Article:
Iyizoba-Ebozue, Z, Murray, LJ orcid.org/0000-0003-0658-6455, Arunsingh, M et al. (3 more authors) (2020) Incidence and patterns of retropharyngeal lymph node involvement in oropharyngeal carcinoma. Radiotherapy and Oncology, 142. pp. 92-99. ISSN 0167-8140

https://doi.org/10.1016/j.radonc.2019.07.021

Incidence and patterns of retropharyngeal lymph node involvement in oropharyngeal carcinoma

Zsuzsanna Iyizoba-Ebozue[1], Louise J Murray[1,2], Moses Arunsingh[1], Sriram Vaidyanathan[3], Andrew F. Scarsbrook[2,3], Robin J D Prestwich[1]

[1]Department of Clinical Oncology, Leeds Cancer Centre, Leeds, UK

[2]Leeds Institute of Medical Research at St James's, University of Leeds, UK

[3]Department of Nuclear Medicine and Radiology, Leeds Cancer Centre, Leeds, UK

Corresponding Author:

Robin Prestwich

Email: Robin.Prestwich@nhs.net

Address: Level 4, Leeds Cancer Centre, St. James's University Hospital, Beckett St., Leeds, LS9 7TF, UK

Tel: 0044 113 2067838

Fax: 0044 113 2067886

Word Count: 2975

Abstract

Introduction

The aim was to evaluate in oropharyngeal carcinoma the: 1) incidence and predictors of retropharyngeal (RP) lymph node (LN) involvement, 2) pattern of ipsilateral/bilateral/contralateral-only RP LNs 3) location of RP LNs in relation to contouring guidelines.

Methods

Single centre retrospective analysis of 402 patients with oropharyngeal carcinoma treated non-surgically between 2010-2017. All patients had a baseline FDG PET-CT and contrast-enhanced MRI and/or CT. All cases with reported abnormal RP LNs underwent radiology review.

Results

Abnormal RP LNs were identified in 40/402 (10%) of patients. On multivariate analysis, RP LN involvement was associated with posterior pharyngeal wall/soft palate primaries (OR 10.13 (95% CI 2.29-19.08), p=0.002) and contralateral cervical LN involvement (R 2.26 (95% CI 1.05-4.86), p=0.036). T stage, largest LN size, levels of ipsilateral LN level involvement, HPV and smoking status did not predict risk. 5/402 (1.2%) patients had bilateral RP involvement. 3/402 patients (0.7%) had contralateral-only RP LNs. All patients with contralateral RP LNs had contralateral neck nodes or primary cancers extending across midline. In 5/40 (12.5%), involved RP LNs were superior to hard palate/upper edge of body of C1 vertebra.

Conclusions

RP LNs were identified in 10% of oropharyngeal carcinoma patients, and were associated with contralateral neck disease and/or posterior pharyngeal wall/soft palate primary. Contralateral RP LN involvement was rare and associated with contralateral neck disease and/or primary crossing midline, suggesting potential for omission from target volumes for selected patients. Involvement of RP LNs close to the skull base highlights the need for generous elective outlining.

Keywords: oropharyngeal cancer; retropharyngeal lymph nodes; radiotherapy; PET-CT

Introduction

Data regarding the incidence of retropharyngeal lymph node (RP LN) metastases in oropharyngeal cancer are limited due to the difficulty of surgical access [1] with pathological data based upon small series [2, 3]. Imaging studies report a variable incidence (2-21%) of RP LN metastases [4-11]. MRI is superior to CT for the detection of RP LNs [1, 12, 13]. 2-[Fluorine-18]-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography-computed tomography (PET-CT) is considered the most sensitive imaging modality for LN detection in head and neck cancers [14, 15], and has been found to increase diagnostic efficacy for RP LNs in combination with CT or MRI [10, 16]. Consistent with this finding, in a small series of dissections, all FDG-avid RP LNs were found to have pathological evidence of involvement [3]. However, in most series only a limited proportion of patients underwent PET-CT staging [6-9].

Knowledge of patterns/risks of RP LN involvement is required to determine the need for elective bilateral RP treatment or potential for omission of ipsilateral and/or contralateral RP LNs. Early reports of RP LN recurrences following the advent of intensity modulated radiotherapy (IMRT) highlighted the importance of adequate target volume delineation [17, 18], leading to bilateral RP LNs commonly being included in radiotherapy target volumes. However, RP LN irradiation increases toxicity due to proximity to the parotid and superior pharyngeal constrictors [8, 19]. Some recent clinical series have suggested potential for omission of contralateral RP LNs [20-22].

RP LNs are located in the retropharyngeal space extending from skull base to the level of the C3 vertebra caudally [1]. In 2003 consensus outlining guidelines RP LNs were defined as extending from the upper edge of hyoid to skull base, medial to the internal carotid artery [23]. The updated 2013 consensus guidelines [24] redefined the superior extent as the upper edge of the C1 vertebral body or hard palate. In addition RP LNs were divided into medial and lateral with the lateral nodes considered the critical group [24]. Whilst adopting these guidelines, an ongoing trial recommends contouring of lateral RP LNs 'at the level of the oropharynx' [25]. The location of radiologically abnormal RP LNs can guide defining the RP region at risk.

This purpose of this study in patients with oropharyngeal carcinoma treated with (chemo)radiotherapy who had baseline PET-CT and MRI and/or contrast enhanced CT was to: 1) determine the incidence and predictors for RP involvement; 2) evaluate the pattern of RP LN involvement ie. ipsilateral, bilateral or contralateral without ipsilateral RP LNs, and 3) evaluate location of RP LNs in relation to contouring guidelines.

Methods

Study population

Institutional review board approval was obtained. This was a single centre retrospective analysis. Patients were identified from a database of patients scheduled to receive (chemo)radiotherapy at Leeds Cancer Centre between January 2010-June 2017. Inclusion criteria were: squamous cell carcinoma of oropharynx, intention to treat with definitive radiotherapy ± chemoradiotherapy, pre-treatment FDG PET-CT and contrast-enhanced MRI and/or CT of the neck. Exclusion criteria were therapeutic surgery prior to baseline imaging, prior radiotherapy to the neck region and/or distant metastases at baseline. 402 patients were included and demographic and clinical data were obtained from institutional electronic patient records. Staging was documented according to the American Joint Committee on Cancer TNM staging, 7th Edition [26].

Identification of retropharyngeal lymph nodes

Electronic notes, imaging reports and LN gross tumour volumes (GTV) on radiotherapy plans were reviewed for the 402 patients to determine RP LN involvement. All imaging for patients with suspected RP LN involvement was reviewed by a dual-certified Radiologist and Nuclear Medicine Physician with 15 years experience of head and neck imaging. Normal lateral RP LNs are usually smaller than 4-4.5mm in short axis [1]. Radiological criteria [6, 27, 28] were used to identify involved RP LNs: short axis ≥5mm, necrosis and/or abnormal tracer uptake on PET-CT [11, 29]. Further analysis included the SUV_{max} of abnormal LN (if multiple RP LNs most avid one was measured), signal characteristics on MR, short axis diameter, and side of involvement. Images were reviewed using multiplanar reconstruction including sagittal and coronal projections, with corroboration with fixed base of skull structures (eg. cervical vertebral level, styloid process) in order to assess the anatomical level of abnormal RP LN. As this is an anatomical area affected little by neck flexion scan position is unlikely to alter this assessment. However, since the PET-CT scan was performed on a foam head rest with the neck commonly in mild extension, and the diagnostic MRI and CT scans for patients in this series were acquired on multiple scanners without a fixed neck position, correlation was made with the radiotherapy planning CT which was acquired in a neutral position. This anatomical level of abnormal RP LN was classified into: i) at level of oropharynx, ii) below level of hard palate/superior edge of C1 vertebral body (whichever higher), iii) above level of hard palate/superior edge of C1 vertebral body. For the purposes of this classification the most superior RP LN was classified if

multiple RP LNs were identified and the centre of the LN was used to identify the level in line with a prior study methodology [4].

Documentation of involved cervical lymph node number, levels and size

Radiotherapy contours for all 402 patients were reviewed by a Radiation Oncologist. Based upon outlined LN GTVs, the involvement of LN levels as defined in the 2013 consensus atlas [24] was documented. Total number of involved LNs was documented and maximal diameter of the largest involved LN was measured.

Statistical analysis

Analysis was performed using IBM SPSS Statistics, Version 24(Armonk, NY: IBM Corp.). Descriptive statistics were used to illustratethe incidence of RP LN involvement and baseline population. Chi-squared and Mann Whitney U tests were used to investigate potentials differences between clinical variables and the presence or absense of retropharyngeal LNs. A univariate logistic regression was performed to identify predictors of retropharyngeal LNs using the variables: gender, tumour site (three groups: tonsil; base of tongue/vallecula; soft palate/posterior pharyngeal wall), pathological grade, T classification, smoking status, HPV status, involvement of ipsilateral LN levels 1,2,3,4,5a/b (each as separate variables), involvement of contralateral LNs, maximum diameter of largest involved LN (grouped for analysis as <1, $\geq 1<2$, $\geq 2<3$, ≥ 3cm). Factors with a $p<0.2$ were taken forward into a multivariate backwards likelihood logistic regression. Total number of LNs and N classication are closely related to whether or not LNs were present in any specific region, and were therefore excluded from the logistic regression analysis. Statistical significance was considered for a $p<0.05$.

Results

Table 1 provides baseline characteristics of the 402 patients studied who all underwent PET-CT prior to non-surgical treatment, along with a diagnostic MRI (n=339) or contrast-enhanced CT (n=83) (41 patients had both). 43/402 patients with RP LNs were identified following review of notes/radiology reports/radiotherapy plans. Following imaging review, 40/43 (10%) patients were classified as having radiologically abnormal RP LNs. The median short-axis diameter of involved RP LNs was 9mm (range 5-29). RP LNs were metabolically active on PET-CT in 37/40 patients, median SUV_{max} 6.8 (range 3-26.3). 30 of these 37 patients had also undergone a diagnostic contrast-enhanced MRI and abnormal RP LNs were identified in 29/30 cases on the MRI. In the case in which the RP LN was avid on PET but not identified on MRI the SUV_{max} was 5.2 and a short axis size of 9mm on CT (MRI had movement artefact). Of the FDG-avid nodes, a corresponding abnormality could be identified on CT in 30/37 patients (either on the low-dose CT component of the PET-CT (n=23) or a diagnostic contrast-enhanced CT (n=7)). In 2 patients abnormal RP LNs were identified only on the basis of FDG uptake (SUV_{max} 5 and 5.1) and were not identified on the accompanying diagnostic contrast-enhanced CT (neither had undergone MRI). For the remaining 5 patients in whom the FDG avid RP LN were not identified on CT, abnormal RP LNs were visible on MRI. In the 3 patients with abnormal RP LNs which were not avid on PET-CT, these were all identified on MRI with short axis 5-9mm.

Table 1 summarises patient and disease characteristics for patients with and without abnormal RP LNs. RP LN involvement was more common in the small group with posterior pharyngeal wall/soft palate primary tumours, higher nodal stage, involvement of ipsilateral level III/IVa LNs, involvement of contralateral LNs, and increasing total number of involved LNs. Soft palate or posterior pharyngeal wall extension was documented in 6/34 patients with a tonsil or base of tongue primary and abnormal RP LN. There was no significant difference between RP positive and negative groups based on T stage, histological grade, p16 status, or smoking status. **Figure 1** illustrates the percentage of patients with positive RP LN for each of the factors of T and N stage, sub-site, p16 status, total number of nodes and LN diameter. 1/41 patients with N0 disease (other than RP LNs) had an involved RP LN; this patient has a T2N0 tonsil tumour with extension onto the adjacent soft palate. **Table 2** summarises the univariate and multivariate backwards logistic regression. The only factors significantly associated with risk of RP LNs on multivariate analysis were posterior pharyngeal wall/soft palate primary cancers and involvement of contralateral neck lymph nodes. Total number of LNs involved were also significantly associated with RP LNs but not included in the multivariate analysis because they are closely related to involvement of specific nodal levels/contralateral neck involvement.

In all 40 cases RP LNs were located in the lateral RP compartment with no involvement of the medial group. No cases were identified with involvement of retrostyloid LNs. Abnormal RP LNs were ipsilateral-only in 32/40 patients, bilateral in 5/40 patients and contralateral only in 3/40 patients. 4 of the 5 patients with bilateral RP LNs had bilateral cervical LN disease (including contralateral level 2) along with non-lateralised primary tumours (2 midline soft palate, posterior pharyngeal wall and T4 tonsil); the remaining patient without contralateral cervical nodal disease had a T4 N2b tonsil tumour extending across midline around the posterior pharyngeal wall. 2 of the 3 patients with contralateral-only RP LNs had bilateral cervical LN disease; the remaining patient had a T4 N2b base of tongue cancer with a large primary extending across the midline.

The abnormal RP LNs were at the level of the oropharynx in 15 of 40 (38%) cases. In total the abnormal RP LNs were below the level of the hard palate or upper edge of the body of C1 (whichever was higher) in 35/40 (87.5%) cases; in 3 of these cases a small portion of the involved LN was above the upper edge C1. In 5/40 (12.5%) of cases the abnormal RP LN was located above the level of the hard palate/upper edge of the body of C1; four of these five cases had tonsil primary tumours (two with soft palate extension) and one had a soft palate primary. To account for differences in neck flexion on diagnostic imaging, correlation was made with the planning CT scan in neutral position; the abnormal RP LN was visible on the planning CT in 4 of these 5 patients and the classification of anatomical level was not altered. **Figure 2** provides two examples of patients with RP LNs above the upper edge of body of C1/hard palate, showing images on diagnostic imaging and the planning CT scan.

Discussion

In this cohort the incidence of abnormal RP LNs was 10%. Table 3 compares other recent (2010-17) radiology-based series. The rates of RP LN involvement in our series and the large partially overlapping reports from the MD Anderson Cancer Center (Gunn et al. 10% [7], Lin et al. 9% [6]). Some smaller series with higher rates of T3/4 disease report higher rates of RP LN involvement [4, 9, 11]. There was no significant difference in rate of RP LN involvement in HPV positive and negative groups of patients. Similarly, Tang et al. [8] did not report any difference in rates of RP LN involvement between HPV positive and negative cases. This is consistent with the observation that patterns of cervical LN metastases are similar in HPV positive and negative cases [32].

The elective irradiation of bilateral RP LN regions in oropharyngeal carcinoma is widely practiced [6, 7, 25, 30, 31] following reports of RP LN recurrences [17, 18]. This has been challenged in an elegant series by Spencer et al. [20] who prospectively eliminated contralateral RP LNs in 234 patients with head and neck cancer and a contralateral node-negative neck; no contralateral RP LN recurrences were identified and quality of life outcomes were superior. Kjem et al. [21] analysed 700 patients (including 362 with oropharyngeal carcinoma) treated within protocols advising RP LN regions were only treated electively in the presence of abnormal RP LNs or disease involving the posterior pharyngeal wall; only one RP recurrence was identified which was not treated in an elective volume. Leeman et al. [22] omitted high contralateral RP LN irradiation in 102 oropharyngeal carcinoma patients with no RP LN treatment failures. It is important to recognize that in IMRT series in which RP LN regions are spared, some dose is delivered [22]. It is critical to identify patients at risk of RP LN involvement to guide treatment within elective radiotherapy target volumes.

Contralateral LNs and/or posterior pharyngeal wall/soft palate primary were independently associated with RP LN involvement on multivariate analysis. T stage, grade, p16 and smoking status, size of largest LN, involvement of specific ipsilateral LN levels were not independently associated with RP LNs. The lack of association with LN size are notable in view of guideines advising ipsilateral retrostyloid irradiation in the presence of bulky ipsilateral level 2 LNs [33]. Other series did not report any association between tumour subsite and RP LN involvement although posterior pharyngeal wall/soft palate tumours were rare [8-10]. Total number of lymph nodes was significantly associated with RP LN (not included in multivariate analysis as confounded by inclusion of involved LN levels). McLaughlin et al. [34] in a study of mixed sites found that the number of involved LN levels was the most significiant factor for the presence of RP LNs. However, RP LN disease can occur without any other LN involvement. Lin et al. identified 7/73 cases with involved

RP LNs and no other cervical disease. In our series, only 1/41 otherwise N0 cases had RP LN involvement.

The rate of contralateral RP LN involvement is a key factor in determining whether omission of contralateral RP LN volumes is appropriate. Several series do not differentiate ipsilateral, bilateral and contralateral-only RP LN involvement [9-11]. In this study, a total of 8/402 (2%) patients had contralateral RP LN involvement (5/37 (14%) bilateral, 3/402 (0.7%) contralateral-only); all had either contralateral cervical nodal disease and/or primary tumours crossing the midline. A useful comparision can be made with the series of 796 HPV-positive oropharynx cancer patients reported by Lin et al. [6]: bilateral RP LN disease was present in 4/66 (6%) patients with ipsilateral RP LN involvement, and there were 7/796 (0.9%) patients with contralateral RP LN involvement without positive ipsilateral RP LNs (none of the 7 patients had well-lateralised primary tumours although the presence of contralateral cervical LN disease was not reported). In their earlier publication without HPV status, Gunn et al. [7] reported bilateral RP LN involvement in 8/93 (9%) patients with ipsilateral RP LNs and 1/981 (0.1%) patients with contralateral RP LN involvement without ipsilateral RP LNs. Tang et al. [8] found bilateral RP LN involvement in 1/18 (6%) patients with ipsilateral RP LN disease and contralateral-only RP LN involvement in 1/164 (0.6%); in both of these cases with contralateral RP LNs there was other contralateral cervical LN disease. Overall based upon these and our series bilateral RP LN involvement occurs in 6-14% of patients with ipsilateral RP LN involvement and contralateral RP LN disease is rare (0.1-0.9%) in the absence of ipsilateral RP LN disease. Overall our data supports an approach in selected patients in line with that adopted by others [20, 21] of omitting contralateral RP LN irradiation; the risk appears very low in the absence of contralateral neck disease or a primary tumour crossing the midline or infiltrating soft palate or posterior pharyngeal wall. Our current practice with regard to elective RP LN irradiation based upon these data and our data presented here is shown in Table 4.

The location of radiologically involved RP LNs was consistent with Lin et al. [6] who also reported all nodes were in the lateral group. We found that 5/40 (12.5%) were sited cranial to the superior border of the RP LN level - level VIIa in the 2013 consensus guidelines [24]. Overall, 25/40 (63%) were superior to the upper extent of the oropharynx. The position in which the patients were scanned does not account for the cranial extent of the RP LN; this is an anatomical site expected to vary little with neck flexion and correlation was made for these 4 of these 5 patients with the planning CT in a neutral neck position (RP LN not visible on planning CT in one patient). These data suggest that RP LN level contouring needs to be generous in the superior extent to encompass this

anatomical at-risk region. As seen in Figure 2, this level would need to extend to skull base to encompass the full variation in site of RP LN. This would have a potential toxicity impact and correlation with reported series of recurrence patterns following treatment is required to determine whether this superior extent is necessary to avoid skull base LN recurrences.

A limitation of the study is reliance upon radiological evidence without pathological confirmation. Microscopic rates of RP LN involvement are likely higher. A small number of series have reported on retropharyngeal LN dissections [2, 3]. Chung et al. [2] reported on 22 patients with radiological evidence of RP LN disease and pathological involvement rate was 18/22 (82%). Additional limitations of this series are that only 20 patients had stage I/II disease limiting extrapolation to this group.

In summary, abnormal RP LNs were identified in 10% of oropharyngeal carcinoma patients. Involvement of contralateral lymph nodes and/or posterior pharyngeal wall primary increased risk of RP LN involvement. Contralateral RP LN involvement was rare, suggesting that omission of this as an elective target volume could be considered in selected cases. Involved RP LNs were sometimes superior to the definition of level VIIa highlighting the need for generous contouring.

References

[1] Coskun HH, Ferlito A, Medina JE, Robbins KT, Rodrigo JP, Strojan P, et al. Retropharyngeal lymph node metastases in head and neck malignancies. Head Neck. 2011;33:1520-9.

[2] Chung EJ, Kim GW, Cho BK, Cho SJ, Yoon DY, Rho YS. Retropharyngeal lymph node metastasis in 54 patients with oropharyngeal squamous cell carcinoma who underwent surgery-based treatment. Ann Surg Oncol. 2015;22:3049-54.

[3] Moore EJ, Ebrahimi A, Price DL, Olsen KD. Retropharyngeal lymph node dissection in oropharyngeal cancer treated with transoral robotic surgery. Laryngoscope. 2013;123:1676-81.

[4] Bussels B, Hermans R, Reijnders A, Dirix P, Nuyts S, Van den Bogaert W. Retropharyngeal nodes in squamous cell carcinoma of oropharynx: incidence, localization, and implications for target volume. Int J Radiat Oncol Biol Phys. 2006;65:733-8.

[5] Yoshimoto S, Kawabata K, Mitani H, Yonekawa H, Beppu T, Fukushima H, et al. Treatment results for 84 patients with base of tongue cancer. Acta Otolaryngol Suppl. 2007:123-8.

[6] Lin TA, Garden AS, Elhalawani H, Elgohari B, Jethanandani A, Ng SP, et al. Radiographic retropharyngeal lymph node involvement in human papillomavirus-associated oropharyngeal carcinoma: Patterns of involvement and impact on patient outcomes. Cancer. 2019.

[7] Gunn GB, Debnam JM, Fuller CD, Morrison WH, Frank SJ, Beadle BM, et al. The impact of radiographic retropharyngeal adenopathy in oropharyngeal cancer. Cancer. 2013;119:3162-9.

[8] Tang C, Komakula S, Chan C, Murphy JD, Jiang W, Kong C, et al. Radiologic assessment of retropharyngeal node involvement in oropharyngeal carcinomas stratified by HPV status. Radiother Oncol. 2013;109:293-6.

[9] Spector ME, Chinn SB, Bellile E, Gallagher KK, Kang SY, Moyer JS, et al. Exploration for an Algorithm for Deintensification to Exclude the Retropharyngeal Site From Advanced Oropharyngeal Squamous Cell Carcinoma Treatment. JAMA Otolaryngol Head Neck Surg. 2016;142:313-8.

[10] Baxter M, Chan JY, Mydlarz WK, Labruzzo SV, Kiess A, Ha PK, et al. Retropharyngeal lymph node involvement in human papillomavirus-associated oropharyngeal squamous cell carcinoma. Laryngoscope. 2015;125:2503-8.

[11] Tauzin M, Rabalais A, Hagan JL, Wood CG, Ferris RL, Walvekar RR. PET-CT staging of the neck in cancers of the oropharynx: patterns of regional and retropharyngeal nodal metastasis. World J Surg Oncol. 2010;8:70.

[12] Kato H, Kanematsu M, Watanabe H, Mizuta K, Aoki M. Metastatic retropharyngeal lymph nodes: comparison of CT and MR imaging for diagnostic accuracy. Eur J Radiol. 2014;83:1157-62.

[13] Liao XB, Mao YP, Liu LZ, Tang LL, Sun Y, Wang Y, et al. How does magnetic resonance imaging influence staging according to AJCC staging system for nasopharyngeal carcinoma compared with computed tomography? Int J Radiat Oncol Biol Phys. 2008;72:1368-77.
[14] Lonneux M, Hamoir M, Reychler H, Maingon P, Duvillard C, Calais G, et al. Positron emission tomography with [18F]fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: a multicenter prospective study. J Clin Oncol. 2010;28:1190-5.
[15] Prestwich RJ, Sykes J, Carey B, Sen M, Dyker KE, Scarsbrook AF. Improving target definition for head and neck radiotherapy: a place for magnetic resonance imaging and 18-fluoride fluorodeoxyglucose positron emission tomography? Clin Oncol (R Coll Radiol). 2012;24:577-89.
[16] Chu HR, Kim JH, Yoon DY, Hwang HS, Rho YS. Additional diagnostic value of (18)F-FDG PET-CT in detecting retropharyngeal nodal metastases. Otolaryngol Head Neck Surg. 2009;141:633-8.
[17] Eisbruch A, Marsh LH, Dawson LA, Bradford CR, Teknos TN, Chepeha DB, et al. Recurrences near base of skull after IMRT for head-and-neck cancer: implications for target delineation in high neck and for parotid gland sparing. Int J Radiat Oncol Biol Phys. 2004;59:28-42.
[18] Sanguineti G, Gunn GB, Endres EJ, Chaljub G, Cheruvu P, Parker B. Patterns of locoregional failure after exclusive IMRT for oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2008;72:737-46.
[19] Feng FY, Kim HM, Lyden TH, Haxer MJ, Worden FP, Feng M, et al. Intensity-modulated chemoradiotherapy aiming to reduce dysphagia in patients with oropharyngeal cancer: clinical and functional results. J Clin Oncol. 2010;28:2732-8.
[20] Spencer CR, Gay HA, Haughey BH, Nussenbaum B, Adkins DR, Wildes TM, et al. Eliminating radiotherapy to the contralateral retropharyngeal and high level II lymph nodes in head and neck squamous cell carcinoma is safe and improves quality of life. Cancer. 2014;120:3994-4002.
[21] Kjems J, Gothelf AB, Hakansson K, Specht L, Kristensen CA, Friborg J. Elective Nodal Irradiation and Patterns of Failure in Head and Neck Cancer After Primary Radiation Therapy. Int J Radiat Oncol Biol Phys. 2016;94:775-82.
[22] Leeman JE, Gutiontov S, Romesser P, McBride S, Riaz N, Lee N, et al. Sparing of high retropharyngeal nodal basins in patients with unilateral oropharyngeal carcinoma treated with intensity modulated radiation therapy. Pract Radiat Oncol. 2017;7:254-9.
[23] Gregoire V, Levendag P, Ang KK, Bernier J, Braaksma M, Budach V, et al. CT-based delineation of lymph node levels and related CTVs in the node-negative neck: DAHANCA, EORTC, GORTEC, NCIC,RTOG consensus guidelines. Radiother Oncol. 2003;69:227-36.

[24] Gregoire V, Ang K, Budach W, Grau C, Hamoir M, Langendijk JA, et al. Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines. Radiother Oncol. 2014;110:172-81.
[25] Mehanna HM, Sen M, Chester JD, Sanghera P, Paleri V, Gaunt P, et al. Phase III randomised controlled trial (RCT) comparing alternative regimens for escalating treatment of intermediate and high-risk oropharyngeal cancer (CompARE). Journal of Clinical Oncology. 2017;35:TPS6091-TPS.
[26] AJCC Cancer Staging Manual. Seventh Edition. New York: Springer Verlag; 2007.
[27] Zhang GY, Liu LZ, Wei WH, Deng YM, Li YZ, Liu XW. Radiologic criteria of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma treated with radiation therapy. Radiology. 2010;255:605-12.
[28] Chua DT, Sham JS, Kwong DL, Au GK, Choy DT. Retropharyngeal lymphadenopathy in patients with nasopharyngeal carcinoma: a computed tomography-based study. Cancer. 1997;79:869-77.
[29] Matsubara R, Kawano S, Chikui T, Kiyosue T, Goto Y, Hirano M, et al. Clinical significance of combined assessment of the maximum standardized uptake value of F-18 FDG PET with nodal size in the diagnosis of cervical lymph node metastasis of oral squamous cell carcinoma. Acad Radiol. 2012;19:708-17.
[30] Setton J, Caria N, Romanyshyn J, Koutcher L, Wolden SL, Zelefsky MJ, et al. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: an update of the Memorial Sloan-Kettering Cancer Center experience. Int J Radiat Oncol Biol Phys. 2012;82:291-8.
[31] Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. Lancet. 2019;393:51-60.
[32] Amsbaugh MJ, Yusuf M, Cash E, Silverman C, Wilson E, Bumpous J, et al. Distribution of Cervical Lymph Node Metastases From Squamous Cell Carcinoma of the Oropharynx in the Era of Risk Stratification Using Human Papillomavirus and Smoking Status. Int J Radiat Oncol Biol Phys. 2016;96:349-53.
[33] Gregoire V, Eisbruch A, Hamoir M, Levendag P. Proposal for the delineation of the nodal CTV in the node-positive and the post-operative neck. Radiother Oncol. 2006;79:15-20.
[34] McLaughlin MP, Mendenhall WM, Mancuso AA, Parsons JT, McCarty PJ, Cassisi NJ, et al. Retropharyngeal adenopathy as a predictor of outcome in squamous cell carcinoma of the head and neck. Head Neck. 1995;17:190-8.

Figure legends

Figure 1: Risks of RP LN involvement according to potential risk factors. For each factor on the x-axis, the graphs show the percentage of patients with positive RP LN.

Figure 2: Examples of patients with retropharyngeal lymph nodes lying above the upper edge of body of C1/hard palate (ie. above cranial boundary of VIIa lateral RP lymph node level in 2013 consensus guidelines). Patient 1: T4a N2c M0 p16+ squamous cell carcinoma of right tonsil, A) axial fused FDG PET-CT and B) contrast-enhanced CT images, C) axial planning CT and D) sagittal planning CT with GTV for RP LN outlined in blue. Patient 2: T3 N1 M0 squamous cell carcinoma of the right tonsil extending into the adjacent soft palate, E) axial fused FDG PET-CT and F) T2-weighted MR images, G) axial planning CT and H) sagittal planning CT with GTV for RP LN outlined in red. Images from both patients show right RP LN medial to the internal carotid artery and close to skull base.