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Original Article

Total Mucosal Irradiation with Intensity-modulated Radiotherapy in Patients with Head and Neck Carcinoma of Unknown Primary: A Pooled Analysis of Two Prospective Studies

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Abstract

Aims: To determine the clinical outcomes of an intensity-modulated radiotherapy technique for total mucosal irradiation (TM-IMRT) in patients with head and neck carcinoma of unknown primary (HNCUP).

Materials and methods: A single-centre prospective phase II trial design was used in two sequential studies to evaluate TM-IMRT for HNCUP. Patients were investigated for primary tumour site using examination under anaesthetic and biopsies, computed tomography ± magnetic resonance imaging (MRI) or 18-fluorodeoxyglucose positron emission tomography-computed tomography (PET-CT). Patients received IMRT to the potential primary tumour sites and elective cervical nodes. Concomitant chemotherapy was used in patients who received primary radiotherapy or those with nodal extracapsular extension.

Results: Thirty-six patients with HNCUP were recruited; 72% male. Twenty-five patients (69.4%) had p16-positive disease. Two year mucosal and local nodal control rates were 97.1% (95% confidence interval 91.4–100) and 89.8% (78.4–100), respectively. One mucosal primary was detected 7.3 months after TM-IMRT and three patients died from recurrent/metastatic squamous cell carcinoma of the head and neck. Twelve patients (33%) developed grade 3 (Late Effects in Normal Tissue-Subjective, Objective, Management and Analytical; LENT-SOMA) dysphagia with a 1 year enteric tube feeding rate of 2.7%. The high-grade subjective xerostomia rate (LENT-SOMA) at 24 months after IMRT was 15%.

Conclusions: At a median follow-up of 36.1 months, the use of TM-IMRT was associated with good local control. Toxicity was comparable with previously reported TM-IMRT regimens encompassing similar mucosal volumes.

Key words: Head and neck; IMRT; occult-primary; prospective; radiotherapy; squamous cell carcinoma

Introduction

The diagnosis of head and neck carcinoma of unknown primary (HNCUP) comprises about 5% of all head and neck cancers [1,2]. The most common histological subtype is squamous cell carcinoma. Unlike carcinoma of unknown primary presenting at sites below the clavicle, HNCUP presenting with cervical lymph nodes has a much better prognosis, with similar 5 year overall survival rates to head and neck carcinomas with a known primary.

Due to the rarity of HNCUP, no randomised trials have been completed. Following a detailed initial evaluation for the potential primary tumour site, treatment typically includes modified radical neck dissection of involved lymph nodes followed by adjuvant therapy with (chemo-) radiotherapy. Some centres advocate neck dissection alone for patients with N1 cervical lymph node disease and no extracapsular extension (ECE). A valid alternative to neck dissection is primary non-surgical treatment [3,4].

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Particular areas of controversy persist regarding the extent of radiotherapy target volume and radiation dose to be delivered to this volume [5]. Two markedly different approaches are commonly advocated: irradiation of the postoperative hemi-neck only; or total mucosal and comprehensive cervical node irradiation (TMI). The first approach has the advantages of low acute and long-term morbidity, but the disadvantage of leaving any occult primary tumour site untreated. This can make subsequent management very difficult if the primary tumour manifests itself after initial therapy. The second approach of TMI has high acute and late morbidity rates due to irradiation of many critical organs at risk, including the mucosa, major and minor salivary glands, and the pharyngeal neuromuscular structures that are important for swallowing. A systematic review suggested that TMI reduced nodal relapse and prevented the need for further surgery [6]. The dose required to treat the potential site of unknown primary tumour is also controversial, with opinions ranging from elective to radical dose irradiation. In the design of this study, we hypothesised that if the primary tumour site remained undetected after a comprehensive investigation, then the primary tumour could be considered microscopic disease and that delivery of an elective dose would be sufficient.

The purpose of this study was to evaluate prospectively the feasibility of an intensity-modulated radiotherapy technique for total mucosal irradiation (TM-IMRT) to treat the whole upper aerodigestive tract mucosa and uninvolved cervical neck nodes while, at the same time, reducing the dose to salivary glands and the pharynx. In this way, we wished to secure the benefits of TMI without exposing patients to the long-term toxicities associated with conventional TMI techniques.

Materials and Methods

Patients and Trial Eligibility

This study was a pooled analysis of two single-centre, phase II trials. Both studies were approved by the institutional research and ethics committee [Royal Marsden Hospital CCR2823 and CCR3301 and NCT trials registration numbers NCT02112344 (CCR2823) and NCT02068313 (CCR3301)]. The aim of the first study, CCR2823, was to assess the safety and feasibility to deliver TM-IMRT. Once that was completed, subsequent patients with HNCUP were treated within a larger prospective phase II study (CCR3301). The primary aim of CCR3301 was to determine a threshold radiation dose for the parotid glands and allow radiobiological modelling of normal tissue toxicity.

Patients with histologically confirmed metastatic carcinoma to the cervical lymph nodes (including N1 disease with no ECE) with unknown primary tumour site, and World Health Organization/Eastern Cooperative Oncology Group performance status 0 or 1 were eligible. Exclusion criteria were previous radiotherapy to the head and neck, previous malignancy excluding non-melanoma skin cancer, previous or concurrent physical illness that in the investigator's opinion would interfere with the completion of therapy or follow-up. Prophylactic amifostine or pilocarpine was not allowed and use of brachytherapy was prohibited.

Evaluation

All patients underwent a full history and a physical examination by an experienced head and neck surgical oncologist. Fibre optic nasendoscopic evaluation of the upper aerodigestive tract was carried out as an outpatient procedure. All patients were imaged by computed tomography of the head, neck, chest and abdomen, supplemented by whole body 18-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) and/or head and neck magnetic resonance imaging (MRI). ^{18}F-FDG PET-CT was not a routine investigation at our institution during the trial recruitment period. An examination under anaesthesia was carried out in all cases, with biopsy of any suspicious mucosal sites and unilateral or bilateral tonsillectomy. All cases were discussed at the head and neck oncology multidisciplinary team meeting. Patients were staged using AJCC TNM 6th edition, 2002. Patients proceeded to neck dissection, as deemed appropriate for their nodal stage. Patients provided fully informed consent. Baseline blood tests included full blood count, urea, electrolytes and liver function tests. No prophylactic feeding tubes were inserted.

Treatment

Intensity-modulated Radiotherapy for Total Mucosal Irradiation

All patients in both studies were treated using the same TM-IMRT protocol. They underwent a planning computed tomography scan (2 mm slices) of the head and neck immobilised in a customised shell. Target volumes and organs at risk (parotid glands, spinal cord and brainstem) were outlined according to published guidelines [7,8] and radiotherapy planned using five- or seven-field simultaneous integrated boost technique. Clinical target volume 1 (CTV1) was the ipsilateral level 1b to 5 cervical lymph node levels (usually postoperative). CTV2 was the mucosa of the nasopharynx, oropharynx, larynx and hypopharynx and the contralateral level 2 to 5 cervical lymph nodes. For Caucasian patients with Epstein–Barr virus-negative squamous cell carcinoma and lymph node involvement confined to the lower cervical nodes (3 or 4), the nasopharynx was excluded. A CTV to planning target volume (PTV) margin of 3 mm was added to allow for patient and organ motion and set-up errors. The radiation dose to the resulting PTV1 and PTV2 was prescribed to the median of the PTV dose volume histogram. The prescribed dose in 30 fractions was 60 Gy to PTV1 and 54 Gy to PTV2. If macroscopic tumour was present in the neck, 65 Gy was prescribed to PTV1.

Chemotherapy

In the presence of lymph node ECE or when treatment was single modality primary radiotherapy alone, concomitant chemotherapy with two cycles of cisplatin 100 mg/m^2 was given on days 1 and 29 of radiotherapy. Carboplatin [area under the curve (AUC) = 5] was substituted for cisplatin if the glomerular filtration rate was between 30 and 50 ml/min [9]. For inoperable patients, induction chemotherapy was given with two cycles of cisplatin (75 mg/m^2) day 1 and 5-fluorouracil (1000 mg/m^2) days 1–4 on a 21 day cycle before TM-IMRT.

Toxicity and Tumour Assessments

Acute radiation toxicity was measured using National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE v3.0). Patients were reviewed weekly during treatment and for the first month after radiotherapy.

Late toxicity was measured using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer and Late Effects in Normal Tissue-Subjective, Objective, Management and Analytical (LENT-SOMA) systems and was recorded at 3, 6, 12, 18 and 24 months after TM-IMRT.

Patients were assessed for locoregional tumour control by clinical examination monthly in the first year after treatment, bimonthly in the second year and then at 3–6 monthly intervals up to 5 years. Computed tomography scanning was carried out 2 months after the completion of treatment and then as clinically indicated.

End Points and Statistical Analysis

The primary objective of this pooled analysis was to evaluate the feasibility and safety of delivering TM-IMRT. Secondary objectives were local control, progression-free survival (PFS) and overall survival rates and to evaluate acute and long-term toxicity, including xerostomia and dysphagia.

In the initial phase II trial (CCR2823), feasibility was defined as >85% of 18 patients able to complete the full course of radiotherapy, with no treatment breaks or extension to the planned treatment time resulting from treatment-related acute toxicity. Two patients were simultaneously recruited and enrolled from separate clinics to the final study place. Therefore 19 patients were included. Data from a further 17 patients with HNCUP were collected from a second phase II trial (CCR3301) within a larger cohort of head and neck cancer patients.

The incidence of 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 [10]. Clinical end points for this pooled analysis: all patient overall survival, PFS, local control and locoregional control (LRC) were calculated from the start date of radiotherapy using Kaplan–Meier methods. A post-hoc subgroup analysis of overall survival according to previously reported risk groupings (p16 status, N-stage and tobacco use) [11] was calculated from the start date of radiotherapy using Kaplan–Meier methods. The cut-off date for statistical analysis was 1 May 2014.

Results

Patient Characteristics and Treatment Compliance

Between July 2007 and December 2012, 36 patients were entered into the two trials. Twenty-six patients were male (72%) and the median age (range) at diagnosis was 54.2 (43–86.9) years. The histological subtype was squamous cell carcinoma in 35 patients (97%) and one patient had undifferentiated carcinoma of nasopharyngeal type. Cervical nodal disease was unilateral in 33 patients (92%) and most frequently affected cervical lymph node levels 2 and/or 3 (88%). A history of heavy tobacco smoking (>10 pack years) was seen in 18 patients (50%) and a prevalence of p16 positivity, a surrogate for human papillomavirus (HPV) infection, was 25 of 36 patients (69%). All patients underwent computed tomography of the head, neck, chest and abdomen. PET-CT was carried out in 16 patients (44.4%) and MRI in 26 (72.2%) patients. Neck dissections were selective in 13.9%, modified radical in 66.7%, radical in 5.6% and extended radical in 5.6%. Radiotherapy started at a median (interquartile range) of 42 (36–45) days after neck dissection. All patients received the planned course of TM-IMRT in the scheduled time with a median (interquartile range) treatment duration of 41 (39–41) days. Six patients were treated with 65 Gy to PTV1 (in three patients this was primary radiotherapy for inoperable lymphadenopathy and in three patients because of a positive neck dissection margin). Concomitant chemotherapy was administered to 18 patients, 15 (42%) patients for ECE and three (8%) patients with primary radiotherapy, one (3%) patient received induction chemotherapy. Patient and treatment characteristics are presented in Tables 1 and 2.

Acute Toxicity

The acute locoregional toxicities are reported in Supplementary Table S1. The incidence of grade 3 dysphagia and mucositis were 33% and 42%, respectively. Of the patients with grade 3 dysphagia, 10 required feeding via nasogastric tube and two via radiologically inserted gastrostomy tube. The median (range) feeding tube dwell time was 35 (22–804) days, with all patients tube-free at last follow-up. One patient (2.7%) developed grade 4 fatigue at week 1 after completion of TM-IMRT. This recovered to grade 1 by week 8 after treatment. The mean (range) radiation doses to the ipsilateral and contralateral parotid glands were 36.3 (27.3–48.7) Gy and 29.9 (20.1–36.0) Gy, respectively. Twenty-three patients (64%) developed acute ≥ grade 2 xerostomia. All other acute toxicities were predominantly grade 1 or 2. One patient (61 year old, female, p16-negative, never smoker) who received adjuvant TM-IMRT with no induction or concomitant chemotherapy became acutely unwell 16 days after radiotherapy was

Table 1
Patient and tumour characteristics

Characteristic	
Number of patients	36 (100)
Follow-up (months)	
Median (range)	36.1 (0.5–76.6)
Age (year), median (range)	54.2 (43.5–86.9)
Gender	
Male	26 (72)
Female	10 (28)
Performance status	
0	25 (69)
1	11 (31)
Tobacco exposure	
Never smoker	15 (42)
Former smoker	17 (47)
Current smoker	4 (11)
Tobacco-smoking history	
≤10 pack-years	18 (50)
>10 pack-years	18 (50)
P16 expression	
Positive	25 (69)
Negative	9 (25)
Unknown	2 (6)
Nodal stage	
N1	3 (8)
N2a	9 (25)
N2b	19 (53)
N2c	3 (8)
N3	2 (6)
Histology	
Squamous cell carcinoma	35 (97)
UCNT	1 (5)
Levels of nodal involvement	
Level 1b	2 (4)
Level 2	33 (58)
Level 3	17 (30)
Level 4	4 (7)
Level 5	1 (2)
Total	57 (100)

UCNT, undifferentiated carcinoma of nasopharyngeal type.
Values are number (percentage) unless otherwise noted.

Table 2
Treatment characteristics

Characteristic	
Induction chemotherapy	
Cisplatin/5-fluorouracil (two cycles)	1 (3)
None	35 (97)
Concomitant chemotherapy	
Cisplatin day 1, day 29	11 (31)
Carboplatin day 1, day 29	4 (11)
Cisplatin day 1, carboplatin day 29	3 (8)
None	18 (50)
Radiation (IMRT)	
Primary radical	3 (8)
Adjuvant (postoperative)	33 (92)
Involved nodal dose (PTV_1)	
65 Gy	6 (17)
60 Gy	30 (83)
Mucosal tube dose (PTV_2)	
54 Gy	36 (100)
Parotid doses (Gy)	
Ipsilateral, mean (range)	36.3 (27.3–48.7)
Contralateral, mean (range)	29.9 (20.1–36)

IMRT, intensity-modulated radiotherapy; PTV, planning target volume.
Values are number (percentage) unless otherwise noted.

completed and died from pulmonary oedema secondary to acute cardiac failure. No other deaths were reported within 90 days of completing treatment.

Late Toxicity

Supplementary Tables S2A–E (3, 6, 12, 18 and 24 months) list the TM-IMRT-related late adverse events (LENT-SOMA). The most frequent late toxicity was xerostomia, with ≥ grade 2 subjective xerostomia reported in 27%, 17% and 15% of patients at 6, 12 and 24 months, respectively (Figure 1a). One patient (3%) remained feeding tube dependent at 12 months and subsequently underwent a videofluoroscopy at 15 months after TM-IMRT (Figure 1b), where a benign stenosis was noted at the cricopharyngeus. Pharyngoscopy and balloon dilatation were carried out on three occasions at 16, 17 and 24 months after TM-IMRT. The radiologically inserted gastrostomy tube was removed at 29 months and the patient currently has no residual dysphagia 38 months after TM-IMRT. No other grade 3 or higher toxicities were noted at 12 months after TM-IMRT.

Outcomes

Primary Mucosal, Nodal and Distant Control and Overall Survival

At a median follow-up of 36.1 months for all patients (45.5 months for surviving patients), the median time for all survival and recurrence outcomes has not been reached (Figure 2a–d, Table 3). The LRC rate at 2 years was 89.8% (95% confidence interval 78.4–100). The primary mucosal control rate at 2 years was 97.1% (95% confidence interval 91.4–100) and the nodal control rate was 89.8% (95% confidence interval 78.4–100). At data cut-off, six patients (16.7%) had died. Three of these deaths were from causes unrelated to HNCUP. One, with >100 pack-year smoking history, developed a second primary non-small cell lung cancer and died 15 months after treatment. A second patient died from alcoholic liver disease 21.5 months after treatment. Neither had evidence of HNCUP recurrence. A third patient died of acute congestive cardiac failure, which occurred 16 days after the completion of post-operative radiotherapy and was considered unrelated to treatment.

One patient suffered tumour recurrence in the base of tongue 7.3 months after radiotherapy. This patient initially presented with stage T0N2bM0 disease and was p16 positive. Computed tomography and MRI staging did not reveal a primary. However, PET-CT was not carried out. At the time of recurrence, radiological staging revealed synchronous

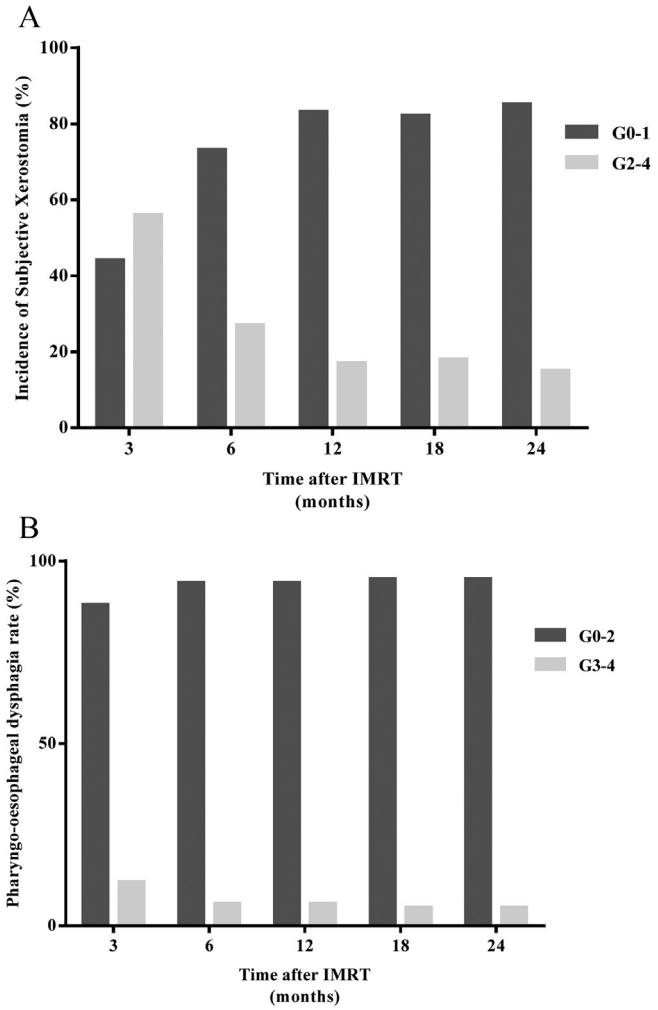

Fig 1. (A) Incidence of subjective xerostomia (Late Effects in Normal Tissue-Subjective, Objective, Management and Analytical; LENT-SOMA) over time, low grade (0–1) versus high grade (2–4). (B) Incidence of subjective pharyngo-oesophageal dysphagia (LENT-SOMA) over time, low grade (0–2) versus high grade (3–4).

metastatic contralateral level 2 and 3 cervical lymph nodes. Both mucosal and lymph node recurrences were within PTV2 and had received 54 Gy in 30 fractions. The recurrence was too extensive for curative resection and the patient received two lines of palliative chemotherapy, but progressed and died 16.4 months after TM-IMRT.

Two other patients developed local nodal recurrences, both were within PTV1, which had received 65 Gy in 30 fractions. The first patient had stage N2c disease and received primary radical chemo-IMRT, but recurred 22.5 months after treatment. He underwent salvage neck dissection and remains disease free 55 months after treatment. The second patient initially presented with unilateral N3 nodal disease with ECE. He received adjuvant chemo-IMRT, but developed cervical nodal and distant metastatic disease 3.7 months after treatment. He received palliative radiotherapy, but died 2 months later.

A post-hoc subgroup analysis of overall survival, according to the three previously reported risk stratification groups (low, intermediate and high) [11] showed that 2 year overall survival rates (95% confidence interval) for low- ($n = 19$), intermediate- ($n = 8$) and high-risk ($n = 7$) patients were 100% (n.d), 70% (50.6–89.6) and 42.9% (21.3–64.5), respectively. Two patients (5.5%) were excluded from this analysis as p16 status was not assessable. No statistically significant difference was seen between risks groups ($P > 0.05$), but numbers were small.

Discussion

In this pooled analysis of two prospective phase II studies, we found that delivery of TM-IMRT for HNCUP was feasible and well tolerated with moderate rates of acute and late radiotherapy-related adverse events.

Nine retrospective studies (Table 4) have reported their toxicity and efficacy outcomes using IMRT for HNCUP. All gave partial or TMI treating the mucosa to various radiation doses. Unlike this study, the radiotherapy technique and target volumes were heterogeneous and only four studies [14,15,18,19] collected prospective toxicity data. However, despite the drawbacks of a retrospective study design, these currently provide the best data on outcomes for IMRT in HNCUP.

Treating the involved nodes or high-risk, postoperative resection bed with a high radiation dose is standard for HNCUP in most series. The 2 year LRC rate in our study (89.8%) was similar to previous reports where LRC > 80% were reported in all IMRT studies (Table 4). Also similar to other studies, no local or distant recurrence occurred later than 2 years after IMRT. The development of a mucosal primary is uncommon after radiotherapy with either IMRT or non-IMRT techniques [6]. Rates of primary mucosal control remain above 90% in all IMRT series (Table 3), including our data, 97.1% at 2 years.

Our study confirms comparable salivary gland toxicity with rates of high-grade xerostomia of 17% and 15% at 12 and 24 months, respectively. In other trials of IMRT for HNCUP, rates of high-grade subjective xerostomia were 5–36% at 6 months and 0–8% at 24 months after IMRT [14,18].

In our study, we report an oesophageal stricture rate of 5%, which compares favourably with the 2–54% reported by others and our 1 year feeding tube rate was 5%, similar to the 0–5% reported by others. Studies with a higher oesophageal stenosis rate had a greater use of chemo-IMRT and a higher median radiation dose to the mucosal tube and pharyngeal muscles. The best reported local and distant control rates by Sher *et al.* [12], with no local or distant recurrence, were probably due to a higher radiotherapy dose (60 Gy to mucosal tube) and a 92% use of concomitant chemotherapy. This came at the cost of significantly increased acute and late toxicity.

Data for the survival benefit of using concomitant platinum chemotherapy in the treatment of HNCUP have been extrapolated from the 6.5% overall survival improvement seen in squamous cell carcinoma of the head and neck with a known primary site (HNCUP patients

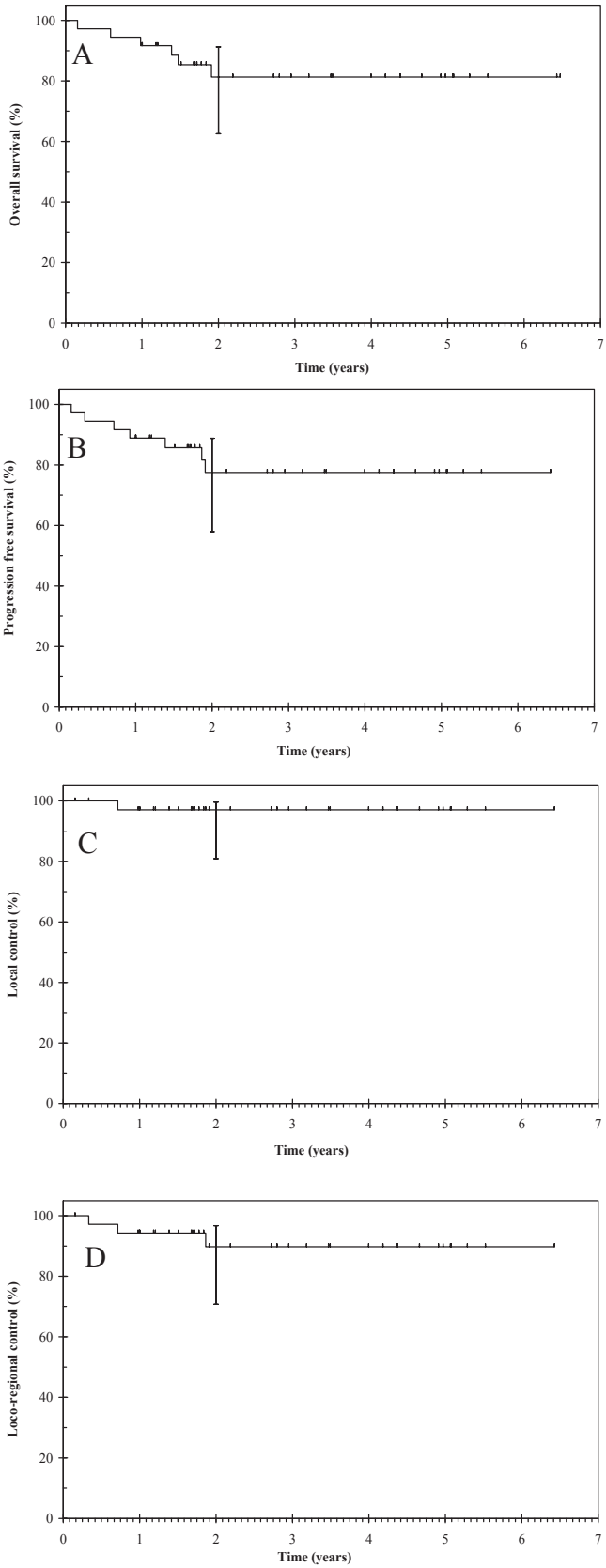

Fig 2. (A) Overall survival rate for patients treated with total mucosal and bilateral neck irradiation. (B) Progression-free survival rate for patients treated with total mucosal and bilateral neck irradiation. (C) Local mucosal (T) control rate for patients treated with total mucosal and bilateral neck irradiation. (D) Locoregional progression-free survival rate for patients treated with total mucosal and bilateral neck irradiation. Vertical bars indicate the 95% confidence interval for the 2 year survival rate.

excluded) [21]. Our data suggest that the acute and late oesophageal and pharyngeal toxicity with the addition of platinum chemotherapy is worsened. Seven of the eight patients who developed acute grade 3 pharyngeal or oesophageal dysphagia, and the single patient who developed an oesophageal stenosis, all received concomitant chemotherapy. The additional toxicity from chemotherapy has previously been noted by Chen *et al.* [22], who reported the outcomes of 60 patients treated for HNCUP at a single institution. Thirty-two patients (53%) received concurrent cisplatin chemotherapy and the oesophageal stricture rate was significantly higher, being 34% in the chemoradiotherapy group compared with 7% in the radiotherapy alone group. The enteric feeding tube rate was also significantly higher at 6 and 12 months, 28% versus 4% and 16% versus 0%, respectively, when comparing chemoradiotherapy with radiotherapy alone groups. No additional benefit for overall survival or LRC with the addition of chemotherapy was shown. In our study we reserved concomitant chemotherapy only for patients with high-risk features, e.g. cervical lymph node ECE or with primary radiotherapy.

The significance of HPV status in oropharyngeal carcinoma was reported by Ang *et al.* [11], who showed that HPV status was a strong and independent prognostic factor alongside tobacco smoking, primary tumour and nodal stage, for overall survival. There are limited data on the incidence of HPV in patients with HNCUP. Two recent studies [12,23] have assessed this. Sher *et al.* [12] tested HPV status in 15 of 24 patients with a prevalence in tested patients of 47%. Smoking history was not reported for the HPV-tested group and neither were survival outcomes related to HPV status. Tribius *et al.* [23] tested cervical lymph node samples from 63 patients treated at two German centres with radiotherapy for HNCUP (2002–2011). They were retrospectively analysed for HPV16/33 and p16 status. The p16 and HPV16/33 positivity rates were 57% and 52%, respectively. Current/former smokers comprised 79%, with 88% of these reporting a >10 pack-year smoking history. No significant 2 year overall survival or PFS difference was seen between HPV16/33+/p-16+ and other groups. The results were reported as being consistent with the data of Ang *et al.* [11], indicating that a heavy smoking history seems to counteract the positive prognostic effect of tumour HPV positivity. In our study, the p16 positivity rate of 69% was similar to Tribius *et al.* [23]. Smoking was less prevalent, but those who did smoke had a higher tobacco exposure (60% current/former smokers and 97% > 10 pack-year smoking history). Our 2 year overall survival and PFS outcomes compared with Tribius *et al.* [23] were also similar at 81.3% and 77.6% (current study) versus 75% and 70%, respectively. Our analysis of tumour control

Table 3
Treatment outcomes at 2 years

Survival	2 year survival rate (95% confidence interval)
Overall survival	81.3% (67.6–95.0)
PFS	77.6% (62.5–92.7)
Locoregional (lymph node and mucosa) PFS	89.8% (78.4–100)
Primary mucosal PFS	97.1% (91.4–100)
Cervical lymph node PFS	89.8% (78.4–100)

PFS, progression-free survival.

and survival for the three prognostic groups proposed by Ang *et al.* showed better outcomes for HPV-positive cases, but this did not reach statistical significance. Presently, there is no clear indication that radiation target volumes or doses can be varied depending on HPV status. It is hoped that further studies specifically with the exclusion of the hypopharynx and larynx in p16+ cases, as reported in retrospective studies [16,24], will clarify this matter. This has the potential for significant amelioration of radiation-induced toxicities.

Finally, the risk of radiation-induced second malignancy must be considered carefully when treating large elective treatment volumes in patients with a good long-term prognosis. No data are yet reported on the second malignancy rate for patients treated with IMRT to the head and neck. The rate in large population-based studies with heterogeneous primary tumour sites is low at 0.5–1% at >10 years after radiotherapy [25–27]. However, it is a potentially life-threatening consequence for a small minority of patients. A meta-analysis of non-IMRT-treated patients showed a linear dose-response relationship between increasing radiation dose to normal tissue and second malignancy rate for most organs [28]. Therefore, a reduction in radiation dose to the putative primary mucosal sites at risk may decrease the rate of second malignancy.

The limitations of this study are the small number of patients and only 44% underwent staging PET-CT, as this was not standard at our institution during the recruitment period. Head and neck MRI was carried out for all patients who did not undergo PET-CT. There were several benefits: it is the largest prospective study to date of HNCUP treatment; all patients received a consistent radiotherapy technique and dose; and detailed prospective acute and late toxicity data were collected.

To our knowledge, this is the largest prospective study of TM-IMRT for the treatment HNCUP. IMRT delivering a high dose (60–65 Gy) to the involved nodal region and a prophylactic dose (54 Gy) to the entire mucosal tube (nasopharynx, oropharynx, larynx and hypopharynx) is feasible and tolerable. Rates of LRC and mucosal failure are comparable with previously reported IMRT studies. Prospective accrual of HNCUP patients treated with this IMRT protocol continues within the Royal Marsden Hospital phase II expansion trial (NCT02068313).

Table 4
Comparison of studies assessing treatment of head and neck carcinoma of unknown primary with intensity-modulated radiotherapy (IMRT) to bilateral neck and putative mucosal sites

Reference	No. patients	Dates	N2c/N3 disease frequency (%)	Chemo-IMRT	IMRT dose to mucosal tube (Gy, median or range)	Oesophageal stricture frequency (%)	Primary mucosal control (%)	Locoregional control (%)	Overall survival (%)
Current study	36	2007–2012	5/36 (14)	18/36 (50)	54	1/36 (5)	2 years, 97.1%	2 years, 89.8%	2 years, 81.2%
Sher *et al.* [12]	24	2004–2009	3/24 (13)	22/24 (92)	60	13/24 (54)	2 years, 100%	2 years, 100%	2 years, 92%
Shoushatari *et al.* [13]	27	2002–2008	8/27 (30)	6/27 (22)	50–61	n/s	5 years, 100%	5 years, 88.5%	5 years, 70.9%
Villeneuve *et al.* [14]	25	2005–2008	4/25 (16)	18/25 (72)	50.4	0	3 years, 100%	3 years, 100%	3 years, 100%
Chen *et al.* [15]	51 (IMRT = 27)	2001–2009	4/27 (15)	17/27 (63)	56–70	4/27 (15)	n/s	2 years, 92%	2 years, 87%
Frank *et al.* [16]	52	1998–2005	10/52 (19)	8/52 (15)	54	1/52 (2)	5 years, 98.1%	5 years, 94.2%	5 years, 81%
Lu *et al.* [17]	18	2000–2006	3/18 (17)	6/18 (33)	60–64	0	2 years, 100%	2 years, 88.5%	2 years, 74.2%
Klem *et al.* [18]	21	2000–2005	4/21 (19)	14/21 (67)	54–56	3/21 (14)	n/s	2 years, 90%	2 years, 85%
Madani *et al.* [19]	51 (IMRT = 23)	1994–2006	6/23 (26)	3/23 (13)	66	0	2 years, 100%	n/s	2 years, 74.8%
Janssen *et al.* [20]	28	2006–2012	8/28 (29)	20/28 (71)	66–70	0	3 years, 100%	3 years, 93%	3 years, 76%

Number treated with IMRT is specified where comparison of two radiotherapy techniques. Outcomes reported are for IMRT-treated patients only.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clon.2016.04.035.

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