD2_{(51.8Gy)}$, taking into account the increase in overall treatment time, was calculated as 47.5 Gy. DL 2 was chosen to represent an increase in BED of 9% for the primary tumour (approximately 76 Gy), for a nodal $EQD2$ of about 51 Gy.

DL 1 was designed as a feasibility study of hypofractionated IMRT with the doses prescribed equivalent to 70 Gy in 35 fractions and, therefore, no increase in toxicity rates was expected. Dose escalation was performed once feasibility was demonstrated in DL 1. However, the stopping rules determined that if 0/15 patients had $\geq$ Grade 3 late complications at 1 year then a $\geq$ 20% risk of Grade 3 late complication rate would be excluded with 95% power. If 1 or 2 patients developed $\geq$ Grade 3 late complications at the first

DL then the number of patients recruited at that level would be increased to 30 to improve statistical power and escalation to the second DL would only be allowed if no further patients developed grade 3 late toxicity (incidence of $\geq$ Grade 3 late complication rate predicted to be 0–17% and 0–22%, respectively, with 95% power). If more than 2 patients suffered $\geq$ Grade 3 late complication then recruitment to that level would be stopped (incidence of $\geq$ Grade 3 complication predicted to be 2–27% with 95% power).

IMRT technique

All patients were immobilised using a custom-made cabulite head and neck mask. Target volumes and organs at risk (OAR) were delineated on RT planning CT scans following ICRU 50 and 62 guidelines. The entire larynx and hypopharynx complex, including the thyroid cartilage, was included in the primary clinical target volume (CTV1), from 1 cm above the tip of the epiglottis to below the cricoid cartilage or 2 cm above and/or below the superior and inferior extent of the tumour, whichever was larger. Uninvolved barriers to tumour spread, such as bone and fasciae, were excluded. Adjacent structures (i.e. muscle) infiltrated by tumour were included in the CTV1, as well as all involved nodal levels and the retropharyngeal nodes at the level of the hypopharynx. The elective nodal volume (CTV2) included uninvolved levels 2–5 and supraclavicular fossa (SCF) nodes bilaterally and delineation was performed according to the consensus guidelines [14]. A 3 mm margin was added to the CTV1 and CTV2 to obtain the planning target volumes PTV1 and PTV2, respectively [15]. The organs at risk (OAR) delineated were the spinal cord, brain stem, parotid glands, submandibular glands and oral cavity.

The Helios inverse planning module of CadPlan v6.3.5 (Varian Medical Systems, Palo Alto, CA) and Eclipse (Varian Medical Systems, Palo Alto, CA) were used to create IMRT plans, using a simultaneous integrated boost technique (SIB), for dynamic delivery on a Varian 2100CD linear accelerator using 6 MV photons. Inverse planning in Helax-TMS and PINNACLE³ (Philips Radiation Oncology Systems, Milpitas, CA) was used, using the same SIB technique, for step and shoot delivery on an Elekta linear accelerator (Elekta Oncology Systems, Crawley, UK). Five- and 7-beam arrangements were used. Plans were prescribed to the median of the PTV1 such that 95% of each PTV was encompassed by 95% of the prescription dose with maximum doses to the spinal cord of 48 Gy. Maximum mean dose to the parotid glands was 24 Gy where possible.

Follow up (FU)

All patients were assessed prior to commencement of treatment. Acute toxicity was evaluated for 10 weeks after commencement of chemo-IMRT (i.e. for the 6 weeks of chemo-IMRT and the first 4 weeks of recovery) and at week 14 (8 weeks post treatment). Toxicity scoring was performed according to the NCI CTC v.2.0 criteria. Indications for enteral feeding were weight loss >10% and inability to maintain an adequate calorie intake. Late toxicity was collected at 3, 6, 12, 18 and 24 months and yearly thereafter using the RTOG and LENT SOM scoring systems.

The prevalence of an acute reaction at a specified point in time was defined as the proportion of patients scored as

Table 1
Dose schedule for both cohorts

	Initial dose	Dose escalation
Primary	63.0 Gy in 28#	67.2 Gy in 28#
tumour site	(2.25 Gy per fraction)	(2.4 Gy per fraction)
Elective	51.8 Gy in 28#	56 Gy in 28#
nodal areas	(1.85 Gy per fraction)	(2 Gy per fraction)

having that grade of reaction relative to the total number of patients assessed at that specific time point [16]. The incidence of a given reaction was defined as the total number of patients reaching that grade reaction at any time, divided by the total number of evaluable patients [16]. The mean time with a specific grade (G) 3 early reaction was defined as the time in weeks spent with that reaction divided by the number of patients who reached that grade.

Patients were assessed for response at 4–6 weeks following completion of treatment. Complete response (CR) was defined as the complete disappearance of disease as evaluated clinically by nasendoscopy and/or computed tomography. Where residual lesions were present in the larynx or hypopharynx, biopsies were performed to determine the presence of persistent disease. The response rate was defined as the proportion of patients that achieved a specified level of response.

Results

This study commenced in September 2002. A total of 30 patients, 15 in each dose level, were treated. Table 2 shows the patient characteristics. Overall, mean treatment time was 39 ± 3 days in DL 1 and 38 ± 1 days in DL 2, and no patient required treatment breaks. Compliance with both neoadjuvant and concomitant chemotherapy was high (Table 2). Table 3 depicts the acute and late toxicity observed.

Acute toxicity

Overall, during neoadjuvant chemotherapy, 1 patient experienced G4 neutropaenia, one had G3 and 7 had G2. Two patients experienced severe tinnitus, 2 had severe nausea and vomiting and one had renal impairment.

No patient experienced acute grade 4 toxicity. The incidences of G2 and G3 acute toxicity observed in both dose levels are shown in Table 3. During and for the first 8 weeks after chemo-IMRT, the median minimum Karnofsky performance scores (KPS) were 70 (30–90) in DL 1 and 70 (60–90) in DL 2. Median maximum fatigue was grade 2 (1–3) in both dose levels.

Radiation dermatitis

In the DL 1, the peak prevalence of moist desquamation (G3) was 17%, seen in the first week after chemo-IMRT. In DL 2, this figure was 21%, in the last week of treatment. Dry desquamation (G2) started in week 4 in both dose levels and moist desquamation in week 5. At 3 weeks post chemo-IMRT, no patient had moist desquamation and at 8 weeks only 13% of patients in DL 2 had G1 erythema. The average time with G3 dermatitis, in patients who reached that grade, was 1.3 ± 0.6 weeks in the first and 2.0 ± 1.0 weeks in dose level 2.

Radiation-induced dysphagia, pain and mucositis

Fig. 1 shows the prevalence of dysphagia and pain and mucositis as a function of time from the start of chemo-IMRT in both dose levels.

The peak prevalence of grade 3 dysphagia (requirement for enteral feeding) was 64% for DL 1, seen in weeks 7 and 8 (1 and 2 weeks post-IMRT), and 83% in week 9 for DL 2 (Fig. 1). In DL 1, 13% patients still required enteral feeding at week 14 and the same proportion of patients required a soft diet (G2), which

Table 2
Patient characteristics

	Cohort 63 Gy	Cohort 67.2 Gy
Median follow up in weeks (range)	87 (55–162)	40 (9–64)
Median age (range)	59 (37–77)	66 (60–85)
Gender		
Male	11	10
Female	4	5
Primary tumour site		
Larynx	7	7
Hypopharynx	8	8
T stage		
T1	0	1
T2	3	3
T3	8	8
T4	4	3
N stage		
N0	4	8
N1	4	2
N2a	1	0
N2b	3	2
N2c	2	3
N3	1	0
Neoadjuvant chemotherapy	15	13
Concomitant chemotherapy	15	14

Table 3
Incidence of acute G2 and G3 toxicity (NCI CTC v. 2.0) expressed in percentage values and maximum RTOG and LENT SOM toxicity at 1 year in DL 1 and 6 months in DL 2 expressed in absolute number of cases (cases with toxicity/cases evaluable)

	63.0 Gy cohort		67.2 Gy cohort	
	G2	G3	G2	G3
Acute toxicity				
Dermatitis	67%	20%	47%	20%
Mucositis	33%	67%	47%	40%
Dysphagia	20%	67%	13%	87%
Pain	47%	27%	53%	40%
Xerostomia	60%	0	73%	7%
	63.0 Gy cohort at 1y		67.2 Gy cohort at 6m	
Maximum RTOG toxicity				
Skin	G1 (2/11)		G1 (3/10)	
Mucosal	G1 (1/11)		G1 (6/10)	
Oesophageal	G2 (1/11)		G3 (1/10)	
Saliva	G2 (1/11)		G1 (7/10)	
Laryngeal	G1 (3/11)		G2 (2/10)	
Maximum LENT SOM toxicity				
Skin (oedema)	G1 (3/11)		G1 (4/10)	
Mucosa	G0 (4/11)		G1 (3/10)	
Oesophageal	G1 (2/11)		G3 (1/10)	
Saliva	G2 (1/11)		G2 (1/10)	
Laryngeal	G1 (3/11)		G2 (2/10)	

had resolved a month later. In DL 2, at week 14, 23% patients had G3 and 38.5% had G2 dysphagia. In this DL, 1 patient re-

quired enteral feeding up to 1 year following completion of treatment and 20% were still on a soft diet at week 18, which had resolved at 6 months post-treatment.

The peak prevalence of grade 3 pain was 27%, seen in week 7 in DL 1 and 45.5% in week 9 in DL 2 (Fig. 1). In DL 1, 47% of patients required opioids for pain control and 80% in DL 2. The time to onset of G3 dysphagia and pain was similar in both dose levels but resolution was delayed in DL 2 (Fig. 2). Overall, average times with dysphagia and pain were longer in DL 2, 5.9 ± 3.4 and 4.1 ± 2.1 weeks, respectively.

The peak prevalence of confluent mucositis (G3) was 58%, seen in week 7 (1 week post-chemo-IMRT) in DL 1 and 33% in week 6 in DL 2. Patchy mucositis (G2) started in week 3 in both dose levels and healing, represented by a reduction in the prevalence of G3 mucositis commenced in week 9 (3 weeks post-chemo-IMRT). Fig. 1 shows a prolonged healing time for DL 2, with prevalence of G2 mucositis of 58% in week 10, i.e. 4 weeks post-chemo-IMRT and 15% in week 14. However, these 2 patients did, in fact, not attend for their week 14 FU and their toxicity was assumed to be the same as on week 10, i.e. grade 2. By week 18 mucositis had healed in both patients.

The peak functional consequences of mucositis, i.e. dysphagia and pain, were correlated with maximum grade mucositis. A highly significant positive correlation was found, in DL 1, between maximum grades of mucositis and

pain and between maximum grades of mucositis and dysphagia, with Spearman's rank correlation coefficients 0.7 ($p = 0.002$) and 0.6 ($p = 0.02$), respectively. No significant correlation was found in DL 2.

Xerostomia

The peak prevalence of xerostomia in DL 1 was G2 in 73%, seen in week 7. In DL 2 it was G3 xerostomia in 9% in week 9 (Fig. 3). The prevalence of G3 xerostomia was low and the time course of G2 xerostomia was similar in both dose levels, with a somewhat earlier onset in DL 2, and more rapid resolution in DL 1 (Fig. 3).

Late toxicity

Late RTOG and LENTSOM toxicity scores observed at 1 year in DL 1 and at 6 months in DL 2 are shown in Table 3. Only 1 patient in dose level 2 experienced G3 dysphagia, that was, in fact, a consequential late reaction.

Response

A complete response (CR) was documented in 25 patients (83%), 12 in the first and 13 in DL 2. The overall response rate, CR plus partial responses (PR), was 100%. Of those patients with PR in DL 1, 1 had a differential response (CR in the primary and PR in the nodal disease) and 2 had PR both in the pri-

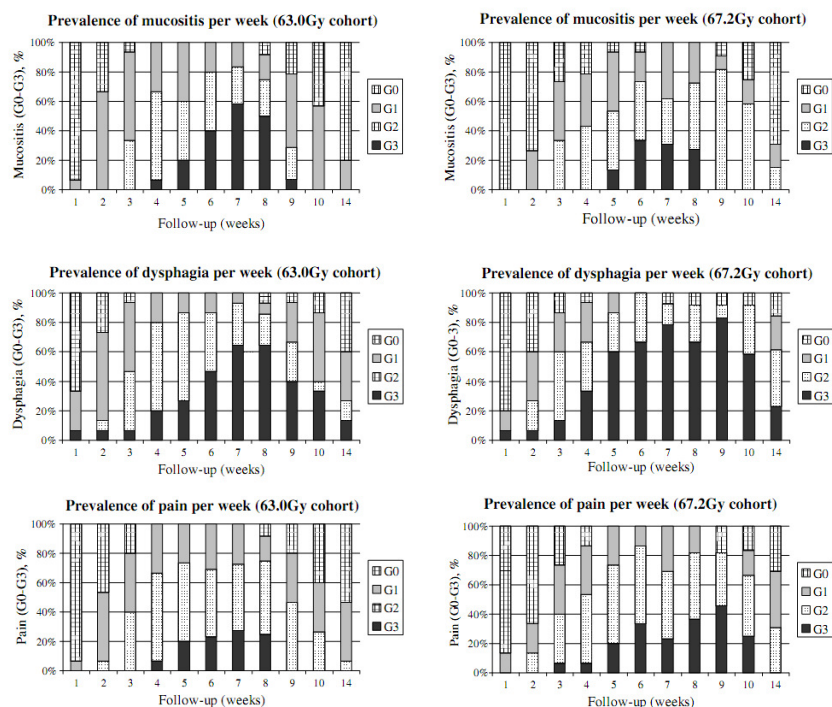


Fig. 1. Prevalence of acute mucositis, dysphagia and pain over time for both cohorts.

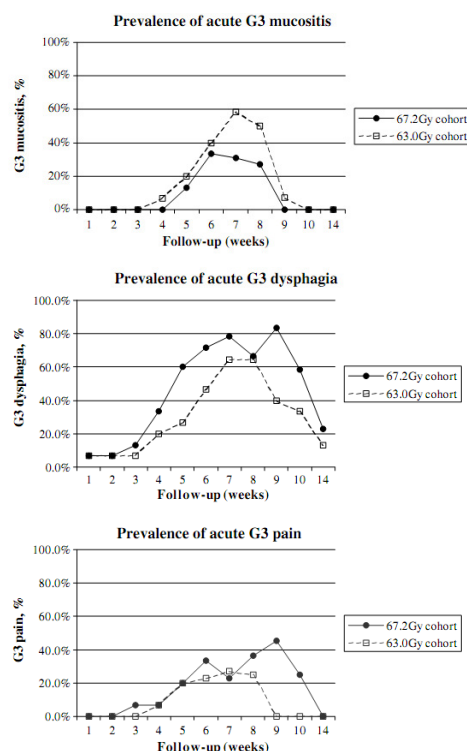


Fig. 2. Prevalence in percentage points of G3 acute mucositis, dysphagia and pain for both cohorts over time.

mary and nodes. In DL 2, 1 patient had a PR in the nodes and the other a PR in the primary. All patients who failed to achieve a CR were managed with salvage surgery, neck dissection alone for the neck failures and plus pharyngo-laryngectomy in patients with PR in the primary. Three of these 5 patients remain alive and disease-free after salvage surgery.

At a median FU of 87 weeks in DL 1 and 40 weeks in the second, median OAS figures were 17 months (12–37) and 8 months (1–14), respectively. Twenty-three (77%) patients are still alive, of whom 22 (73%) are alive and disease-free.

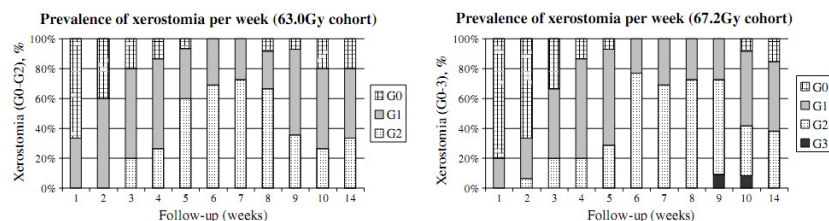


Fig. 3. Prevalence of xerostomia in percentage points for both cohorts over time.

There have been 5 (33%) deaths in DL 1, 3 of progressive disease and 2 of second malignancy. One patient died of carcinoma of the bronchus and another of carcinoma of the oesophagus diagnosed 15 and 18 months, respectively, after the original diagnosis. In DL 2, 2 patients died of intercurrent cardiovascular disease. Median time to recurrence was 9 months (6–13). Five recurrences have been reported to date, all in DL 1, three in the high dose volume (HDV), within the PTV1, one in the low dose volume (LDV), within the PTV2 and one in both the LDV and the lung. The overall laryngectomy rate was 10%, 13% in the first and 7% in DL 2.

Discussion

In this phase I dose escalation study we have shown that neoadjuvant chemotherapy followed by radical chemo-IMRT is feasible and that a 9% escalation of the radiation dose to the primary target volume is possible without treatment breaks or dose limiting toxicity. Both radiotherapy and chemotherapy compliance were excellent.

This study was designed to determine the toxicity of combining the delivery of a higher biologically effective radiation dose using IMRT, which can potentially reduce normal tissue damage, with the radio-sensitising properties of concomitant cisplatin. The small number of patients and the design of this study as a dose escalation protocol, as well as the still short follow up period, make it difficult to draw meaningful conclusions from the outcome data. However, some observations can be made. All patients responded to treatment, with an overall CR rate of 83%. It could be argued that these excellent response rates could potentially be related, in part, to the IMRT technique, which can avoid areas of low dose within the target volume. All loco-regional recurrences observed to date appeared in DL 1, a fact that may be a reflection of the short median follow-up in DL 2. However, the effect of an escalated dose of radiation is likely to contribute to improved local control. IMRT is associated with a potential increase of geographical miss. In our study, no recurrences were observed outside the treated volumes. Of the 5 recurrences observed, 3 were in the high dose volume, suggesting the existence of resistant tumour clonogens within this volume. IMRT could potentially be used to further escalate the dose to the GTV in an attempt to overcome resistance factors such as hypoxia. In addition, the fact that 2 patients in our study recurred in the low dose volume suggests dose escalation of the elective neck possibly warrants further evaluation. This is contrary to the generally accepted view that dose escalation of elective tissue is not appropriate.

The incidence of moist desquamation was rather low in both dose levels (20%). In our study, the skin was specifically excluded from the target volume and the immobilisation shell was cut out to avoid any build-up effect and to allow skin-sparing. It is interesting to note that the incidence of confluent mucositis (G3) was lower in the dose escalated DL (40% vs. 67%). This most likely represents an underestimation of the true incidence of this grade of mucositis. Most of these patients had high dose target volumes that extended only 1–2 cm above the epiglottis and mucositis in this PTV1 often could only be assessed by flexible nasendoscopy, which is excessively uncomfortable during radical chemoradiotherapy. In agreement with other authors [16,17], we also found a significant positive correlation in the first DL, between maximum grades of mucositis and pain and between maximum grades of mucositis and dysphagia. Overall, patients in the dose escalated DL had higher rates of G3 dysphagia, pain and xerostomia, but these were manageable and did not lead to any unplanned treatment breaks. Although the incidence of G3 mucositis was lower in DL 2, a longer time to resolution was observed. Fig. 2 clearly shows how G3 dysphagia and pain peaked higher, later and lasted longer than in DL 1. This was expected and, reassuringly, recovery was observed in all patients but one, who was still PEG-dependent 1 year following completion of treatment. The time course of acute reactions was similar in both dose levels, with the peak prevalence of acute toxicity occurring towards the end or shortly after completion of treatment. This highlights the importance of close follow-up in the first few weeks post-treatment in this group of patients. One patient in each DL required enteral feeding from the start of treatment due to weight loss secondary to the presence of bulk disease. This was included in the analysis from the beginning to incorporate the radiation toxicity seen as the RT progressed.

Follow up is too short to draw any conclusions on the late toxicity observed. To date, it has been low and, remarkably, the incidence of PEG feeding much lower than that reported in the literature in studies evaluating conventionally-delivered altered fractionation regimens plus concomitant chemotherapy, with reported incidences of long-term PEG feeding as high as 30% [7,8].

Dose escalation caused higher acute toxicity, but there was no dose-limiting toxicity and no treatment breaks. Pending further follow up the late toxicity observed to date was moderate and similar to what would be expected with conventional radiotherapy.

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Paper 10



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CLINICAL INVESTIGATION

Head and Neck Cancer

DOSE-ESCALATED INTENSITY-MODULATED RADIOTHERAPY IS FEASIBLE AND MAY IMPROVE LOCOREGIONAL CONTROL AND LARYNGEAL PRESERVATION IN LARYNGO-HYPOPHARYNGEAL CANCERS

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Purpose: To determine the safety and outcomes of induction chemotherapy followed by dose-escalated intensity-modulated radiotherapy (IMRT) with concomitant chemotherapy in locally advanced squamous cell cancer of the larynx and hypopharynx (LA-SCCL/H).

Methods and Materials: A sequential cohort Phase I/II trial design was used to evaluate moderate acceleration and dose escalation. Patients with LA-SCCL/H received IMRT at two dose levels (DL): DL1, 63 Gy/28 fractions (Fx) to planning target volume 1 (PTV1) and 51.8 Gy/28 Fx to PTV2; DL2, 67.2 Gy/28 Fx and 56 Gy/28 Fx to PTV1 and PTV2, respectively. Patients received induction cisplatin/5-fluorouracil and concomitant cisplatin. Acute and late toxicities and tumor control rates were recorded.

Results: Between September 2002 and January 2008, 60 patients (29 DL1, 31 DL2) with Stage III (41% DL1, 52% DL2) and Stage IV (52% DL1, 48% DL2) disease were recruited. Median (range) follow-up for DL1 was 51.2 (12.1–77.3) months and for DL2 was 36.2 (4.2–63.3) months. Acute Grade 3 (G3) dysphagia was higher in DL2 (87% DL2 vs. 59% DL1), but other toxicities were equivalent. One patient in DL1 required dilatation of a pharyngeal stricture (G3 dysphagia). In DL2, 2 patients developed benign pharyngeal strictures at 1 year. One underwent a laryngo-pharyngectomy and the other a dilatation. No other G3/G4 toxicities were reported. Overall complete response was 79% (DL1) and 84% (DL2). Two-year locoregional progression-free survival rates were 64.2% (95% confidence interval, 43.5–78.9%) in DL1 and 78.4% (58.1–89.7%) in DL2. Two-year laryngeal preservation rates were 88.7% (68.5–96.3%) in DL1 and 96.4% (77.7–99.5%) in DL2.

Conclusions: At a mean follow-up of 36 months, dose-escalated chemotherapy-IMRT at DL2 has so far been safe to deliver. In this study, DL2 delivered high rates of locoregional control, progression-free survival, and organ preservation and has been selected as the experimental arm in a Cancer Research UK Phase III study. © 2012 Elsevier Inc.

Dose escalation, IMRT, Larynx, Hypopharynx.

INTRODUCTION

Laryngeal and hypopharyngeal cancers account for nearly 15,000 new cases annually in the United States (1). Radical chemoradiation or surgery (laryngectomy/pharyngo-laryn-

gectomy) with or without adjuvant radiation/chemoradiation are the main treatment options for locally advanced tumors. Concomitant cisplatin with radiotherapy for locally advanced squamous cell cancer of the larynx and hypopharynx (LA-SCCL/H) can achieve locoregional failure-free rates of

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60–65% at 2 years, with a laryngeal preservation rate of 35–65% (2–4). These treatment modalities offer similar overall survival rates when compared with surgery and have improved locoregional control and laryngeal preservation rates over the last 30 years (5, 6). However, further improvement has been limited by treatment-related toxicities.

A meta-analysis confirmed improved locoregional control and overall survival when altered, as opposed to standard, fractionation regimens were delivered (7). Unfortunately, combining concomitant chemotherapy with altered fractionation using conventional radiotherapy techniques causes severe normal tissue toxicities and consequential morbidity (8, 9). Intensity-modulated radiotherapy (IMRT) delivers radiation more conformally and reduces the volume of normal tissue in the high-dose volume (10). This has allowed us to investigate accelerated hypofractionated IMRT in LA-SCCL/H.

The purpose of this Phase I/II study was to determine the safety and outcomes of delivering induction chemotherapy followed by concomitant chemotherapy and dose-escalated IMRT (chemotherapy-IMRT) in LA-SCCL/H.

METHODS AND MATERIALS

Study objectives and patient eligibility

Patients with histologically proven LA-SCCL/H (T1–4, N0–3, M0) suitable for primary chemotherapy-IMRT were eligible. Patients aged <18 years or with a previous malignancy other than nonmelanomatous skin cancer were excluded. Pretreatment evaluations comprised history and examination, examination under anesthesia, biopsy, dental assessment, hematologic and biochemical parameters, and computed tomography scan of the head, neck, and chest. Disease was staged according to the 1997 American Joint Committee on Cancer criteria (11). All patients provided written informed consent, and the study was approved by the institutional research and ethics committee (Royal Marsden Hospital CCR 1978).

The primary objective was to test the feasibility of delivering induction chemotherapy and modestly accelerated dose-escalated chemotherapy-IMRT. Secondary objectives were to record acute and long-term toxicities, locoregional control, and progression-free and overall survival.

Trial design

A sequential cohort Phase I/II dose-escalation design was used. Initially, 15 patients were enrolled to each dose level (DL). For DL1, planning target volume 1 (PTV1) comprising primary site and involved nodal levels received 63 Gy in 28 fractions over 38 days. Radiobiological calculations have been previously described (12). The equivalent dose at 2 Gy/fraction (EQD2), when corrected for the reduction in overall treatment time, was 70 Gy. The elective nodal levels (PTV2) received 51.8 Gy (EQD2 = 47.5 Gy). Dose Level 2 represented an increase in biologically equivalent dose of 9% for the primary tumor (76 Gy), thus delivering 67.2 Gy in 28 fractions to PTV1 and 56 Gy in 28 fractions to PTV2 (EQD2 = 51 Gy).

Treatment

Chemotherapy schedule. At the time of trial design there was no clear consensus as to the role of induction chemotherapy. Induction

chemotherapy using cisplatin and 5-fluorouracil (5-FU) had been routinely used at our institution with good results (13). All patients received induction chemotherapy: two cycles of cisplatin (75 mg/m², Day 1) and 5-FU (1000 mg/m², Days 1–4) on a 21-day cycle (13). Patients received cisplatin 100 mg/m² on Days 1 and 29 of IMRT. Where cisplatin was contraindicated, carboplatin was administered.

Radiotherapy technique. Patients were immobilized with a custom-made mask. Target volumes and organs at risk (brain stem, spinal cord, and parotid glands) were delineated according to International Commission on Radiation Units and Measurements Reports 50 and 62 guidelines, as previously described (12, 14, 15).

Radiotherapy was delivered using five- or seven-beam simultaneous integrated boost IMRT techniques. Radiation dose was prescribed to the median of the PTV1 dose volume histogram such that 50% of the volume received the prescription dose, and 95% of each PTV was encompassed by 95% of the prescription dose, with maximum dose constraints applied to 1 cm³ of the spinal cord and brainstem being 46 Gy and 54 Gy, respectively, in both dose levels. A mean dose constraint of 24 Gy was applied to each parotid gland.

Outcome assessment

Complete response was defined as complete disappearance of disease as evaluated clinically, including nasoendoscopy and computed tomography. Response Evaluation Criteria In Solid Tumors were used to record radiologic response (16). Where residual lesions were present in the larynx, hypopharynx, or neck, biopsies or fine-needle aspirations were performed to determine the presence of persistent disease. Neck dissection was undertaken if patients demonstrated a clinical or radiologic partial response, stable disease, or progressive disease after radiotherapy. Recurrence was defined as clinical, radiologic, and/or histopathologic evidence of disease presenting 3 months after completion of radiotherapy. Where possible, patients proceeded to salvage surgery for persistent or recurrent disease.

Acute toxicity scores were recorded using National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 weekly during chemotherapy-IMRT, for 4 weeks of recovery, and at Week 14. Indications for enteral feeding were weight loss >10%, risk of aspiration, and inability to maintain adequate caloric intake. Late toxicity scores (Radiation Therapy Oncology Group [RTOG]/European Organization for Research and Treatment of Cancer and Late Effects in Normal Tissues–Subjective, Objective, Management, and Analytic scale [LENT-SOMA]) were recorded at follow-up, at 3, 6, 12, 18, and 24 months after radiotherapy, and yearly thereafter for 5 years.

Statistical analysis

Dose Level 1 was designed as a feasibility study of hypofractionated chemotherapy-IMRT equivalent to 70 Gy in 35 fractions. Dose escalation to DL2 was scheduled once feasibility was demonstrated. The stopping rules determined that if none of 15 patients had Grade ≥3 late complications at 1 year then a ≥20% risk of Grade 3 late complication rate would be excluded with 95% power. If any patient developed Grade ≥3 late complications at DL1, then the number of patients recruited at that level would be increased to 30 to improve statistical power, and escalation to DL2 would only be allowed if no more than 2 patients developed Grade 3 late toxicity (incidence of Grade ≥3 late complication rate predicted to be 0–17% and 0–22%, respectively, with 95% power). If more than 2 patients had a Grade ≥3 late complication then recruitment

to that level would be stopped (incidence of Grade ≥ 3 complication predicted to be 2–27% with 95% power). The dose-limiting toxicity (DLT) was defined as the proportion of patients with any Grade 3 or Grade 4 toxicity at 1 year after completion of treatment. The two dose cohorts are sequential studies, and their outcomes are reported separately.

Outcome measures after chemotherapy-IMRT were described by local (at primary site) and regional (neck) control. Locoregional control rate was defined as the proportion of patients with no evidence of recurrent local and/or neck disease. Locoregional progression-free survival was calculated as time from diagnosis to recurrent local or nodal disease. Patients with persistent disease at primary site or neck were included as locoregional events. Laryngeal preservation rates were the proportion of patients who achieved local control and avoided laryngectomy. Disease-free survival was defined as time from diagnosis to development of locoregional and/or distant disease. Patients who underwent salvage surgery for locoregional control were classified as disease free. Overall survival was measured from diagnosis to death from any cause. Survival analyses were estimated using the Kaplan-Meier method. The incidence of an acute or late toxicity was defined as the total number of patients reaching that grade at any time divided by the total number of assessable patients (17).

RESULTS

Patient characteristics and treatment compliance

From September 2002 to January 2008, 29 patients were treated in DL1 and 31 in DL2. Table 1 lists the pretreatment demographic and tumor characteristics. Disease stage was 41% Stage III and 53% Stage IV in DL1 and 52% Stage III and 48% Stage IV in DL2. All patients in DL1 and 94% in DL2 received induction chemotherapy, with 100% and 97% compliance for concomitant chemotherapy-IMRT, respectively. Median (range) time to complete radiotherapy was 38 (37–43) days for DL1 and 38 (37–45) days for DL2.

Acute toxicity

Acute toxicities have been reported previously (12) and are updated in Table 2. There were high incidences of acute Grade 3 dysphagia: 59% in DL1 and 87% in DL2, which peaked during treatment, with early recovery by 8 weeks after radiotherapy (Grade 3 dysphagia 12% and 23% in DL1 and DL2, respectively). Grade 3 mucositis, dermatitis, pain, and fatigue were similar in both groups. The incidence of acute Grade 3 xerostomia was higher in DL2 (26%: 16% hypopharynx, 10% larynx) compared with DL1 (10%: all laryngeal cancers). Mean (range) doses to the parotid glands in the laryngeal cohort in DL1 were ipsilateral (IL), 22.4 (14.9–44.8) Gy and contralateral (CL), 21.5 (10.1–42.4) Gy; and in the hypopharynx cohort were IL, 34.6 (24.0–49.5) Gy and CL, 25.2 (19.2–32.0) Gy. In DL2, the mean doses in the laryngeal cohort were IL, 32.4 (17.6–57.0) Gy and CL, 25.1 (13.6–50) Gy; and in the hypopharynx cohort were IL, 35.2 (21.9–58.0) and CL, 23.2 (17.5–31.4). One patient died in DL2, 17 days after completing chemotherapy-IMRT after a myocardial infarction. No other deaths were reported within 90 days of completing treatment.

Table 1. Patient characteristics ($n = 60$)

Characteristic	Dose Level 1 (63 Gy/28 Fx)	Dose Level 2 (67.2 Gy/28 Fx)
No. of patients	29	31
Follow-up (mo), median (range)	49.0 (35.7–78.3)	35.7 (17.7–62.8)
Age (y), mean (range)	58 (35–80)	63 (43–85)
Sex (male)	23 (79)	24 (77)
Performance status		
0	24 (83)	30 (97)
1	5 (17)	1 (3)
Primary tumor site		
Larynx	17 (59)	16 (52)
Hypopharynx	12 (41)	15 (48)
T stage		
T1–2	9 (31)	7 (23)
T3	14 (48)	17 (54)
T4a	6 (21)	7 (23)
N stage		
N0	10 (35)	13 (42)
N1	7 (24)	7 (23)
N2	10 (35)	11 (35)
N3	2 (6)	0
TNM stage		
I	1 (3)	0
II	1 (3)	0
III	12 (41)	16 (52)
IVA	13 (46)	15 (48)
IVB	2 (7)	0
Neoadjuvant chemotherapy completed according to protocol		
Yes	29 (100)	29 (94)
No	0	2 (6)
Concomitant chemotherapy completed full schedule	29 (100)	30 (97)

Abbreviation: Fx = fractions.

Values are number (percentage) unless otherwise noted.

Chemotherapy toxicity

In DL1, 94% of patients completed 2 cycles of induction chemotherapy: cisplatin and 5-FU, 1 patient (3%) received 2 cycles of carboplatin and 5-FU, and another patient (3%) changed from cisplatin to carboplatin for their second cycle of induction chemotherapy. In DL2, 88% of patients received induction cisplatin and 5-FU, 6% received carboplatin and 5-FU, and 1 patient (3%) was postoperative. The second cycle of cisplatin and 5-FU was omitted in 1 patient (3%) after a myocardial infarction.

Eighty-one to eighty-three percent of patients received concomitant cisplatin. Carboplatin was administered in 17% of patients in DL1 and 19% in DL2. Grade 2 neutropenia was reported in 41% and 42% in DL1 and DL2, respectively. There were no cases of neutropenic sepsis. Sixty-two percent of patients in DL1 received blood transfusions during radiotherapy and 52% in DL2.

Late toxicity at 1 year

Table 3 lists the late IMRT-related adverse effects. Twenty-one of 29 patients (72%) in DL1 were assessable

Table 2. Type and frequency of acute toxicity (CTCAEv3.0) observed in the Dose Level 1 and Dose Level 2 cohorts (n = 60)

Acute toxicity	Dose Level 1 (n = 29)					Dose Level 2 (n = 31)				
	G0	G1	G2	G3	G4	G0	G1	G2	G3	G4
Dermatitis	0	8 (28)	14 (48)	7 (24)	0	0	9 (29)	15 (48)	7 (23)	0
Dysphagia-pharyngeal	1 (3)	1 (3)	9 (32)	17 (59)	1 (3)	0	0	2 (6)	27 (87)	0
Dysphagia-esophageal	0	3 (10)	8 (28)	17 (59)	1 (3)	0	0	4 (13)	27 (87)	0
Dysphagia-esophageal at 8 wk	11 (42)	6 (23)	5 (19)	3 (12)	1 (4)	4 (14)	7 (23)	12 (40)	7 (23)	0
Fatigue	0	7 (24)	18 (62)	4 (14)	0	0	6 (19)	20 (65)	5 (16)	0
Mucositis	1 (3)	4 (14)	11 (38)	13 (45)	0	0	4 (13)	13 (42)	14 (45)	0
Pain	0	8 (28)	15 (52)	6 (21)	0	0	1 (3)	20 (65)	10 (32)	0
Xerostomia	2 (6)	7 (24)	17 (59)	3 (10)	0	0	7 (23)	16 (52)	8 (26)	0

Abbreviations: CTCAE = common terminology criteria for adverse events; G = grade.
Values are number (percentage).

at 1 year and 24 of 31 (77%) in DL2. An initial cohort of 15 patients in DL1 reported no Grade ≥ 3 toxicity at 1 year. The study progressed to DL2. In DL2, 1 patient remained dependent on gastrostomy feeding (Grade 3) at 1 year. At 20 months, videofluoroscopy demonstrated a benign cricopharyngeal stricture. The mean dose delivered to the inferior constrictor muscles was 65.5 Gy. Dilatation was unsuccessful, and the patient underwent laryngopharyngectomy. Dose Level 2 was expanded to 31 patients, and a second patient reported Grade 3 dysphagia 10 months after radiotherapy. A benign postcricoid stricture was identified and treated by balloon dilatation. Repeat dilatation was required 7 months after the original procedure. In this patient the mean dose delivered to the inferior constrictor muscles was 67.9 Gy. While awaiting completion of 1 year follow-up in DL2, institutional and ethical approval was obtained to allow further recruitment to a total of 29 patients in DL1. One patient in DL1 reported Grade 3 pharyngeal dysphagia 7 months after treatment. A benign stricture at the level of the C5/C6 vertebral bodies was diagnosed and successfully dilated without further complications. All 3 patients who developed pharyngeal strictures in the two cohorts had been treated for laryngeal carcinomas where the pharyngeal muscles were previously unaffected. Overall, 1 patient reported a Grade 3 late toxicity in DL1 at 1 year (1 of 29, an incidence of 3%). Two patients in DL2 reported high-grade late toxicity

(one Grade 3 and one Grade 4) at 1 year (2 of 31, an incidence of 6%). No further Grade 3 or Grade 4 toxicities were reported in either cohort at 2 years (Fig. 1). The incidence of xerostomia (Grade ≥ 2 by LENT-SOMA) at 1 year for DL1 was 8% and 9% for DL2.

Functional outcomes

One patient in DL2 experienced aspiration pneumonia after treatment despite gastrostomy feeding and died 4 months later. Videofluoroscopy was performed in 6 patients (21%) in DL1 and 9 patients (29%) in DL2 within 90 days of completing radiotherapy. There were no cases of silent aspiration, but 4 cases of aspiration risk (14%) in DL1 and 6 cases (19%) in DL2. Two patients (6%) experienced laryngeal penetration in DL2, which resolved after intensive speech and language therapy rehabilitation.

Response to treatment

All patients demonstrated stable disease or partial response to induction chemotherapy and proceeded to concomitant chemotherapy with IMRT. In DL1, the overall complete response rate was 79% and partial response 21%. Two patients (6%) underwent neck dissection after chemotherapy-IMRT, of whom 1 had residual nodal disease. In DL2, the overall complete response rate was 84% and partial response 13%. One patient demonstrated

Table 3. Type and frequency of late radiotherapy adverse effects (LENT-SOMA) at 1 year (n = 60)

Site	Dose Level 1 (n = 29)					Dose Level 2 (n = 31)				
	G0	G1	G2	G3	G4	G0	G1	G2	G3	G4
Skin	16 (76)	4 (19)	1 (5)	0	0	21 (88)	3 (12)	0	0	0
Mucosa	12 (57)	9 (43)	0	0	0	17 (71)	7 (30)	0	0	0
Subcutaneous Tissue	18 (86)	3 (14)	0	0	0	15 (63)	7 (30)	2 (7)	0	0
Larynx	9 (43)	7 (33)	5 (24)	0	0	6 (25)	14 (58)	4 (17)	0	0
Esophagus	15 (71)	5 (25)	0	1 (5)	0	15 (60)	7 (29)	0	1 (4)	1 (4)
Salivary gland	10 (48)	9 (43)	2 (9)	0	0	9 (38)	13 (54)	2 (8)	0	0
Spinal cord	21 (100)	0	0	0	0	24 (100)	0	0	0	0

Abbreviations: LENT-SOMA = late effects in normal tissues-subjective, objective, management, and analytic scale; G = grade.
Values are number (percentage).

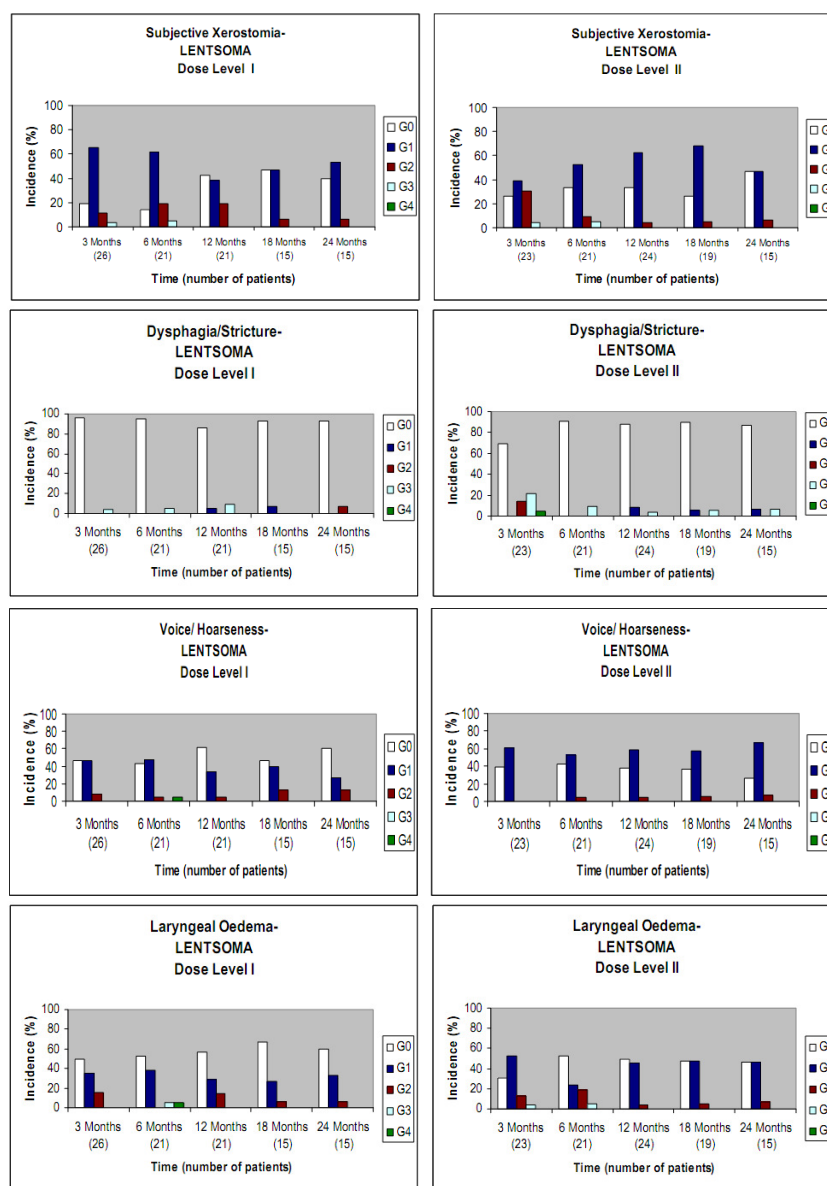


Fig. 1. (a–f) Incidence of long-term toxicities over time. LENTSOMA = Late Effects in Normal Tissues–Subjective, Objective, Management, and Analytic scale.

progressive disease. One patient proceeded to neck dissection after completing chemotherapy-IMRT with confirmed residual disease.

Failure pattern

Median (range) follow-up was 51.2 (35.7–78.3) months for DL1 and 36.2 (17.7–62.8) months for DL2. In DL1,

Table 4. Treatment outcomes at 2 years

Outcome	Dose Level 1 (n = 29)	Dose Level 2 (n = 31)
Follow-up (mo), median (range)	51.2 (12.1–77.3)	36.2 (4.2–63.3)
Local control rate	70.8 (49.7–84.3)	85.9 (66.7–94.5)
Locoregional control rate	67.6 (46.7–81.7)	81.8 (61.6–92.1)
Locoregional progression-free survival	64.2 (43.5–78.9)	78.4 (58.1–89.7)
Disease-free survival	61.5 (58.8–89.9)	78.4 (58.1–89.7)
Larynx preservation rate	88.7 (68.5–96.3)	96.4 (77.2–99.5)
Overall survival	72.4 (52.3–85.1)	74.2 (55.0–86.2)

Values are percentage (95% confidence interval) unless otherwise noted.

locoregional failure occurred in 9 patients (31%). Eight patients (28%) demonstrated persistent or relapsed disease at the primary site, and 1 patient relapsed in the neck. Four patients (14%) proceeded to laryngectomy, whereas 5 (17%) were inoperable or unfit to proceed to radical surgery. Larynx preservation rate at 2 years was 88.7% (95% confidence interval [CI], 68.5–96.3%). Eleven patients (38%) developed distant metastases.

In DL2, locoregional failure was reported in 5 patients (16%). Four patients (13%) demonstrated persistent or relapsed disease at the primary site; 2 patients (6%) proceeded to laryngectomy, with the remainder deemed inoperable or unfit to proceed to radical surgery. The larynx preservation rate at 2 years was 96.4% (95% CI, 77.2–99.5%). One patient relapsed in the neck. Seven patients (23%) developed distant metastases.

Eleven patients (38%) have died in DL1 and 8 (28%) in DL2. Table 4 lists the locoregional control rates and survival rates. Figure 2a and b illustrate the Kaplan-Meier curves for locoregional progression-free survival for DL1 and DL2, respectively. Two-year locoregional progression-free survival for DL1 was 64.2% (95% CI, 43.5–78.9%) and for DL2 was 78.4% (95% CI, 58.1–89.7%). Overall survival at 2

years for the two cohorts was similar: DL1, 72.4% (95% CI 52.3–85.1%) and DL2, 74.2% (95% CI, 55.0–86.2) (Fig. 3a and b).

DISCUSSION

In this sequential cohort Phase I/II study, two accelerated hypofractionated radiotherapy regimens with induction and concomitant chemotherapy were found to be deliverable without treatment breaks. Dose Level 2 confirmed that dose escalation is feasible and has the potential to improve locoregional control rates without increasing long-term toxicities. The primary objective of the study was achieved and supports further evaluation of dose-escalation chemotherapy-IMRT in improving locoregional control and organ preservation.

Locally advanced SCCL/H has benefited from altered radiotherapy fractionation regimens (pure acceleration or altered fractionation with a higher total dose) (18, 19). The RTOG 9003 study concluded that hyperfractionation or accelerated fractionation with concomitant boost provided significantly better locoregional control when compared with conventional fractionation (54.5% vs. 46.0% at 2 years) (20). Accelerated radiotherapy, compared with a conventional treatment of 7 weeks, can achieve maximum shortening in treatment time of 2 weeks, with the normal mucosa being the DLT and any further acceleration requiring a reduction of dose. Further dose escalation schedules with conformal radiotherapy techniques have been unsuccessful because of unacceptable acute and/or late toxicity. Maciejewski *et al.* (9) compared a 70 Gy in 35 daily fractions over 7 days per week fractionation schedule vs. a 5 days per week schedule and found an unacceptably high incidence of severe acute reactions and consequential late effects in the accelerated arm. Jackson *et al.* (8) randomized 66 Gy in 33 daily fractions once daily vs. twice daily. The trial was discontinued early because of an increase in Grade 4 toxicity in the accelerated arm.

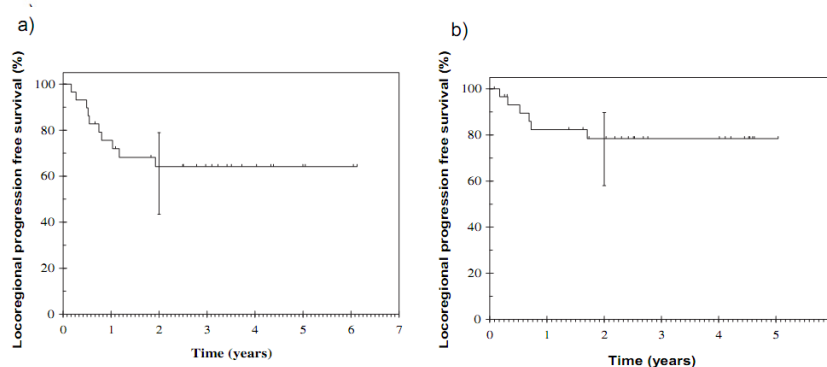


Fig. 2. Locoregional progression-free survival for patients treated at (a) Dose Level 1 and (b) Dose Level 2. Vertical bars indicate 95% confidence interval for the 2-year survival rate.

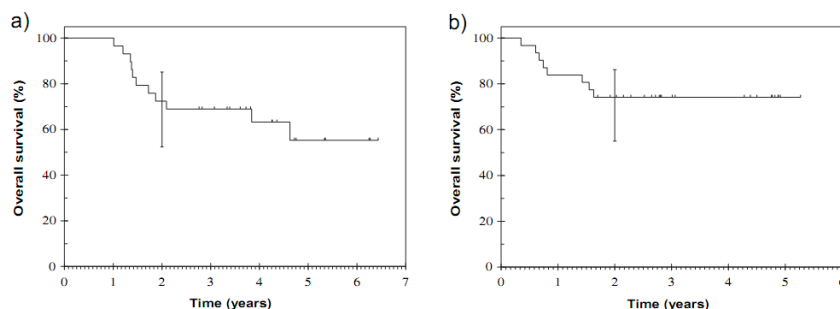


Fig. 3. Overall survival for patients treated at (a) Dose Level 1 and (b) Dose Level 2. Vertical bars indicate 95% confidence interval for the 2-year survival rate.

Phase III trials have demonstrated a lower incidence of patient-reported toxicities with IMRT when compared with conformal radiotherapy techniques in the treatment of oropharyngeal (21) and nasopharyngeal cancers (22, 23). However, dose-escalation IMRT studies in the treatment of locally advanced head-and-neck cancers are sparse. Madani *et al.* (24) assessed the feasibility of positron emission tomography-guided focal dose escalation using IMRT. Patients received 25 Gy in 10 daily fractions to a subvolume within the gross tumor volume. Standard 2.16 Gy per fraction was applied to the remainder of the volume and then to the combined target volumes for the remaining 22 fractions. There were two cases of DLTs (Grade 4 dermatitis and Grade 4 dysphagia). The second dose level delivered 30 Gy in 10 fractions to the positron emission tomography-defined volume within the gross tumor volume. The study was stopped after a treatment-related death (sepsis and renal failure) at the second dose level. Lee *et al.* (25) reported a retrospective review of laryngeal and hypopharyngeal cancers treated with concurrent chemotherapy and IMRT. All patients experienced RTOG Grade ≥ 2 pharyngitis during treatment. Two-year percutaneous endoscopic gastrostomy dependence rates were 31% and 15% for hypopharyngeal and laryngeal cancers, respectively. Percutaneous endoscopic gastrostomy dependence was related to pharyngeal stricture or high-grade dysphagia (25).

In our study, a high incidence of acute toxicities was reported in both dose levels, as expected, but there were no DLTs and no treatment breaks. Acute Grade 3 dysphagia was higher in DL2 and persisted for longer. However, high-grade acute side effects did not translate to a higher incidence of long-term toxicities. Our study defined very conservative stopping rules: the incidence of high-grade dysphagia at 1 year was 6% in DL2, whereas incidences reported in the literature are 30% (25–27). The mean dose delivered to the inferior constrictor muscles in DL2 was 68.1 Gy (range, 65.5–69.3 Gy). We have no reported cases of laryngeal cartilage necrosis or laryngectomy for a dysfunctional larynx. Patients with successful organ preservation also maintained acceptable function. In our

study, no formal functional outcome measures of speech and swallow were undertaken. These will be included in our subsequent studies alongside quality-of-life parameters. The RTOG has described age, tumor stage, primary site (larynx/hypopharynx), and neck dissection after chemoradiation as factors associated with severe late toxicity after concomitant chemoradiation for locally advanced squamous cell cancer of the head and neck (28). They also demonstrated that the peak incidence of severe toxicity occurs at 3 years after treatment. In our study there has been no increase in incidence of high-grade (Grade ≥ 3) radiation-related late toxicities at 2 to 3 years compared with the reports at 1 year.

Within the limitations of this small study, improved treatment outcomes were reported in DL2. Local control rates at 2 years in the two cohorts were 70.8% and 85.9% in DL1 and DL2, respectively, with larynx preservation rates at 2 years of 88.7% and 96.4%. The difference between these two outcome measures is explained by the patients either being unfit for salvage surgery or that the disease was deemed inoperable. Locoregional control rates at 2 years for the two dose levels with a median follow-up of 24 months for DL1 and 21 months for DL2 were reported as 65% and 85%, respectively (29). To emphasize, the study was not powered to determine differences in locoregional control and survival. However, the potential difference in overall response rates and locoregional recurrences between the two cohorts could be due to increased radiobiological effectiveness of DL2. It may be suggested that DL1 represents an inferior radiobiological effective dose. However, when we compare DL1 outcomes with those reported in the literature using conventional dose and fractionation, the locoregional control rates are similar at 60–65% at 2 years for laryngeal cancers. With longer median follow-up of 51.2 months for DL1 and 36.2 months for DL2, an improvement in locoregional control is maintained. We appreciate the limitations of this study of small sample size and sequential non-randomized cohorts but demonstrate the feasibility in testing DL2 in the context of a randomized study. All

recurrences have occurred within the radical dose or elective dose volumes. There were no marginal recurrences. This suggests that further evaluation of dose-escalation strategies specifically to regions of hypoxia within the gross tumor volume to overcome radiation resistance should be considered.

CONCLUSIONS

Dose-escalated chemotherapy-IMRT with moderate acceleration is safe, feasible, and seems to improve locore-

gional control rates for the treatment of laryngeal and hypopharyngeal cancers.

This will now proceed to a Phase III study called ART-DECO (Accelerated RadioTherapy—Dose Escalation versus COnventional dose). The primary objective is to determine whether there is an improvement of locoregional failure-free rate at 2 years compared with standard-dose chemotherapy-IMRT. In conjunction with recently published consensus guidelines for laryngeal preservation studies, we will also evaluate laryngeal and oesophageal dysfunction and associated quality of life (30).

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12. Guerrero Urbano T, Clark CH, Hansen VN, *et al.* A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer. *Radiother Oncol* 2007;85:36–41.
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15. Humphreys M, Guerrero Urbano MT, Mubata C, *et al.* Assessment of a customised immobilisation system for head and neck IMRT using electronic portal imaging. *Radiother Oncol* 2005;77:39–44.
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25. Lee NY, O'Meara W, Chan K, *et al.* Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. *Int J Radiat Oncol Biol Phys* 2007;69:459–468.
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- and neck: A prospective randomized trial. *J Clin Oncol* 2000;18:1458–1464.
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 28. Machtay M, Moughan J, Trotti A, *et al.* Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: An RTOG analysis. *J Clin Oncol* 2008;26:3582–3589.
 29. Nutting CM, Miah AB, Bhide SA, *et al.* Dose escalation chemo-IMRT improves locoregional control rates in organ preservation treatment of locally advanced laryngeal and hypopharyngeal cancers. *Radiother Oncol* 2009;90(Suppl. 2):S11.
 30. Lefebvre JL, Ang KK. Larynx preservation clinical trial design: Key issues and recommendations—a consensus panel summary. *Head Neck* 2009;31:429–441.

Permission to use papers

I was unable to get permission to use papers from the following people due to them having left The Royal Marsden NHS Trust and leaving no further contact details.

Paper	Name
1	C. Mubata M..Humphreys
2	P.Normile
4	C. Kong
5	H. Chantler C. Edwards H. James G. Webster
7	F.Adab M. Tanay BK. Yap
8	C. Mubata
10	R. Nicol S. St Rose M. Tanay



**CITY UNIVERSITY
LONDON**

STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Humphreys M, Guerrero Urbano MT, Mubata C, Miles E, Harrington KJ, Bidmead M, **Nutting CM.**

Assessment of a customised immobilisation system for head and neck IMRT using electronic portal imaging. Radiother Oncol. 2005;77:39-44.

Name of candidate: Christopher Nutting

Title of research thesis: Can Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

Supervisors: Craig/Proctor/Harrington

We, the undersigned, co-authors of the above publication, confirm that the above publication has not been submitted as evidence for which a degree or other qualification has already been awarded.

We, the undersigned, further indicate the candidate's contribution to the publication in our joint statement below.

Signature:

Name: Mandy Humphreys

Date:

Signature: 

Name: Teresa Guerrero Urbano

Date: 22/12/11

Signature: 

Name: Cephas Mubata

Date:

Signature: 

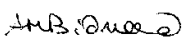
Name: Elizabeth Miles

Date:

Signature: 

Name: Kevin Harrington

Date: 20/12/11

Signature: 

Name: Margaret Bidmead

Date: 19/12/11

Statement indicating the candidate's contribution to the publication
{Statement in support of candidate's contribution to the publication}

CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. MH, CM, EM, and MB collected and analysed scan data. TGU and KH provided clinical support.



STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Nutting CM, Normile PS, Bedford JL, Harrington KJ, Webb S.

A systematic study of techniques for elective cervical nodal irradiation with anterior or opposed anterior and posterior beams. Radiother Oncol. 2003;69:43-51.

Name of candidate: Christopher Nutting

Title of research thesis: Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

Supervisors: Craig/Proctor/Harrington

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We, the undersigned, further indicate the candidate's contribution to the publication in our joint statement below.

Signature:

Name: P Normile

Date:

Signature: 

Name: James Bedford

Date: 13.12.11

Signature: 

Name: Kevin Harrington

Date: 20/12/11

Signature:

Name: Steve Webb

Date:

13.12.11



Statement indicating the candidate's contribution to the publication
{Statement in support of candidate's contribution to the publication}

CN was first author, was responsible for the initial idea, provision of clinical material, plan production, data analysis and manuscript writing. PN, JB and SW produced treatment plans, KJH provided clinical support.



**CITY UNIVERSITY
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STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Miles EA, Clark CH, Urbano MT, Bidmead M, Dearnaley DP, Harrington KJ, A'Hern R, **Nutting CM**.
The impact of introducing intensity modulated radiotherapy into routine clinical practice. Radiother Oncol. 2005;77:241-6.

Name of candidate: Christopher Nutting

Title of research thesis: Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

Supervisors: Craig/Proctor/Harrington

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We, the undersigned, further indicate the candidate's contribution to the publication in our joint statement below.

Signature:

Name: Elizabeth Miles

Date:

Signature:

Name: Catharine Clark

Date: 3/1/12

Signature:

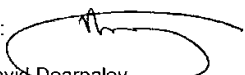
Name: Teresa Guerrero Urbano

Date: 22/12/11

Signature:

Name: Margaret Bidmead

Date: 19/12/11

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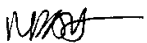
Name: David Dearnaley

Date: 12/11/2011

Signature: 

Name: Kevin Harrington

Date: 20/12/11

Signature: 

Name: Roger A'Hern

Date: 12/12/11

Statement indicating the candidate's contribution to the publication

{Statement in support of candidate's contribution to the publication}

CN was senior author, was responsible for the initial idea, patient recruitment, data analysis and manuscript writing. EM, CC, TGU, MB provided data for the manuscript. DD, and KH provided clinical support



**CITY UNIVERSITY
LONDON**

STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

Title of publication: Guerrero Urbano MT, Clark CH, Kong C, Miles E, Dearnaley DP, Harrington KJ, Nutting CM, PARSPORT Trial Management Group. Target volume definition for head and neck intensity modulated radiotherapy: pre-clinical evaluation of PARSPORT trial guidelines. Clin Oncol (R Coll Radiol). 2007;19:604-13.

Name of candidate: Christopher Nutting

Title of thesis: Can Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

Supervisors: Craig/Proctor/Harrington

We, the undersigned, co-authors of the above publication, confirm that the above publication has not been submitted as evidence for which a degree or other qualification has already been awarded.

We, the undersigned, further indicate the candidate's contribution to the publication in our joint statement below.

Signature: 

Name: Teresa Guerrero Urbano

Date: 22/12/11

Signature: 

Name: Catharine Clark

Date: 3/1/12

Signature:

Name: Christine Kong

Date:

Signature: 

Name: Elizabeth Miles

Date: 06/01/12

Signature:

Name: David Dearnaley

Date: 14/12/11

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Name: Kevin Harrington

Date:


26/12/11

Statement indicating the candidate's contribution to the publication

{Statement in support of candidate's contribution to the publication}

CN was senior author, was responsible for the initial idea, provision of clinical material, data analysis and manuscript writing. TGU, CC and CK produced treatment plans, FM, DPD and KJH provided clinical support



**CITY UNIVERSITY
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STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Clark CH, Hansen VN, Chantler H, Edwards C, James HV, Webster G, Miles EA, Guerrero Urbano MT, Bhide SA, Bidmead AM, **Nutting CM**; PARSPORT Trial Management Group. Dosimetry audit for a multi-centre IMRT head and neck trial. Radiother Oncol. 2009;93:102-8.

Name of candidate: Christopher Nutting

Title of research thesis: Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

Supervisors: Craig/Proctor/Harrington

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We, the undersigned, further indicate the candidate's contribution to the publication in our joint statement below.

Signature:

Name: Catharine Clarke

Date: 3/1/12

Signature:

Name: Vibeke Hansen

Date: 19.12.11

Signature:

Name: H Chantler

Date:

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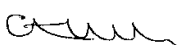
Name: C Edwards

Date:

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Name: G Webster

Date:

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Name: Elizabeth Miles

Date: 6/01/12

Signature:

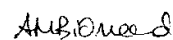
Name: Teresa Guerrero Urbano

Date:

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Name: Shree Bhide

Date: 19/12/2011

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Name: Margaret Bidmead

Date: 19/12/11

Statement indicating the candidate's contribution to the publication

{Statement in support of candidate's contribution to the publication}

CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. CC, VH, HC, CE, HJ GW and MB collected and analysed treatment plans. EA, TGU, and SB provided clinical support.



**CITY UNIVERSITY
LONDON**

STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Clark CH, Miles EA, Urbano MT, Bhide SA, Bidmead AM, Harrington KJ, **Nutting** CM; UK PARSPORT Trial Management Group collaborators. Pre-trial quality assurance processes for an intensity-modulated radiation therapy (IMRT) trial: PARSPORT, a UK multicentre Phase III trial comparing conventional radiotherapy and parotid-sparing IMRT for locally advanced head and neck cancer. Br J Radiol. 2009;82:585-94.

Name of candidate: Christopher Nutting

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Signature: 

Name: Catharine Clark

Date: 3/1/12

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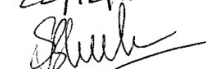
Name: Elizabeth Miles

Date: 6/01/12

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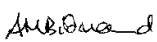
Name: Teresa Guerrero Urbano

Date: 22/12/11

Signature: 

Name: Shree Bhide

Date: 19/12/2011

Signature: 

Name: Margaret Bidmead

Date: 19/12/11

Signature: 

Name: Kevin Harrington

Date: 20/12/11

Statement indicating the candidate's contribution to the publication

{Statement in support of candidate's contribution to the publication}

CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. CC, EM, and MB collected and analysed scan data. TGU, KH and SB provided clinical support.



**CITY UNIVERSITY
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STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Nutting CM, Morden JP, Harrington KJ, Urbano TG, Bhide SA, Clark C, Miles EA, Miah AB, Newbold K, Tanay M, Adab F, Jefferies SJ, Scrase C, Yap BK, A'Hern RP, Sydenham MA, Emson M, Hall E; PARSPORT trial management group. Results of a Phase III Multi-Center Randomized Controlled Trial of Parotid-Sparing Intensity Modulated versus Conventional Radiotherapy in Head and Neck Cancer, Lancet Oncology 2011;12(2):127-36

Name of candidate: Christopher Nutting

Title of research thesis: Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

Supervisors: Craig/Proctor/Harrington

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We, the undersigned, further indicate the candidate's contribution to the publication in our joint statement below.

Signature: 

Name: James Morden

Date: 12/12/11

Signature: 

Name: Kevin Harrington

Date: 20/12/11

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Name: Teresa Guerrero Urbano

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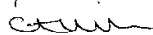
Name: Shree Bhide

Date: 19/12/2011

Signature: 

Name: Catharine Clark

Date: 3/1/12

Signature: 

Name: Elizabeth Miles

Date: 06/01/12

Signature: 

Name: Kate Newbold

Date: 13/12/11

Signature:

Name: Mary Tanay

Date:

Signature:

Name: F Adab

Date:

Signature: Yours sincerely

Name: Sarah Jeffries

Date: 29.12.2011



Dr Sarah Jeffries
Consultant Clinical Oncologist & Network Lead for Neuro-Oncology

Signature: 

Name: Christopher Scrase

Date: 26 December 2011

Signature:

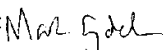
Name: Ben Yap

Date:

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Name: Roger A'Hern

Date: 12/12/11

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Name: Mark Sydenham

Date: 12/12/11

Signature: *M. A. Emson*

Name: Marie Emson

Date: 12/12/11

Signature:

Name: Emma Hall

Date: *E Hall* 12/12/11

Ashley M. Hall 19/12/11

Statement indicating the candidate's contribution to the publication
{Statement in support of candidate's contribution to the publication}

CN was first author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. JM, RAH, MS, ME and EH of the ICR CTSU provided data management, statistical support and trial management. KH, TGU, SB, EM, AM, KN, MT, FA, SJ, CS, and BY were clinical co-investigators.



**CITY UNIVERSITY
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STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Clark CH, Bidmead M, Mubata CD, Harrington KJ, Nutting CM.

Intensity-modulated radiotherapy improves target coverage, spinal cord sparing and allows dose escalation in patients with locally advanced cancer of the larynx. Radiother Oncol. 2004;70:189-98.

Name of candidate: Christopher Nutting

Title of research thesis: Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

Supervisors: Craig/Proctor/Harrington

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We, the undersigned, further indicate the candidate's contribution to the publication in our joint statement below.

Signature:

Name: Catharine Clark

Date: 3/1/12

Signature:

Name: Margaret Bidmead

Date: 19/12/11

Signature:

Name: Cephas Mubata

Date:

Signature:

Name: Kevin Harrington

Date:

20/12/11



**CITY UNIVERSITY
LONDON**

STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Guerrero Urbano T, Clark CH, Hansen VN, Adams EJ, A'Hern R, Miles EA, McNair H, Bidmead M, Warrington AP, Dearnaley DP, Harrington KJ, **Nutting CM**.

A phase I study of dose-escalated chemoradiation with accelerated intensity modulated radiotherapy in locally advanced head and neck cancer. *Radiother Oncol.* 2007;85:36-41.

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Title of research thesis: Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

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Signature: 

Name: Teresa Guerrero Urbano

Date: 22/11/12

Signature: 

Name: Catharine Clark

Date: 31/1/12

✓ Signature: 

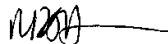
Name: Vibeke Hansen

Date: 15.12.11

Signature:

Name: Elizabeth Adams

Date: 

Signature: 

Name: Roger A'Hearn

Date: 12/12/11

Signature: 

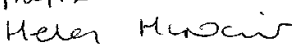
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Date: 6/01/12

Signature:

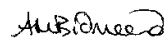
Name: Helen McNair

Date: 13/12/12

Signature: 

Name: Margaret Bidmead

Date: 19/12/11

✓ Signature: 

Name: Alan Warrington

Date: 15/12/11

Signature: 

Name: David Dearnaley

Date: 12/12/11

Signature: 

Name: Kevin Harrington

Date: 20/12/11

Statement indicating the candidate's contribution to the publication
{Statement in support of candidate's contribution to the publication}

CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. TGU, CC, VH, EA, MB, and AW produced treatment plans. EM, HM, DD, and KH provided clinical support. RAH was trial statistician.



**CITY UNIVERSITY
LONDON**

STATEMENT OF CO-AUTHORS of JOINT PUBLICATIONS

TO WHOM IT MAY CONCERN

Title of publication: Miah AB, Bhide SA, Guerrero-Urbano MT, Clark C, Bidmead AM, St Rose S, Barbachano Y, A'Hern R, Tanay M, Hickey J, Nicol R, Newbold KL, Harrington KJ, Nutting CM.

Dose-Escalated Intensity-Modulated Radiotherapy Is Feasible and May Improve Locoregional Control and Laryngeal Preservation in Laryngo-hypopharyngeal Cancers. Int J Radiat Oncol Biol Phys. 2011 Jan 13

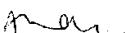
Name of candidate: Christopher Nutting

Title of research thesis: Intensity-Modulated Radiotherapy (IMRT) Be Used To Reduce Toxicity And Improve Tumour Control In Patients With Head And Neck Cancer?

Supervisors: Craig/Proctor/Harrington

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Signature: 

Name: Aisha Miah

Date: 18/12/11

Signature: 

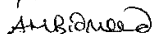
Name: Teresa Guerrero Urbano

Date: 22/12/11

Signature: 

Name: Catharine Clark

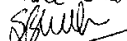
Date: 3/1/12

Signature: 

Name: Margaret Bidmead

Date: 19/12/11

Name: Shree Bhude

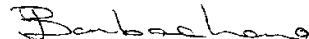
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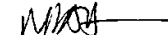
Name: Suzanne St Rose

Date:

Signature: 

Name: Yola Barbachano

Date: 19/12/11

Signature: 

Name: Roger A'Hern

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Statement indicating the candidate's contribution to the publication

{Statement in support of candidate's contribution to the publication}

CN was senior author, was responsible for the initial idea, principle investigator of the clinical trial, patient recruitment, data analysis and manuscript writing. AM, SB, TGU, CC, and MB produced treatment plans. MT, JH, RN, KN, and KH provided clinical support. SSR, YB and RAH were trial statisticians.

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