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FULL PAPER

Helical tomotherapy with simultaneous integrated boost dose painting for the treatment of synchronous primary cancers involving the head and neck

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Objective: To demonstrate the feasibility of helical tomotherapy (HT)-based intensity-modulated radiotherapy (IMRT) for the treatment of synchronous primary cancers arising from the head and neck.

Methods: 14 consecutive patients with histologically proven squamous cell carcinoma of the head and neck were determined to have a second primary cancer in the upper aerodigestive tract on further evaluation and were treated with HT using simultaneous integrated boost IMRT. Megavoltage CT scans were acquired daily as part of an image-guided registration protocol. Concurrent platinum-based systemic therapy was given to nine patients (64%).

Results: HT resulted in durable local control in 21 of the 28 primary disease sites irradiated, including a complete clinical and radiographic response initially observed at 17 of the 20 sites with gross tumour. The mean displacements to account for interfraction motion were 2.44 ± 1.25, 2.92 ± 1.09 and 2.31 ± 1.70 mm for the medial–lateral (ML), superior–inferior (SI) and anteroposterior (AP) directions, respectively. Table shifts of >3 mm occurred in 19%, 20% and 22% of the ML, SI and AP directions, respectively. The 2-year estimates of overall survival, local-regional control and progression-free survival were 58%, 73% and 60%, respectively.

Conclusion: The effectiveness of HT for the treatment of synchronous primary cancers of the head and neck was demonstrated.

Advances in knowledge: HT is a feasible option for synchronous primary cancers of the head and neck and can result in long-term disease control with acceptable toxicity in appropriately selected patients.

The proportion of patients with newly diagnosed head and neck cancer who are found to have a synchronous second primary tumour has been estimated to range from 5% to 15%.[1–3] Slaughter et al[4] described the concept of field cancerization as the most logical explanation for the development of multiple cancers in the upper aerodigestive tract. With the routine adoption of panendoscopy and the widespread utilization of positron emission tomography (PET) as a component of the initial staging evaluation, the number of patients diagnosed with synchronous cancers involving the head and neck appears to be increasing.[5] Despite the increased prevalence, uncertainty exists regarding the optimal manner in which patients with synchronous primary cancers of the head and neck should be managed. For patients receiving radiotherapy, the large areas at risk for tumour recurrence make treatment delivery a therapeutic and technical challenge.

Intensity-modulated radiotherapy (IMRT) reduces radiation to critical structures while maintaining desired doses to user-defined targets through a computer-derived optimization process (*i.e.* inverse planning) and non-uniform beam intensities. Because of its ability to achieve conformal dose distributions to convex and concave targets, IMRT represents the standard in the radiotherapeutic management of head and neck cancer. Helical tomotherapy (HT) is a specialized form of IMRT, which is also based on inverse planning but relies on a rotational gantry and a binary multileaf collimator system rather than a fixed number of beam angles for radiation delivery. We report here our experience with HT for the treatment of synchronous primary cancers involving the head and neck.

METHODS AND MATERIALS

Patient identification and characteristics

From February 2006 to April 2012, 14 consecutive patients (9 males and 5 females) were treated with HT for synchronous primary cancers involving the head and neck. Table 1 shows the clinical characteristics of the patients. All

Table 1. Patient characteristics

Factor	*n* (%)
Age (years)	
≤60	5 (36)
>60	9 (64)
Smoking history	
<20 PPD	2 (14)
20–50 PPD	7 (50)
>50 PPD	5 (36)
Karnofksy performance status	
90–100	8 (57)
80	4 (29)
70	2 (14)
Ethnicity	
White, non-Hispanic	9 (64)
Black	2 (14)
Hispanic	1 (7)
Asian	1 (7)

PPD, pack per day.

patients presented initially with histologically proven squamous cell carcinoma of the head and neck and were determined to have a second, biopsy-proven primary cancer in the upper aerodigestive tract with further evaluation. No patient had clinical or radiographic evidence of distant metastasis at diagnosis. The median age of the patients was 67 years (range, 49–85 years).

All patients were presented before our institution's weekly multidisciplinary tumour conference prior to treatment. Pre-HT evaluation consisted of routine history and physical examination, complete blood counts, liver function tests, chest radiography and dental evaluation. All patients underwent CT of the head and neck, as well as whole-body PET. Nine patients (64%) were treated by primary HT alone. The remaining five patients (36%) were treated by HT post-operatively following gross surgical resection of either one or both primary tumours. In general, post-operative patients possessed high-risk features, such as multiple lymph node disease, extracapsular extension and perineural or angiolymphatic invasion, or when there was uncertainty about the adequacy of the excision. Concurrent platinum-based chemotherapy was given with HT to nine of the patients (64%) with an additional patient (7%) receiving cetuximab.

Simulation and target volume delineation

The patient was immobilized with the neck in a hyperextended position using a perforated, thermoplastic mask with a Timo cushion (S-type; Med-Tec, Orange City, IA) mounted on a carbon fibre board (S-type; Med-Tec). The CT data were then downloaded into a contouring workstation where delineation of target and normal tissue structures was performed and then transferred into the TomoTherapy® Hi-Art treatment planning system (TomoTherapy, Inc., Madison, WI) for treatment planning. Our process for HT planning has previously been described.[6]

For definitive HT (using radiation alone), the gross tumour volume (GTV) was defined as the extent of disease as demonstrated by imaging and physical examination. Grossly positive lymph nodes were identified as those >1 cm or with necrosis. PET findings were used to further refine the GTV to include only areas with standardized uptake value >3. The high-risk clinical target volume 1 (CTV1) was defined as the GTV plus a subclinical margin of 0.5–1.0 cm to account for microscopic disease. For patients with oesophageal cancer, the GTV-to-CTV expansion was generally 0.5 cm circumferentially but was up to 5.0 cm longitudinally to account for submucosal lymphatic spread. For post-operative HT, the CTV1 was the operative bed at risk for microscopic residual disease. For both definitively and post-operatively treated patients, the CTV2 typically included the electively treated cervical and supraclavicular neck. In some additional cases, a CTV3 was devised at the physician's discretion to designate an area at lowest risk within the prophylactically treated low neck. Automated expansions of 0.3–0.5 cm were performed to create planning target volumes (PTVs) designated PTV1, PTV2 and PTV3, if necessary.

Dose specification

Prescription doses varied based largely on the site of disease and whether surgery had been performed (Table 2). HT was delivered in 30–35 fractions using a simultaneous integrated boost technique to deliver varying doses to separate regions depending on physician-assigned gradients. For patients receiving definitive radiation therapy, the goal was to provide a dose of 66–70 Gy to 95% or more of the PTV1 (containing the index tumour) and 54–63 Gy to 95% or more of the PTV2, while sparing neighbouring critical structures. For patients treated post-operatively, the goal was to deliver a dose of 60–66 Gy to at least 95% of PTV1. For the entire subject population, the median dose to the PTV1 was 66 Gy (range, 60–72 Gy). The second primary tumour was typically included in the PTV1, although in selected cases (oesophagus or post-operative tumours), the site was included in PTV2 or PTV3.

Treatment planning

The objective was to generate an isodose distribution with the prescription dose tightly encompassing the user-defined PTVs, while minimizing the spillage to critical structures. HT planning parameters were 2.5-cm jaw (field width in the longitudinal direction of couch), pitch of 0.3° and an initial modulation factor of 3.0. A convolution/superposition-based calculation algorithm was used for heterogeneity correction. Excessive inhomogeneity (>115% prescription dose) was avoided whenever possible. Overlap between the targets and uninvolved avoidance structures was not permitted in the optimization process. The plans were evaluated by the physician both quantitatively with dose–volume histogram analysis and qualitatively by visually inspecting dose distribution on axial, coronal and sagittal slices (Figures 1–4).

Image guidance

Megavoltage CT (MVCT) images were acquired daily on the HT machine over a longitudinal field that typically ranged from C7

Table 2. Treatment parameters for each of the 14 patients irradiated for synchronous primary cancers of the head and neck

Site	Stage	Surgery	Radiation therapy dose/fractions (Gy)	Chemotherapy	Worst acute toxicity
Retromolar trigone	T4N0	N	70/33	None	Grade III mucositis
Oesophagus	T2N0	N	60/33		
Larynx	T3N0	N	70/33	Carbo/taxol	Grade III oesophagitis
Oesophagus	T3N0	N	56/33		
Base of tongue	T1N1	N	70/33	Carbo/taxol	Grade III oesophagitis
Oesophagus	T3N1	N	54/33		
Tonsil	T1N1	Y	66/33	Cisplatin	Grade III oesophagitis
Thyroid	T4N0	Y	66/33		
Base of tongue	T4N0	N	70/33	Cisplatin	Grade II oesophagitis
Thyroid	T4N1	Y	60/33		
External ear	T2N0	N	66/33	None	Grade I oesophagitis
Tonsil	T1N0	N	66/33		
Base of tongue	T1N2b	N	70/33	Cisplatin	Grade II laryngeal
Larynx	T3N0	N	70/33		
Tonsil	T3N1	Y	60/33	Cisplatin	Grade II mucositis
Tonsil	T2N0	N	70/33		
Tonsil	T1N0	Y	66/33	Cisplatin	Grade II mucositis
Tonsil	T1N0	Y	66/33		
Tonsil	T2N0	N	66/30	None	Grade II oesophagitis
Oesophagus	T1N0	N	54/30		
Larynx	T3N1	N	70/33	Cetuximab	Grade III oesophagitis
Tonsil	T1N0	N	66/33		
Larynx	T2Na	Y	60/30	Cisplatin	Grade III mucositis
Oral tongue	T2N0	Y	60/30		
Cheek	T2N0	N	66/33	None	Grade I xerostomia
Parotid	T1N0	N	66/33		
Hypopharynx	T4N0	N	70/33	Carbo/taxol	Grade III oesophagitis
Oesophagus	T3N0	N	54/33		

carbo, carboplatin; N, no; taxol, paclitaxel; Y, yes.

to the base of the skull using a coarse resolution in-slice thickness and a nominal beam energy of 3.5 MV. After reconstruction of the MVCT images, the physician-defined region of interest was fused with the treatment-planning CT images at the HT treatment console display using automated registration bone presets followed by manual adjustments if needed. Three patients (21%), all of whom experienced >10% weight loss during treatment and experienced difficulties with mask fitting and immobilization, underwent adaptive replanning at a median dose of 34 Gy (range, 30–44 Gy).

Statistical analysis

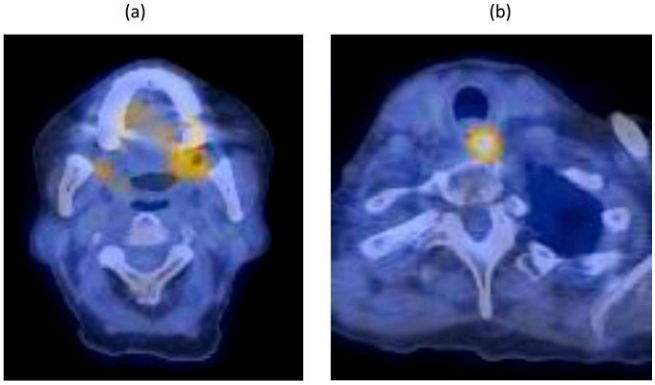
The end points analysed were overall survival, local-regional control and disease-free survival. Patient follow-up was reported to the date last seen in clinic or to the date of expiration. All events were measured from the last day of treatment. Median follow-up was 31 months (range, 6–65 months) among surviving patients. Estimates of local-regional control, disease-free survival and overall survival were calculated using the Kaplan–Meier method.[7] Acute and late normal tissue effects were graded according to the Radiation Therapy Oncology Group/European Organization for the Treatment of Cancer radiation toxicity criteria.[8] This study was approved by all relevant institutional review boards.

RESULTS

Outcomes

8 of the 14 patients were alive at the time of this analysis. The 2-year estimate of overall survival for the entire patient population was 58%. Among the six patients who died during the

Figure 1. A case illustration of a 79-year-old female who presented to her dentist with a 3-month history of oral pain and was found to have a left retromolar trigone mass. Biopsy revealed poorly differentiated squamous cell carcinoma, and on routine panendoscopy under anaesthesia, a second primary cancer (also biopsy-proven squamous cell carcinoma) was identified in the cervical oesophagus. 18-fludeoxyglucose positron emission tomography/CT confirmed the presence of two primary cancers: (a) an oral cavity cancer (T4N0) originating from the left retromolar trigone with adjacent bony sclerosis with maximum standardized uptake value (SUV) of 6.2 and (b) an oesophagus cancer (T2N) located posterior to the cricoid and extending inferiorly with maximum SUV of 11.4. The patient opted for definitive radiation therapy to address both primary cancers and had a complete clinical response at both sites. Unfortunately, she developed widespread lung metastasis approximately 6 months after the completion of treatment.



evaluation period, two died as a result of progressive disease at local-regional sites, two from complications related to distant metastatic disease and two of intercurrent disease.

Durable local control was achieved at 21 of the 28 primary disease sites irradiated, including a complete clinical and radiographic response initially observed at 17 of the 20 sites with gross tumour. Four patients treated by HT (three definitive and one post-operative) experienced local-regional recurrence after initially being without evidence of disease at a median of 9 months (range, 4–18 months) from completion of HT. Initial sites of local-regional recurrence were neck (two patients), oesophagus (one patient) and hypopharynx (one patient). None of these local-regional recurrences was surgically salvageable, and these patients opted for best supportive care in all cases. The 2-year actuarial estimate of local-regional control was 73%. Spatial evaluation of local-regional failures revealed that all of the recurrence at the primary site or neck occurred in the high-dose PTV1.

Five patients (36%) developed distant metastasis at a median of 8 months after completion of HT (range, 3–17 months). Three of these represented the first site of disease failure, with the remaining two cases occurring simultaneous or subsequent to local-regional disease failure. The most common initial site of distant metastasis was the lungs (three patients) followed by the liver (two patients) and bone (one patient). Four out of the five patients developed metastasis at more than one site. Subsequent treatment after development of distant metastasis was made on an individualized basis but included chemotherapy (three patients) and best supportive care (two patients). The 2-year estimate of progression-free survival was 60%.

Three patients (21%) developed third primary tumours after completion of treatment for synchronous primary cancers involving the head and neck. Two patients developed biopsy-proven lung cancer approximately 14 and 20 months after completion of HT for synchronous primary cancers involving the supraglottic larynx/thyroid gland and tonsil/oesophagus, respectively. Both underwent surgical treatment (sublobar resection) for pathological Stage I non-small-cell lung cancer and are currently without evidence of disease. An additional patient developed cancer of the thoracic oesophagus approximately 32 months after completion of HT for hypopharynx/tonsil cancer and underwent an additional course of definitive radiation therapy with concurrent chemotherapy.

Dosimetric and alignment data

Summary dosimetric (average) data for all 14 patients irradiated were as follows: spinal cord (maximum dose), 43.0 Gy (range, 36.0–48.7 Gy); brainstem (maximum dose), 48.1 Gy (range, 37.9–58.5 Gy); spared parotid gland (mean dose), 25.5 Gy (range, 21.9–33.3 Gy); ipsilateral cochlea (maximum dose), 40.2 Gy (range, 31.3–54.8 Gy); and mandible (maximum dose), 66.4 Gy (range, 58.9–74.1 Gy).

The mean shift to account for interfraction motion was 2.44 $\pm$ 1.25, 2.92 $\pm$ 1.09 and 2.31 $\pm$ 1.70 mm for the medial–lateral (ML), superior–inferior (SI) and anteroposterior (AP) directions, respectively. Pre-treatment shifts of $>$3 mm occurred in 19%, 20% and 22% of the ML, SI and AP directions, respectively.

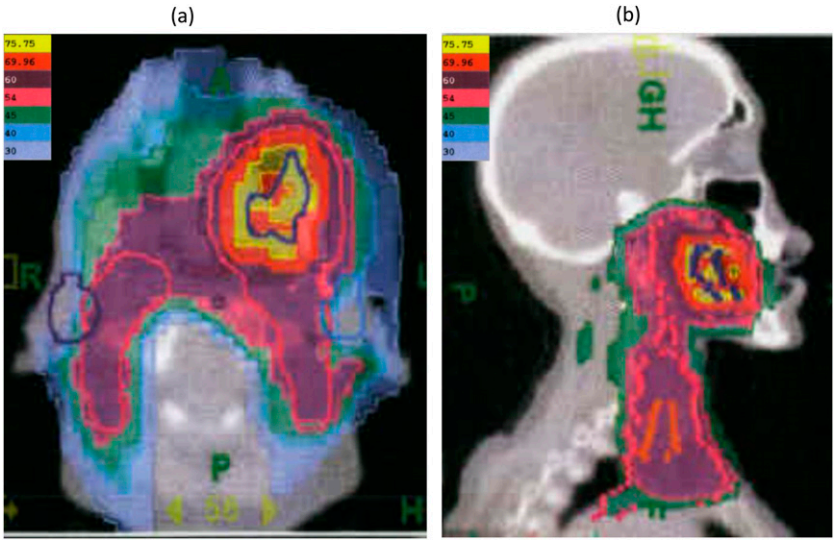
Toxicity

The common acute complaints were skin erythema, odynophagia, taste alterations and increased phlegm production, which occurred in essentially all patients (Table 2). Six patients (43%) experienced grade 3 mucositis (confluent and requiring narcotics). In the late setting, 12 patients (86%) complained of some subjective degree of xerostomia, 6 (43%) patients reported severe in-field subcutaneous fibrosis, 8 patients (57%) complained of grade 3 oesophageal toxicity (inability to swallow solids beyond 3 months post-treatment) and 4 patients (29%) remained gastrostomy-tube dependent at last follow-up.

DISCUSSION

This series illustrates the feasibility of HT to irradiate the fairly large volumes required in the management of synchronous primary cancers of the head and neck (Figures 1–4). Notably, we were able to achieve reasonable rates of local-regional control with acceptable toxicity, even with the majority of patients receiving concurrent chemotherapy. Although it is speculative to assess how the use of HT may have influenced the therapeutic ratio in this setting, we believe the highly conformal plans and creation of sharp fall-off gradients generated by HT was of critical importance.

Figure 2. Illustrative helical tomotherapy treatment plan for patient from Figure 1a demonstrating representative (a) axial and (b) sagittal views. The retromolar trigone tumour was irradiated to a dose of 6996 cGy in 33 fractions, with the oesophageal tumour receiving a lower dose of 6000 cGy simultaneously. The prescribed dose to the ipsilateral and contralateral cervical neck was 5940 and 5400 cGy, respectively.



The goal of this study was not to comment on the superiority of HT *vs* linear accelerator-based IMRT. Although treatment-planning studies have suggested that HT can potentially offer an improved dose distribution for the treatment of head and neck cancer, it is speculative how these findings may be of clinical relevance, especially in the setting of the large fields utilized.[9–11] It is important to recognize that much of radiation planning for head and neck cancer is non-standardized and heavily dependent on operator bias. While heavily dependent on a computer-based optimization process, multiple aspects of IMRT planning such as the selection of constraints, dose gradients, design of beam angles, delineation of targets/critical organs and prioritization of organs at risk are manually derived and dependent on the experiences of the user. Plan acceptability also varies between individuals.

Our findings are even more notable considering that adaptive replanning was only performed in three patients. Others have suggested that more routine replanning might improve the accuracy of dose delivery, especially since change in anatomy and weight can render targeting difficult.[12] These potential uncertainties attest to the paramount importance of consistent patient set-up and immobilization when delivering IMRT for head and neck cancer. In the present series, all patients were positioned

Figure 3. A case illustration of a 65-year-old male who was status post-bilateral tonsillectomy for T1N0 squamous cell carcinoma involving both right and left tonsils. Surgical pathology revealed positive microscopic margins bilaterally, and the patient opted for post-operative radiation therapy with concurrent cisplatin. The representative helical tomotherapy treatment plans in the (a) axial and (b) coronal views demonstrate the delivery of 6600 cGy in 33 fractions to the bilateral tonsillar beds. Areas at high risk for microscopic disease involvement, including the bilateral cervical neck and retropharyngeal lymph nodes, received a dose of 5940 cGy, and the low neck (supraclavicular fossa) received a dose of 5400 cGy, with treatment delivered simultaneously. A, anterior; P, posterior.

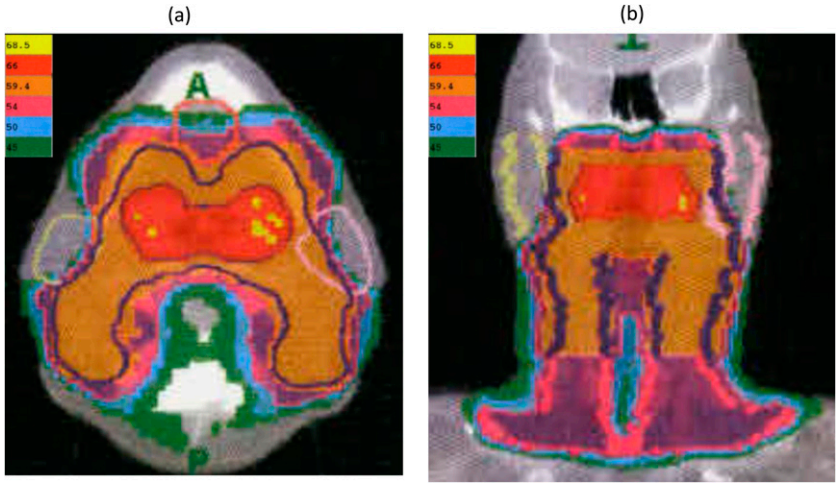
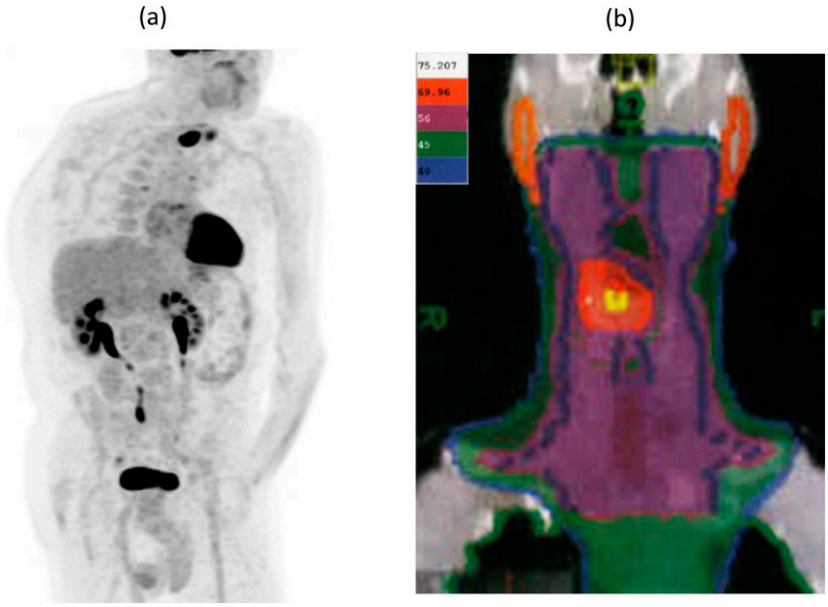


Figure 4. A case illustration of a 70-year-old male who presented with a 3-month history of hoarseness and was diagnosed with T3N0 squamous cell carcinoma of the glottic larynx. On positron emission tomography/CT (a), a second primary cancer was detected in the cervical oesophagus, with biopsy confirming squamous cell carcinoma. The maximum standardized uptake value for the larynx and oesophageal cancers were 9.5 and 15.5, respectively. The patient opted for definitive radiation therapy with concurrent carboplatin and paclitaxel. The representative helical tomotherapy treatment plans in (b) coronal view demonstrate the delivery of 6996 cGy in 33 fractions to the larynx cancer with a lesser dose of 5600 cGy to the oesophageal cancer and adjacent lymph nodes. All treatment was delivered simultaneously in 33 fractions.



and treated using daily MVCT imaging as per our institution's image-guidance protocol with HT. By obtaining volumetric images of the patient in the treatment position, image guidance enables detection and adjustment of set-up errors thus facilitating target localization and verification of dose delivery. In the authors' opinion, this strategy confers an additional degree of precision and helps account for interfraction uncertainty that can have clinical consequences. This approach can thus minimize any differences between the planned and delivered dose. Notably, the lack of observed marginal misses suggests that the tight margins utilized with image-guided radiotherapy are sufficient.

The literature reporting on the management of synchronous primary cancers involving the head and neck is extremely limited, but survival has generally been considered to be poor. Erkal et al[1] reviewed the outcomes of 180 patients treated for synchronous and metachronous squamous cell carcinomas of the head and neck and showed that survival varied depending on such factors as disease site, race and history of tobacco use. Rennemo et al[13] reported on 49 patients with synchronous primaries involving the head and neck and showed that median survival after multitude of different treatments was 10 months. Similarly, Di Martino et al[14] reported that patients who presented with synchronous primary tumours of the head and neck had a 5-year overall survival of only 12%, which was significantly worse than the 26% observed for patients with metachronous tumours. Nonetheless, the authors argued in favour of an aggressive treatment regimen. Kagei et al[15] reported on outcomes among 44 patients with synchronous malignancies of the head and neck and the oesophagus. Incorporating a variety of treatment strategies, the authors reported a 5-year overall survival of 19%. The more favourable results seen in our series is almost certainly owing to selection bias, as we excluded patients with infraclavicular primary cancers located a great distance away from the original head and neck cancer. However, the impact of aggressive treatment using contemporary radiation therapy techniques cannot be discounted.

The high incidence of swallowing dysfunction observed is almost certainly related to the locations of many of the primary tumours in this study. It is now clear that radiation therapy for cancers of the larynx/hypopharynx and cervical oesophagus results in the delivery of high doses to the anatomical swallowing structures (*e.g.* pharyngeal constrictor complex, cricopharyngeal inlet, arytenoids/epiglottis), which places patients at high risk for stricture as well as other structural abnormalities.[16]

The fact that three patients, representing nearly a quarter of the population, developed a third primary cancer shows the importance of careful work-up before initiating aggressive treatment as well as the necessity of continued surveillance in this high-risk population. Routine counselling regarding the importance of smoking cessation and alcohol abstinence should also be provided when appropriate. Although field cancerization from effects of tobacco smoke and/or alcohol has been established for quite some time, more recent literature suggests that human papillomavirus (HPV) profoundly affects the risk of second cancer. In a retrospective study of 318 cases of oropharyngeal cancer treated at the Princess Margaret Hospital HPV-positive patients had a significantly lower risk of both synchronous (1% *vs* 9%) and metachronous (6% *vs* 16%) malignancies.[17] Morris et al[18] recently showed that the increasing

recognition of HPV-associated head and neck cancer have altered patterns of synchronous cancer development.

CONCLUSION

While the preferred treatment for synchronous cancers of the head and neck likely depends on such factors as disease location, tumour extent and patient performance status, our findings demonstrate the feasibility of using HT as definitive therapy in selected cases. However, whether the highly conformal plans generated by HT, which help keep inadvertent dosing of normal critical organs to a minimum, represent a true clinical improvement over those achieved by other linear accelerator devices is uncertain.[19] Notably, in a previous study, we showed that the dosimetric gains associated with HT failed to translate into actual clinical improvements in several quality of life domains.[18] Nonetheless, the results of the present series are particularly relevant owing to the widespread utilization of panendoscopy and PET as part of the initial evaluation, and the increasing incidence of synchronous primary cancers of the head and neck. Given the relatively poor prognosis, treatment should be individualized, considering the balance between aggressive attempt for cure and minimizing toxicity.

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