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Radiotherapy for oropharyngeal carcinoma with an uninvolved contralateral neck: the safety of omission of contralateral high level II and retropharyngeal lymph nodes from elective target volumes

Abstract

Introduction: The aim was to analyse outcomes and patterns of failure in patients with oropharyngeal carcinoma (OPC) treated with definitive volumetric modulated arc therapy with omission of contralateral high level II lymph nodes (HLII) and retropharyngeal lymph nodes (RPLN) in the contralateral uninvolved neck.

Methods: Patients with OPC treated between January 2016-July 2019 were retrospectively identified. In the absence of contralateral neck disease, institutional protocols allowed omission of contralateral HLII, and contralateral RPLN in the additional absence of ipsilateral RPLN, soft palate/posterior pharyngeal wall primary.

Results: 238 patients with OPC and an uninvolved contralateral neck received definitive (chemo)radiotherapy with bilateral neck treatment. Median follow up was 30.6 months. 2 year local control, regional control and overall survival were 91.0%, 91.6% and 86.5% respectively. Contralateral HLII was omitted in 159/238 (66.8%) patients; this included 106 patients in whom the primary tumour was at/crossed midline. The contralateral RPLN region was omitted from elective target volumes for 175/238 (73.5%); this included 114 patients with a primary tumour at/crossed midline. Mean contralateral parotid dose when contralateral HLII and RPLN were both omitted was 24.4Gy, compared with 28.3Gy without HLII/RPLN omission ($p<0.001$).Regional progression occurred in 18/238 (7.6%) patients , all involving the ipsilateral neck with one bilateral. There were no recurrences in the contralateral HLII or RPLN regions.

Conclusion: In patients with OPC and an uninvolved contralateral neck receiving bilateral (chemo)radiotherapy, the omission of contralateral RPLN and HLII from elective target volumes was was safe and could lead to reduced contralateral parotid doses.

Keywords: oropharyngeal cancer; radiotherapy; retropharyngeal lymph nodes; level 2 lymph nodes

Introduction

Modern intensity modulated radiotherapy (IMRT) for head and neck squamous cell carcinoma (HNSCC) is highly conformal; accurate selection and delineation of target volumes is essential. HNSCC drain to lymph node regions via predictable routes providing the opportunity for a selective approach to lymph node selection. Following the introduction of IMRT, initial contouring guidelines recommended a comprehensive approach to selection of lymph nodes levels for inclusion within elective target volumes [1, 2]. In 2019 updated guidelines were published for selection of lymph node levels for definitive treatment of head and neck cancers [3].

The international consensus lymph node level outlining guidelines define the superior extent of the level II lymph node region as the caudal aspect of the lateral process of C1 [4]. Sparing of high level II (HLII) lymph nodes in the contralateral clinically/radiologically uninvolved neck was initially reported by Eisbruch et al. [5] with a reduction in xerostomia [6]. The proposed definition [5] for HLII was for the most cranial axial CT image for delineation of level II to be where the posterior belly of the digastric muscle crosses the jugular vein, ensuring irradiation of the subdigastric lymph node. A retrospective series from the University of Washington [7] reported upon clinical outcomes following serial changes in institutional protocols with omission of the contralateral HLII followed by omission of contralateral retropharyngeal lymph nodes (RPLN) in the contralateral uninvolved neck. There were no recurrences in contralateral HLII or RPLN in this cohort of predominantly post-operative HNSCC and an improved quality of life was reported. There are limited other data regarding sparing of HLII and this approach was not adopted in recent UK trials including or exclusively in patients with oropharyngeal carcinoma (OPC) [8-10] and is not part of the consensus lymph node level outlining guidance [4].

The need for elective irradiation of the contralateral RPLN in the treatment of node negative or ipsilateral-only node positive OPC has been controversial. Early series of IMRT outcomes reported on RPLN recurrences and recommended inclusion of bilateral RPLN regions [5, 11]. Elective treatment of bilateral RPLN in OPC is widely practiced, reported in multiple institutional series [10, 12-14] and in recent [8] and ongoing [10] UK trials in patients with OPC. However, omission of the contralateral RPLN is supported by radiology-based series finding a very low incidence of contralateral RPLN involvement [12, 15-17]. A small number of series have reported that omission of the contralateral RPLN is safe [7, 18-20] and this forms part of the 2019 lymph node level selection consensus [3].

The approach of omitting contralateral HLII and RPLN from elective target volumes was introduced into our institutional protocols in 2016 for patients treated with definitive (chemo)radiotherapy for OPC with either N0 or ipsilateral-only N+ neck. The aim of this report is to evaluate the safety of this approach.

Methods

Study group

This single centre retrospective analysis was approved by the institutional review board. An electronic database was used to identify patients receiving (chemo)radiotherapy between January 2016-June 2019. Inclusion criteria for the analysis were: OPC, squamous cell carcinoma, curative treatment intent with radiotherapy ± chemotherapy, clinically and radiologically uninvolved contralateral neck, bilateral neck radiotherapy. Exclusion criteria were an upfront or primary neck dissection (ipsilateral and/or contralateral) and prior radiotherapy or therapeutic surgery for a HNSCC. Electronic patient records were used to extract demographic and clinical data. The AJCC TNM staging, 8th Edition [21] was implemented part way through the study period. To facilitate analysis, patients staged according the prior 7th Edition [22] were retrospectively restaged following review of clinical electronic notes according the 8th Edition [21]. Scoring of p16 immunohistochemistry status was performed using a threshold of strong and diffuse nuclear and cytoplasmic staining in ⩾70% of the tumour [23]. Standard practice was for patients to have a baseline PET-CT pre-treatment.

Management

Chemotherapy

Standard concurrent chemotherapy was cisplatin 100mg/m^2 for 2-3 cycles (delivered on weeks 1 and 5 or weeks 1,4,7 depending upon clinician preference). In the event of a contraindication to cisplatin, carboplatin was substituted.

Radiotherapy

All treatment during the study period was delivered by volumetric modulated arc therapy (VMAT). Patients were treated supine with a 5-point thermoplastic mask. Planning CT scans were acquired with intravenous CT contrast and 2mm CT slices. A geometric approach to outlining was used. Prior to the publication of the international consensus '5 plus 5' outlining guidelines [24], the approach for constructing the high dose clinical target volume (CTV) was based upon primary tumour plus 10mm (whole site or subsites within the oropharynx were not routinely outlined) and involved lymph nodes + 5-10mm. From early 2018 our protocols allowed for delineation according the consensus '5 plus 5' guidelines [24].

Elective lymph node levels were defined according to consensus guidelines [4]. Institutional protocols included the option of unilateral only neck treatment for lateralised primary tumours of

the tonsillar fossa or anterior tonsillar pillar which are >1cm from midline, with <1cm of extension onto adjacent soft palate or base of tongue [25, 26]; these patients needed to have limited burden of ipsilateral neck nodal disease. Patients not meeting these criteria were routinely treated with bilateral neck radiotherapy. The minimum elective neck node levels included levels II-IVa and ipsilateral VIIa; in a node positive side of the neck levels Ib-Va/b were routinely included. In cases of involvement of level IVa or lower Va/b, levels IVb and Vc were included. Contralateral RPLN were only routinely included in elective target volumes according to institutional protocols in cases with evidence of ipsilateral RPLN disease, for any primary tumours arising from or involving the posterior pharyngeal wall or soft palate or with any contralateral neck lymph node disease. When level II lymph node involvement was present, ipsilateral level VIIb was included [27]. For patients with an uninvolved contralateral neck the uppermost extent of the contralateral level II included in the elective target volume was limited to the level at which the posterior belly of the digastric muscle crossed the posterior edge of the internal jugular vein (Figure 1); this applied to all primary tumour sites within the oropharynx and applied to cases with the primary tumour involving soft palate, posterior pharyngeal wall or crossing midline. Pharyngeal constrictor muscles were not outlined as organs at risk. The planning target volume (PTV) was created by auto-expansion of the CTV by 4 mm. Standard dose fractionations as per Royal College of Radiologists dose fractionation guidelines [28] were 70Gy in 35 fractions over 7 weeks or an option of 65Gy in 30 fractions over 6 weeks (the latter used in our practice for patients treated without concurrent chemotherapy, with lower doses to prophylactic dose regions (54-63 Gy in 30-35 fractions over 6-7 weeks). The objective for the contralateral parotid gland was a mean of 24Gy. Prospective peer review of contouring took place throughout this period.

Response assessment and follow-up

Response was routinely assessed 4 months after treatment by clinical examination, naso-endoscopy if indicated and FDG PET-CT. Patients were routinely followed up for at least 5 years.

Retrospective review of contouring

Contours for each radiotherapy plan were retrospectively reviewed. Each was classified into whether contralateral RPLN and/or contralateral HLII had been omitted. For cases with omission of contralateral HLII a measurement was made of the distance between the top of level II (caudal aspect of transverse process of C1) and the superior slice of the elective nodal CTV with HLII omitted. The primary tumour GTV was used to classify whether the primary disease approached or crossed

midline. Lymph node GTV(s) were used to document which lymph node levels were involved, total number of involved lymph nodes and size of largest lymph node.

Statistical analysis

Analysis was performed using IBM SPSS Statistics, Version 24 (Armonk, NY: IBM Corp.). Omission of contralateral HLII and RPLN from elective target volumes did not take place in all patients in whom this would have been possible according to institutional protocols. To assess whether there was any selection bias for selection of patients for this approach Chi-squared and Mann Whitney U tests were used to investigate potential differences between clinical variables between groups with/without contralateral HLII and RPLN omission from elective target volumes. Follow up and survival outcomes were calculated from the first day of radiotherapy. Overall survival (OS), progression free survival (PFS), local control, regional control and distant metastases-free survival (DMFS) were considered as endpoints and were calculated using the Kaplan–Meier method. A p-value of <0.05 was considered statistically significant.

Results

342 patients treated with definitive (chemo)radiotherapy for oropharyngeal carcinoma were identified. 299/342 (87%) were treated with a dose fractionation of 70Gy in 35 fractions and the remained received 65Gy in 30 fractions. 264/342 (77.2%) had a clinically and radiologically uninvolved contralateral neck. 238/264 (90.2%) received bilateral neck irradiation (ie. received elective radiotherapy to the contralateral neck). Median follow up of these 238 patients was 30.6 months (range 4.3-51.3). and 2 year local control, regional control, distant metastasis-free survival (DMFS), progression free survival (PFS) and overall survival was 91.0%, 91.6%, 91.1%, 81.3% and 86.5% respectively. Regional lymph node progression occurred in 18/238 (7.6%) of patients. Ipsilateral lymph node progression occurred in each of these 18 cases. Bilateral lymph node progression only occurred in one patient with a T3N2bM0 p16 negative tonsil tumour; contralateral HLII and RP LN were not omitted from target volumes for this patient and the contralateral lymph node progression was in the lower level II lymph node region. There were no cases of contralateral-only regional progression. Figure 2 provides examples of typical clinical target volumes for patients treated with and without inclusion of the contralateral HLII and RPLN. 154 patients were treated with omission of contralateral HLII and RPLN, 77 patients without omission of either, 7 patients with either HLII (n=2) or RPLN (n=5) omitted. Mean contralateral parotid dose for patients treated with both contralateral HLII and RPLN omitted versus both included in target volumes was 24.4Gy versus 28.3Gy ($p<0.001$).

Sparing of contralateral HLII

Figure 3A illustrates the identification of the subgroup of patients who underwent (chemo)radiotherapy with omission of the contralateral RPLN region from elective target volumes. Contralateral HLII was not included in the target volume as per institutional protocols in 159/238 (67%) of patients with a contralateral node negative neck, as shown in Figure 2. For the 159 patients in whom the contralateral HLII was omitted, the median craniocaudal distance between the superior slice of the CTV with HLII omitted and the conventional most cranial slice of level II (caudal aspect of transverse process of C1) was 10 mm (interquartile range 8-12mm, range 6-20mm). In the 79 patients in whom the upper contralateral level II was treated, 15 were not spared due to outlining within a clinical trial protocol; no reasons were documented for the remaining 64 patients who could have had HLII omitted according to institutional protocols, raising the potential for selection bias beyond the protocols. Table 1 summarises patient, disease and treatment characteristics for the 238 patients with/without omission of the contralateral upper level II lymph node region. There

were no statistical differences in the pattern of lymph node level involvement, total number of lymph nodes and size of the largest involved lymph node between the spared/not spared groups, primary subsite, T stage or the proportion of primary tumours at or crossing midline. Mean contralateral parotid dose for patients treated with and without omission of contralateral HLII from target volumes was 24.3Gy and 28.2Gy ($p<0.001$).

Out of the 159 patients in whom contralateral HLII was spared, 20/159 (12.6%) experienced disease progression. This included lymph node progression in 6 patients, with this being associated with primary progression in two patients and distant metastases in one patient. In all 6 cases of lymph node progression, progression occurred in the ipsilateral neck only with no recurrences in the contralateral HLII.

Sparing of contralateral RPLN

Figure 3B illustrates the identification of the subgroup of patients who underwent (chemo)radiotherapy with omission of the contralateral RPLN region. The contralateral RPLN region was omitted from elective target volumes for 175/238 (73.5%) patients receiving bilateral neck irradiation with a contralateral N0 neck. In the 63 patients in whom the contralateral RPLN was included documented reasons included: outlining within a clinical trial protocol in 15 patients, exclusion criteria within institutional protocols due to involvement of ipsilateral RPLN nodes in 11 patients (2 of these patients also within clinical trials), primary of posterior pharyngeal wall or soft palate in 9 patients; there was no documented reason for the remaining 30 patients. Table 2 summarises patient, disease and treatment characteristics for the 238 patients with/without sparing of the contralateral RPLN region. Two patients with a soft palate tumour were treated with omission of contralateral RPLN, although within institutional protocols patients with soft palate tumours would have bilateral RPLN irradiation. There were a higher proportion of patients with base of tongue/vallecula primary tumours who underwent sparing of contralateral RPLN ($p<0.001$). There was no significant difference in the pattern of lymph node level involvement , total number of lymph nodes involved or size of largest involved lymph node. A lower proportion of patients in whom contralateral RPLN were omitted versus included had a primary tumour at or crossing midline (65% versus 81%, $p=0.023$). Mean contralateral parotid dose for patients treated with and without omission of contralateral RPLN was 24.4Gy and 32.7Gy ($p<0.001$).

Disease progression occurred in 22/175 (12.6%) of patients in whom the contralateral RPLN were not included in target volumes. This included 10 patients with lymph node progression (including 3 with primary progression ,1 with distant progression and 1 with local and distant progression). In each of these 10 cases lymph node progression was ipsilateral only. There were no cases of disease progression in the contralateral RPLN region.

Discussion

Based on retrospective re-evaluation of individual contours, contralateral HLII sparing took place in 159/238 (67%) of OPC patients with a contralateral uninvolved neck, receiving bilateral neck irradiation. This was associated with significant reduction in mean contralateral parotid dose. There were no cases of lymph node progression in the contralateral neck, including the spared HLII. Omission of HLII did not take place for 79/238 (33%) of patients; this is a key issue raising the possibility for some form of selection bias beyond criteria identified in our protocols. 15 patients were participating clinical trials and HLII sparing was not part of the trial protocols. As shown in Table 1, there were no significant differences in patient/disease/treatment characteristics between patients who had HLII omitted and those who did not, other than for smoking history (for which there were a higher proportion of patients with 'unknown' status for the HLII omission group). This includes no significant differences in lymph node size, pattern of lymph node involvement and total number of involved lymph nodes. These data suggest that selection biases based on clinical characteristics are unlikely. An alternative explanation is that of clinician contouring habits and gradual uptake of a change in practice. The protocol was implemented at the start of 2016 and, perhaps inevitably, there was a period of time during which compliance with this change was limited.

The original series from the University of Michigan [5] reported on the IMRT outcomes in a heterogenous group of 133 HNSCC patients (80/133 (60%) with OPC) treated radically or adjuvantly with HLII sparing (the superior extent of the CTV was defined as the axial CT slice where the posterior belly of digastric crossed the internal jugular vein) with no recurrences superior to the subdiagastric lymph nodes. This was the only series other than ours which has reported on the impact on contralateral parotid doses and the approach was associated with lower contralateral parotid doses [6]. Raktoe et al. [29] reported a recurrence pattern analysis in 131 OPC patients treated with radical (chemo)radiotherapy; this group used a superior contralateral level II border of the transverse process of C2 and did not report edge or out-of-field recurrences at that site. In the series from Washington University [7], a total of 406 patients with an uninvolved contralateral neck and received radiotherapy without coverage of the contralateral HLII lymph nodes (defined using the same definition as Eisbruch et al. [5] (n=211/406 (52%) with OPC and 258/406 (64%) post-operative) with no reported recurrences in the spared region. Cumulatively, our data together with these three series include a total of 581 OPC patients with an uninvolved contralateral neck who underwent contralateral HLII sparing with no recurrences in the spared HLII region.

The rate of contralateral RPLN involvement is a major factor in determining the safety of sparing. Pathological data regarding the incidence of RPLN metastases are limited to very small series due to the difficulty of surgical access [30]. Large radiology-based studies [12, 15, 17] have reported an approximately 10% rate of RPLN involvement, independent of human papilloma virus (HPV) status [16, 17]. In our report of 402 patients based on PET-CT plus MRI and/or CT [17], 5/37 patients with ipsilateral RPLN involvement had bilateral RPLN abnormality. Posterior pharyngeal wall, soft palate primary and/or contralateral neck disease were each independently associated with RPLN disease. 3/402 (0.7%) had contralateral RPLN involvement without abnormal ipsilateral RPLN and only one of these patients had an uninvolved contralateral neck. In a series of 796 HPV positive OPC patients [12] bilateral RPLN disease was present in 4/66 (6%) of patients with ipsilateral RPLN involvement, and 7/796 (0.9%) of patients were found to have contralateral RPLN involvement without evidence of ipsilateral RPLN disease; the presence or otherwise of contralateral neck disease in these patients was not reported. In an earlier series from the same group [15] 1/981 (0.1%) patients with OPC had radiological evidence of contralateral RPLN involvement without ipsilateral RPLN disease. Of note, these series describe involvement of the lateral not medial RPLN groups (VIIa) [12, 17]. Overall, these data suggest that contralateral RPLN disease is very rare without either ipsilateral RPLN or contralateral neck disease. Data regarding soft palate or posterior pharyngeal wall subsites are limited but suggest a higher risk of RPLN disease; logically significant extension from another OPC primary site onto the posterior pharyngeal wall or soft palate may adopt similar risks.

Bilateral irradiation of the RPLN in patients treated for OPC has been routine within studies reported by multiple institutions [12, 13, 15] and clinical trials [8, 10]. However, in the series from the University of Washington [7] contralateral RPLN were eliminated from target volumes (for patients with uninvolved contralateral neck with no other criteria for omission of contralateral RPLN reported) for 234 HNSCC patients (117/234 (50%) OPC) with no RPLN recurrences and was associated with improved quality of life. In the DAHANCA protocols the retropharyngeal region was only treated in cases of involvement of the posterior pharyngeal wall; in a report of 700 patients from the DAHANCA database (52% OPC), RPLN recurrences were only observed in 2 patients (one of whom had a caudal posterior pharyngeal wall primary) [18]. In 102 OPC patients there were no RPLN recurrences following omission of the high contralateral RPLN (included to C1 vertebral body) in patients with a contralateral node negative neck [19]. In a small recent series [20], there were no recurrences in the contralateral RPLN which was omitted in 38 OPC patients. The 2019 lymph node selection guidelines recommend inclusion of the contralateral VIIa lymph node level for N0-2b

disease with posterior pharyngeal wall disease for p16-ve OPC and state that there is no data to suggest a different approach to p16+ disease [3].

In our series of OPC patients without contralateral neck disease, 175/238 (74%) had the contralateral RPLN region omitted with no recurrences in that site. This included 106/175 patients with primary tumours which reached or crossed midline. Contralateral RPLN sparing did not take place in 63/238 (26%) patients, including 15 patients treated within clinical trials and 20 patients in whom omission of contralateral RPLN was contra-indicated within institutional protocols (9 soft palate/posterior pharyngeal wall primary, 11 with abnormal ipsilateral RPLN). Although there was a lower proportion of patients in the group with RPLN omitted with a primary tumour at/crossing midline, the majority of patients with a tumour at or crossing midline did not have the contralateral RPLN included in target volumes (n=114). Omission of contralateral RPLN was associated with significantly lower contralateral parotid doses.

There are limitations to this retrospective analysis. Duration of follow up is relatively limited. Sparing of contralateral HLII and RPLN was not implemented in 33% and 26% of patients respectively. The relatively high mean doses to contralateral parotid without omission of contralateral HLII or RPLN, do suggest the possibility of selection bias, although this is not seen on analysis of baseline characteristics. It is important to note that comparison of contralateral parotid doses with the PARSPORT study [31] (which used 65Gy in 30 fractions) is challenging, as in our series the majority of patients received 70Gy in 35 fractions. Although no disease recurrences were found in the omitted regions, it should be recognised that there is still some delivered dose. Since most patients had both contralateral HLII and RPLN omitted it is not possible to determine the relative contribution of each to reducing contralateral parotid doses. We do not have reliable prospectively collected toxicity data to report to evaluate the benefit of this approach, although mean contralateral parotid doses provide a dosimetric surrogate for toxicity. Spencer et al. [7] did report a toxicity benefit with this approach but there is no other robust published data to allow evaluation of the potential toxicity benefits of either HLII or contralateral RPLN sparing.

In summary, in this large series of patients with OPC and an uninvolved contralateral neck receiving (chemo)radiotherapy, the omission of contralateral RPLN and HLII from elective target volumes was safe and can be considered in routine practice.

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Figure Legends

Figure 1: Omission of HLII where posterior belly of digastric crosses the posterior aspect of internal jugular vein. Example of axial planning CT slices (2mm slice thickness). A is the most inferior slide, with A to E extending superiorly. Image in D is the level where the posterior belly of digastric muscle crosses posterior aspect of internal jugular vein, and would be the most superior slice of CTV delineation when HLII omitted from elective CTVs. Yellow arrow in A: internal jugular vein; Red arrow in B: posterior belly of digastric muscle. Green arrow in D: posterior belly of digastric crosses posterior aspect of internal jugular vein.

Figure 2: Example coronal image of radiotherapy plans for patients treated with and without omission of contralateral HLII and RPLN from target volumes. A) T2N1M0 p16+ve tonsil squamous cell carcinoma extending onto base of tongue, treated with 70Gy in 35 fractions in a clinical trial without omission of contralateral (left) HLII and RPLN from elective target volume. B) T4N1M0 p16+ve base of tongue squamous cell carcinoma, treated with 70Gy in 35 fraction with omission of contralateral (right) HLII and RPLN from elective target volume. Light blue=high dose volume, green=elective lymph node volume.

Figure 3: Flow diagram to show identification of patients with OPC undergoing definitive (chemo)radiotherapy including bilateral neck irradiation, with A) omission of contralateral HLII and B) contralateral RPLN.