# Current thinking on the management of abnormal retropharyngeal nodes in patients with oral, oropharyngeal, and nasopharyngeal squamous cell carcinoma: a structured review

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## Abstract

The management of enlarged retropharyngeal lymph nodes (RLN) in patients with confirmed oral, oropharyngeal, or nasopharyngeal squamous cell carcinoma (SCC) has prognostic relevance and is a challenge for the clinical teams. There is, however, no consensus regarding their clinical management or radiographic evaluation. The aim of this review therefore was to present the current thinking on management to help improve outcomes. We searched several online databases using the key terms "retropharyngeal node", "oral cancer", "head and neck cancer", "oropharyngeal cancer", "nasopharyngeal cancer", "nasopharynx", "oral cavity", "oropharynx", "TORS", and "radiotherapy". A total of 1024 papers were screened, of which 32 were eligible. There was no consensus about the management of RLN. There is a lack of randomised studies and a lack of consistency in the presentation of results. Management should be tailored in patients with nasopharyngeal carcinoma (NPC), and prophylactic irradiation is warranted as these nodes are at high risk of metastasis. In patients with non-NPC tumours, we prefer to resect them during primary operations when there is radiological uncertainty or evidence that they are affected, as the combination of radiological and histological outcomes will further our understanding. In both NPC and non-NPC tumours, sampling may also help to standardise the radiological criteria for the diagnosis of RLN by contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) CT.

*Keywords:* retropharyngeal nodes; squamous cell carcinoma; oral; oropharyngeal; nasopharyngeal cancer

## Introduction

The retropharyngeal lymph nodes (RLN) lie within a fat pad in the retropharyngeal space, one of the deep neck compartments that extends from the clivus to the upper mediastinum. It is located anterior to the prevertebral fascia and muscles, posterior to the pharyngeal mucosal space, anteromedial to the carotid space, and posteromedial to the parapharyngeal

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space, and is close to the cervical sympathetic trunk and ganglion. The fat pad extends from the level of the carotid bifurcation to just below the base of the skull.[1]

The retropharyngeal space is divided into the suprahyoid (contains fat and lymph nodes) and infrahyoid (contains only fat, so can be involved only by non-nodal disease) spaces. The RLN comprise one medial and two lateral groups. The medial group, which lies behind the pharyngeal midline anterior to the medial parts of the longus colli muscle at a level between the first and fourth cervical vertebra, is small and rarely present in adults. The lateral groups, better known as the nodes of Rouvière, are clinically more important. They are contained within a sliver of fatty tissue that is located immediately medial to the internal carotid artery, anterior to the lateral masses of the atlas, and ventral to the longus colli muscle.[1,2] There are typically between one and three lateral nodes, which are 2-5 mm in size in adults.[3]

They receive afferents from the nasopharynx, oropharynx (particularly the lateral and posterior pharyngeal walls), and hypopharynx. Nevertheless, metastatic deposits have been recorded from the oral cavity, maxillary sinus, posterior ethmoids, cervical oesophagus, larynx, and thyroid gland. Efferent lymphatics drain to the upper deep cervical lymph nodes.[3–5]

The clinical significance of involved RLN was illustrated in 1964 by AJ Ballantyne from the University of Texas, MD Anderson Hospital, Houston.[6] Thirty-four patients with squamous cell carcinoma (SCC) of the pharyngeal wall were treated by total pharyngectomy and dissection of the RLN from the base of the skull to the oesophageal introitus. The patients with nodal metastases had a dismal outcome.

In general, reported rates of RLN metastases in cancer of the head and neck and subsites vary widely because of the lack of consensus in diagnostic approach and treatment.[3] The aim of this review therefore, was to evaluate current practice and developments in the evidence-based understanding of the management of abnormal nodes in nasopharyngeal carcinoma (NPC), oropharyngeal SCC, and SCC of the oral cavity.

## Material and methods

We searched PubMed, Handle-on-qol, Medline, Embase (Excerpta Medica), Science Citation, Index/Social Sciences Citation Index, and Ovid Evidence-Based Medicine databases using the key terms "retropharyngeal node", "oral cancer", "head and neck cancer", "oropharyngeal cancer", "nasopharyngeal cancer", "nasopharynx", "oral cavity", "oropharynx", "TORS", and "radiotherapy". Only manuscripts written in the English language were included. All instruments included in the Preferred Reporting Items for Systematic Reviews and Meta-analyses PRISMA guidance were considered in the search and presentation of results.[7] A total of 1024 papers were identified, and after evaluation of the abstracts and available full texts, 32 papers were scru-
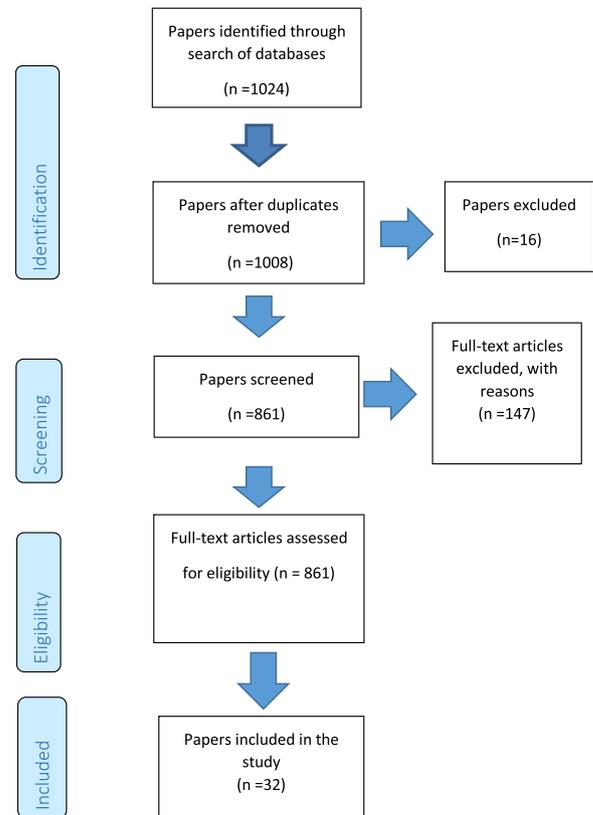


Fig. 1. Search results.

tinised (Fig. 1). The data collected pertained to the topic of the paper, sample size, site of primary tumour, diagnostic method, treatment, and outcome.

## Results

A total of 32 papers satisfied our criteria (Fig. 1). Most were retrospective in nature. A detailed description is tabulated in Table 1.[4–6,8–36] RTN were involved most often in NPC, followed by SCC of the oropharyx and oral cavity. Different diagnostic methods and treatment protocols were used, and in most cases, positive nodes were radiologically confirmed by computed tomography (CT), magnetic resonance imaging (MRI), or fluorodeoxyglucose positron emission tomography (FDG PET).

There were differences in the discrimination of invaded nodes between centres in the US and the Far East that showed that the axial dimension of the lateral lymph nodes was more than 10 mm compared with more than 5 mm (the latter referred to NPC). Other criteria included nodes with cystic or central necrosis, those with ill-defined margins suggesting extracapsular spread, or with hyper-enhancement on post-contrast images as compared with the adjacent musculature, groups of two or more lymph nodes in the ipsilateral retropharyngeal space, and any finding of a medial RLN on FDG-avid

Table 1
Details from papers used in this structured review.

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Ballantyne 1964[6] | Retrospective & case studies | 34 | Pharyngeal wall cancer (n = 34); oropharynx and hypopharynx (n = 11) | N/A | Resection of primary ± ND including RLN. | | Follow up <3years: 16/19 with RLN (-) alive, 10/15 RLN (+) alive. | RLN involvement in 44% of the 34 cases of pharyngeal-wall cancer. RLN may be significantly involved in spread of oro- and hypopharygeal malignancies (data not shown). Removal of positive RLN may aid survival in such cancers. RLN involvement may induce a pain complex. |
| Baxter 2015[12] | Retrospective | 165 | Oropharyngeal SCC – HPV-associated | PET or CT | Radiotherapy (IMRT or IGRT) or concurrent chemotherapy. Neoadjuvant chemotherapy in 18.2% of patients. | RLN were involved in 16 patients (9.70%). No significant association between RLN status and recurrence-free survival was identified after adjustments for T and N stage | Average follow up was 2 years. In patients positive for RLN pretreatment, odds for recurrence or death were 5.2-times greater (31.3% cf. 8.1%, p = 0.004). | The PET/CT combination is useful in identifying RLN. Further studies are required to measure the sensitivity and specificity of PET/CT for detecting RLN, and their impact on treatment and outcomes of HPV-associated OPSCC |
| Boeve 2017[5] | Retrospective | 11 | Oral maxillary cancer (10/11 SCC; 1/11 melanoma) | Histopathology | SLN +/- SND, MRND (3/11 had previous treatment for oral cavity SCC) | In 10 patients sentinel lymph nodes were detected at cervical levels I, II, or III in the neck. In 2 (17%) patients the sentinel lymph node was parapharyngeal. 8/11 (73%) patients had only cervical region sentinel lymph nodes. | N/A | The study suggests cervical level I-III sentinel lymph nodes are involved preferentially in oral maxillary cancer. In 17% there was combination of cervical plus RLN SLN. |
| Chan 2013[13] | Prospective analysis | 82 | NPC (with persistent or recurrent RLN involvement after previous treatment.) | MRI | Radiotherapy or chemoradiotherapy | Mean follow-up 38 months. Mean size of RLN on MRI was 1.6 cm; mean standard uptake value maximum (SUVmax) on PET scan was 6.8. RLN were resected through maxillary swing approach, 87.8% contained viable malignant cells. Rate of microscopic extracapsular spread was 30.6%. | 5-year actuarial tumour control rates and overall DFS after resection of isolated RLN was 79.6% and 59%, respectively. | PET scans may be useful for diagnosis of persistent or recurrent RLN after previous radiotherapy for NPC. Maxillary swing technique facilitates resection with clear margins. |

Table 1 (*Continued*)

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Chan 2018[14] | Retrospective | 145 | NPC (recurrent) - with RLN metastasis (group I), - with parapharyngeal space (PPS) invasion (group II) - with internal carotid artery (ICA) encasement (group III). | – | – | Local tumour recurrence rate significantly higher in groups II and III. Systemic metastasis rate & 5-year OS significantly worse in group III. | 5-year OS for groups I, II and III was 81.2%, 68.4%, 48.5%, respectively. | Upstaging of recurrent NPC encasing the ICA to T3 may be warranted given its worse prognosis. |
| Chen 2011[15] | Retrospective | 181 | NPC (no distant metastases, stage III/IV diseases in 95.6%) | MRI | All had neoadjuvant chemotherapy followed by radiotherapy; 17/181 had concurrent chemotherapy. | The pre-treatment RLN volume (RNV) was greater in patients who developed distant failure than in those without distant failure (p = 0.0536). DMFFS correlated with N-stage, sex and RNV. | 7-year DMFFS in patients with RNV > 4.68 and ≤4.68 cm3 was 66.4% and 83.5%, respectively (p = 0.0043) | In patients with advanced NPC, RNV measured by MRI is a potential predictor of distant metastasis. |
| Chua 1997[16] | Retrospective | 364 | NPC | CT | All had radiotherapy, 87 also had neoadjuvant chemotherapy for locally-advanced disease. | RLN incidence was 29.1%. Identification of RLN on CT in NPC did not show a significant correlation with prognostic variables. Involvement of RLN on CT in N0 disease not deemed adequate evidence for N1 classification. | Differences in survival rates not significant. 5-year relapse-free survival for patients with RLN(+) was less than for those with RLN(-) (54% cf 64%, p = 0.05). 5-year distant metastasis-free rates were also reduced in RLN(+) (74% cf 77%, p = 0.30). | – |
| Chung 2011[17] | Retrospective | 76 | Tonsillar SCC advanced in 81.6% (stage III&IV) | CT, MRI, or PET-CT | Operation alone (16/76 patients), operation with postoperative radiotherapy (38/76), operation with chemoradiation (22/76). RLN dissection (34/76). | – | DSS significantly different RLN(-) cf RLN(+) (82.1% cf 55.6%, p = 0.021). | RLN metastasis significantly associated with positive preoperative image, posterior pharyngeal wall invasion, > N2 stage, contralateral node metastasis, or ipsilateral multilevel involvement. Primary lesions proximal to midline or advanced ipsilateral nodal disease necessitate bilateral neck dissection. Elective RLN dissection should be considered for advanced neck and primary tumours, particularly when posterior pharyngeal wall is invaded. |

Table 1 (*Continued*)

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Chung 2015[18] | Retrospective | 54 | Oropharyngeal SCC | MRI, PET-CT or CT: overall imaging sensitivity of 66.7%, specificity 87.5%, and NPV of 87.5% | Resection of primary with RLN dissection - all patients. Operation alone (14/54 patients), postoperative radiotherapy (14/54) and chemoradiation (26/54). HPV genotyping 52/54 | RLN metastasis confirmed in 22 patients. High-risk HPV + status did not correlate significantly with RLN metastasis. | Overall 5-year DFS and OS both 66.7 %. RLN (+) conferred worse DSS and OS rate (DSS; 54.5 cf 75 %; p = 0.05, OS; 50 cf 78.1 %). In the 14 patients, who could not have postoperative adjuvant treatment overall 5-year DFS and OS both 53.8 %. | Elective RLN dissection should be considered for advanced neck and primary tumours, particularly in posterior pharyngeal wall invasion or when there is a high suspicion in imaging. |
| Dirix 2006[19] | Cohort | 208 | Oropharyngeal SCC | CT | Radiotherapy alone in 84.1% of patients, operation with postoperative radiotherapy in 11.5%, concomitant chemoradiotherapy in 4.4%. | – | 5-year OS 45%. No significant difference between RLN(+) and RLN(-) groups (36% cf. 46%, p = 0.3), but 23% (46/201) died of other causes. DSS was lower in the RLN(+) group (38% cf. 58%, p = 0.03). | At 5 years, regional recurrence was greater in patients with RLN involvement (45% cf. 10%, p = 0.004). RLN involvement can predict regional recurrence. |
| Gunn 2013[9] | Retrospective | 981 | Oropharyngeal cancer (base of the tongue (47%), tonsil (46%) | CT used in 96% of patients. 26 (3%) had MRI, 13 (2%) PET ± CT. | IMRT in 77% of patients, systemic therapy in 58%. | Median follow-up 69 months. Incidence of RLN involvement was 10%; greatest in pharyngeal wall primaries (23%), lowest for tongue-base (6%). RLN involvement associated with poorer local control, recurrence-free survival, DMFS and OS on multivariate analysis. | 5-year actuarial OS higher for patients without radiological RLN involvement than with RLN involvement (82% cf 52%, p < 0.001) | RLN involvement in OPC identified in 10% of patients and is associated with detrimental effects on recurrence, distant relapse, and survival. |
| King 2000[20] | Retrospective | 150 | NPC | MRI | Radiotherapy | RLN involvement (94%) more common than NRLN (76%) in 115 patients. NRLN involvement in the absence of RLN involvement seen in only 6% of all patients. | No evidence of nodal disease at long-term follow up (6-42 months, n = 71) | RLN involved in most initial metastases. RLN involved at the oprohrayngeal level more often than previously thought |

Table 1 (*Continued*)

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Leeman 2017[21] | Retrospective | 102 | Oropharyngeal carcinoma (unilateral, cN0-N2b) | Fibreoptic nasopharyn-goscopy and CT and/or MRI. | IMRT ± concurrent chemotherapy | No failures in treated ipsilateral RLN nodes or spared contralateral high RLN nodes in any patient. | Median follow-up 26.9 months. 2-year rates of the p16+ subgroup and entire cohort for OS and freedom from local, regional, distant, and retropharyngeal failure were 98.0% and 95.1%, 98.1% and 97.7%, 96.4% and 96.7%, 98.1% and 95.1%, and 100% and 100%, respectively. | In patients with p16+ OPC and unilateral disease, sparing of contralateral high RLN nodes from treatment volumes is safe. |
| Liao 2008[22] | Retrospective | 420 | NPC | CT, MRI | N/A | MRI showed RLN involvement in more cases than CT (MRI, 69% cf CT, 52.1%). | N/A | MRI resulted in different clinical and T-stages and is preferable to CT staging of NPC. |
| Liu 2006[23] | Retrospective | 275 | NPC | MRI | N/A | Incidence of metastatic lateral RLN decreases gradually between levels C1-3 In NPC the first echelon nodes include both RLN and cervical level II nodes, incidence of involvement was equal (81.4% cf 81.4%) | N/A | – |
| Ma 2007[24] | Retrospective | 749 | NPC | MRI | Radiotherapy | Incidence of RLN metastasis was 51.5%. RLN metastasis has a detrimental effect on DMFS in NPC and prognosis of N0 disease. | 5-year survival better in patients without RLN metastasis; OS (58.7% cf 72.2%, $p < 0.001$) and DMFS (75.0% cf 84.6%, $p < 0.001$). Only DMFS displayed a marginal significant difference after adjusting for T and N classification ($p = 0.079$). | RLN metastasis should be designated as N1 disease. |
| Ng 2007[25] | Retrospective | 202 | NPC | MRI | 3D conformal radiotherapy - all patients. 41% of patients had additional chemotherapy. | Nodal involvement high in NPC (96% of patients) and mainly occurred at II (94%), III (85%) and RLN (80%). RLN involvement only affected the N-category in 3.5% of patients; RLN impact on tumour control was not significant. Replacing supraclavicular fossa (SCF) with levels IV and Vb (LL) as a criterion for defining N3 is predictive for distant control and OS and may be useful in practice. | 3-year OS was 94% for N0/1, 84% for N2 and 53% for N3s ($p < 0.01$) based on the AJCC/UICC classification. | – |

Table 1 (*Continued*)

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Ou 2012[26] | Retrospective | 119 | NPC (with RLN metastasis only) | MRI | Definitive radiotherapy in all patients. Elective neck irradiation to levels II, III, Va (89/119 patients). Whole neck irradiation, including levels II–V (30/119). | Nodal relapse developed in 4 patients, 1 was out-of-field relapse. No significant differences detected between nodal recurrence in elective neck irradiation and whole neck irradiation. IMRT and 3D conformal radiotherapy improved regional control, compared with conventional 2D radiotherapy (p = 0.074). In 2D-radiotherapy, a higher dose (>5600 cGy) to the upper neck improved regional control (p = 0.006). Dose was the only independent prognostic factor of NFS on multivariate analysis. | Median follow-up 36.6 months. 5-year LFS, NFS, DMFS and OS were 81.4%, 92.7%, 91.8%, and 93.6%, respectively. | Whole neck irradiation for NPC patients with only RLN metastasis was not superior to elective irradiation of levels II, III, VA, but further confirmation is required. IMRT was associated with improved regional control. The prophylactic radiation dose of the upper neck region in patients with RLN metastasis may need to be increased. |
| Samuels 2015[27] | Retrospective | 185 | Oropharyngeal cancer (HPV+) | Histology | Radiotherapy (IMRT) and concurrent chemotherapy | 29 (16%) of the HPV + patients had RLN involvement. Median follow up 49 months. No RLN recurrences. Stages T4 or N3, and RLN involvement, were independently and significantly associated with both OS and distant failure. | 5-year OS, FFS and DFFS for patients with RLN involvement cf patients without RLN involvement was 57% cf. 81% (p = 0.02), 63% cf 80% (p = 0.015) and 70% cf 91% (p = 0.002), respectively. | RLN involvement in HPV + OPC is an independent prognosticator for distant failure, corresponding with worse OS. Such patients may not be suitable for de-escalation of treatment. |
| Shi 2014[28] | Retrospective | 142 | NPC (N1, M0) | MRI | Radiotherapy ± chemotherapy | Median follow-up 48 months. RLN and cervical lymph node involvement (CLN) was an independent prognostic factor for DMFS and PFS (p = 0.019, p = 0.019), but not significant for LRFS (p = 0.051). | 5-year LFS, NFS, LRFS, DMFS, PFS, OS of the whole group was 82.3%, 83.0%, 81.0%, 82.1%, 75.3% and 89.8%, respectively. | In NPC, N1, RLN and CLN involvement may be a prognostic factor for distant metastasis and disease progression. |

Table 1 (*Continued*)

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Shimizu 2006 [29] | Retrospective | 77 | Oropharyngeal cancer | Histopathology | Resection - neck dissection | RLN metastasis in 29% of patients with primaries of the lateral or posterior wall. No RLN metastasis identified in patients with anterior or superior wall primaries. Survival rate with <2 positive LN was better than >3 positive LN, survival rates associated with extracapsular spread were also poorer than those for LN metastasis alone (both p < 0.05). | 5-year OS of all patients was 54%. 5-year OS in stage II, stage III and stage IV lesions was 100%, 69%, and 43%, respectively. | RLN involvement must be considered in oropharyngeal cancer, particularly when of lateral or posterior wall origin. Intensified adjuvant therapy is necessary for multiple nodal involvement, particularly in the presence of extracapsular spread. |
| Spector 2016 [30] | Retrospective | 205 | Oropharyngeal SCC (previously untreated, advanced stage (III, IV)) | CT or CT/PET | Radiotherapy and concurrent chemotherapy | RLN involvement identified in 18% of patients: 12/89 (13%) base of tongue cancers, 24/109 (22%) tonsils, and 1/7 (14%) other oropharyngeal subsites. | N/A | Prevalence of RLN involvement positively correlated with closer proximity to posterior tonsillar pillar. In patients with advanced OPSCC there is no clear algorithm for de-escalation of treatment (exclusion of the retropharyngeal site) based on pretreatment imaging. |
| Tang 2013 [31] | Retrospective | 165 | Oropharyngeal carcinoma | MRI, PET-CT or CT | Radiotherapy | – | 2-year OS and EFS rates poorer with RLN involvement than without (OS; 71% cf 89%, EFS; 71% cf 81%); difference was not significant. | RLN involvement was associated with stage N2c-3 and N2b disease with either advanced T-stage, ≥3 involved cervical LN, and ≥1 involved contralateral LN, or lateral/posterior subsites. |
| Tang 2014 [11] | Retrospective | 749 | NPC (non-metastatic) | MRI | IMRT in all patients, additional chemotherapy given to 86.2% (424/492) of those with stage III or IV disease. | RLN metastasis incidence was 64.2% (481/749). | 5-year DFS and DMFS significantly poorer in RLN metastasis (DFS; 70.6% cf. 85.4%, p = 0.001, DMFS; 79.2% cf. 90.1% p = 0.001). | In NPC, RLN metastasis remains an independent prognostic factor for DFS and DMFS. RLN metastasis classification as N1 remains appropriate. Classification of RLN metastasis as N1a should be further investigated. |

Table 1 (*Continued*)

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Tauzin 2010[8] | Retrospective | 101 | Oropharyngeal SCC -biopsy confirmed | Histopathology and PET-CT | IMRT in all patients. 47 (88.7%) had concurrent chemotherapy, 3(5.7%) also had neoadjuvant chemotherapy, and 1 (1.9%) also had post-radiation chemotherapy. 5 patients (9.4%) did not have chemotherapy. | RLN involvement was 20.8% (11/53). Advanced T stage and advanced clinical N stage cancer (≥ N2) had higher odds (OR: 5.6250 and 3.9773, respectively) of being RLN positive than N0-1 patients. | N/A | Pretreatment PET-CT is a suitable staging tool for treatment planning in oropharyngeal cancer, as rates of RLN and nodal metastasis are consistent with those reported. |
| Tham 2009[32] | Retrospective | 395 | NPC T2-4 N0-N1 only included | CT | All had radiotherapy, 1 also had neoadjuvant chemotherapy. | RLN metastasis was related to a higher rate of distant metastasis (p = 0.04). The prognosis for N0 disease with RLN involvement was similar to N1 disease. | 5-year OS (%), N0: 71.4, N1: 58.8, RLN metastasis negative: 68.3, RLN positive: 57.8 (rates reported separately). Kaplan-Meier curves: showed better DMFS and OS rates in N0 than in N1. RLN positive N0 patients were more than twice as likely to have distant metastases, or to die, than RLN negative patients. | – |
| Troob 2017[10] | Retrospective case-control | 67 | Oropharyngeal SCC, undergoing transoral robotic RPLND (n = 30), not undergoing transoral robotic RPLND (n = 37) | CT (neck) & CT/PET (whole body) | Chemoradiation or resection with postoperative radiotherapy or adjuvant chemotherapy. RPLND after resection of primary tumour. | RLN metastasis identified in 20% (6/30) of patients undergoing RPLND. No difference between groups in duration of stay, feeding tube dependence, net change in perioperative weight, or rates of haemorrhage and postoperative complications. RPLND altered adjuvant treatment recommendations in 1/ 30 patients. | N/A | RPLND is not associated with poorer complication rates including swallowing outcomes. RPLND may aid staging and selection of appropriate adjuvant treatment. |
| Tseng 2013[33] | Retrospective | 36 | Oral cavity SCC (with RLN metastases (n = 10) or RLN relapse (n = 26)) | FDG-PET/CT | Resection of primary tumour. For clinically positive neck nodes - classic radical or modified neck dissections. For clinically negative neck nodes - supra-omohyoid neck dissections. ± postoperative radiotherapy. | Median follow-up 14 months. Level IV/V neck lymph node involvement and concomitant contralateral neck lymph node metastases (N2c) were associated with lower DSS and DFS rates. Salvage treatment yielded the greatest survival benefit in patients without N2c disease and ipsilateral RLN involvement alone (p = 0.005). | 2-year DSS and DFS for untreated patients with RLN involvement was 20% and 24%, respectively. 2-year DSS and DFS for patients treated for relapse was 12.8% and 9.6%, respectively. All patients presenting with involved neck lymph nodes at levels IV/V died within 6 months. | Oral cavity SCC with RLN metastasis has a poor prognosis. Definitive treatment is warranted in OSCC with RLN involvement defined by FDG PET/CT as level IV/V and N2c and/or contralateral RLN recurrent disease. |

Table 1 (*Continued*)

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Umeda 2005[34] | Retrospective & case studies | 77 Retrospective study (n = 72), case study (n = 5) | Maxillary carcinoma: gingiva (n = 48), antrum (n = 22) hard palate (n = 1), maxillary bone (n = 1), posteriorly invasive with upper jugular region lymph nodes metastases (n = 5). | N/A | Gingival carcinoma: 43 had maxillectomy ± adjuvant radiotherapy, 4 had combination treatment and 1 intracavity irradiation. Antral carcinoma: 9 had maxillectomy, 13 a combination of external irradiation, maxillary sinus excision, and regional intra-arterial infusion chemotherapy. Posteriorly invasive maxillary carcinoma: 5 had en bloc resection | All 5 patients who had en bloc resection remain alive without recurrence. | 5-year survival: 73% for gingival carcinoma, 45% for antral carcinoma. | Further investigation of en bloc resection may be warranted. En bloc resection may increase survival and reduce parapharyngeal and retropharyngeal recurrence. |
| Umeda 2009[4] | Case report | 3 | Oral cavity SCC | CT or MRI | Patient 1: partial maxillectomy, bilateral neck dissection including the right LRLN with postoperative radiotherapy. Patient 2: marginal mandiblectomy with neck dissection, later chemoradiotherapy. Patient 3: bilateral neck dissection with postoperative radiotherapy. | No posterior invasion but all developed lateral RLN involvement. | Only patient 1 remains alive with no evidence of tumour 14 months after the last operation. | Treatment of lateral RLN metastasis in oral cancer is challenging; best outcomes may be yielded with early detection and treatment. |
| Wang 2009[35] | Retrospective | 618 | NPC | MRI | Radiotherapy alone 205 (33.2%) Combined chemoradiotherapy 413 (66.8%) | Incidence of metastatic RLN decreases gradually between levels C1-3. In NPC the first echelon nodes appear to be level IIb nodes rather than RLN, the incidence of RLN involvement was less than level IIb nodes (72.2% cf 86.5%). RLN involvement correlates with involvement of the parapharyngeal space and Level II, III, IV, and/or V nodes, but not with T stage. | N/A | – |

Table 1 (*Continued*)

| First author, year, and reference | Study | Sample size | Type of primary | Surveillance study | Treatment | Outcome | Survival | Main conclusions |
|---|---|---|---|---|---|---|---|---|
| Wang 2015[36] | Retrospective | 3100 | NPC - (previously untreated) | MRI | N/A | 2679 (86.4%) cases had involved lymph nodes. Levels most often involved: IIa 1798 (67.1%); IIb 2341 (87.4%); VIIa 2012 (75.1%). | N/A | Patterns of nodal spread described in accordance with updated consensus guidelines. Lateral group RLN were primarily involved, medial RLN involvement was rare. The newly suggested upper border of level II and posterior border of level V do not sufficiently incorporate all level II or V NPC lymphadenopathies. |

cf – Compared with.

N/A - Information not documented or not relevant to study.

HNSCC - Head and neck SCC.

HPV - Human papillomavirus.

IGRT - Image-guided radiotherapy.

IMRT - Intensity-modulated radiotherapy.

NPC - Nasopharyngeal carcinoma.

NRLN - Non-retropharyngeal lymph node.

OSCC - Oral cavity SCC.

RLN - Retropharyngeal lymph node.

SCC - Squamous cell carcinoma.

SCG -Superior cervical sympathetic ganglion.

**Survival terms:**

DFFS - Distant failure-free survival.

DFS - Disease-free survival.

DMFFS - Distant metastasis failure-free survival.

DMFS - Distant metastasis free survival.

DSS - Disease-specific survival.

EFS - Event free survival.

FFS - Failure-free survival.

LRFS- Local regional recurrence-free survival.

LFS- Local recurrence-free survival.

NFS- Nodal recurrence-free survival.

OS - Overall survival.

PFS - Progression-free survival.

RFS - Regional relapse free survival.

CT/PET with an anatomical correlation of less than 1 cm. Sensitivities and specificities are shown in Table 1.[4–6,8–36]

With regard to papers that focused on primary non-nasopharyngeal tumour sites (n = 21), eight reported diagnosis of RLN after dissection of the retropharyngeal space and histological analysis. Almost all were retrospective case series, and the incidence of metastasis to these nodes ranged from 19% - 50%. The criteria for dissection of the retropharyngeal space varied and depended on whether the nodes were deemed clinically to be at high risk of involvement, and on radiological staging (with wide variation in the criteria for detecting metastasis to the RLN). Primary tumour sites also varied between case series. Twelve papers presented data on the radiological diagnosis of RLN with incidences that ranged from 9% - 30%. However, the radiological criteria for a diagnosis of metastasis were inconsistent. There was equipoise in terms of overall survival (OS) in patients with involved nodes: five papers reported that it was significantly worse, and four that the difference between patients with and without involved nodes was not significant.[9,18,37]

## Discussion

Involvement of the RLN varied depending on the subsites studied, and may be explained by the anatomy and drainage patterns specific to those sites, aetiopathogenesis, and biology. Involved nodes are seen most commonly in cases of NPC (although this varies between 29.1% and 88.6%[3]), followed by oropharyngeal carcinoma, and SCC of the oral cavity. Tang et al reported an incidence of metastasis to the RLN of 64.2% (481/749) in patients with non-metastatic NPC who were treated mainly with radiotherapy. There were significant differences in five-year disease-free survival (DFS; 70.6% compared with 85.4%, p < 0.001) and distant metastasis-free survival (DMFS; 79.2% compared with 90.1%, p < 0.001) between patients with and without metastasis to the RLN.[11]

In line with this, Shi et al retrospectively studied 142 patients with non-metastatic NPC.[28] The neck was staged with MRI, and lateral RLN with a shortest diameter of 5 mm or more were considered metastatic. Any visible node in the median retropharyngeal group was considered malignant. The median follow-up was 48 months, and five-year distant metastasis-free survival, progression-free survival, and OS of the whole group was 82.1%, 75.3%, and 89.8%, respectively. On multivariate analysis, the presence of RLN and cervical lymph nodes was an independent factor for distant metastasis and progression-free survival (p < 0.05).

In their study of 3100 cases of newly-diagnosed NPC with MRI, Wang et al found that 75.1% of patients had enlarged nodes in level VIIa.[38] Most radiologically pathological nodes belonged to the lateral groups; only six (0.2%) belonged to the medial group. This provides a caveat for the sparing of medial group nodes from the clinical target volume. Intensity-modulated radiotherapy (IMRT) could contribute to the sparing of the pharyngeal constrictor muscles, and so reduce the incidence of dysphagia.[36] Overall, the treatment of NPC relies on chemoradiotherapy. A high incidence of involved RLN warrants radiotherapy, although the spinal cord and pharyngeal muscles are at risk.

Rates of metastasis to the RLN in oropharyngeal SCC generally lag behind and range from 6% to 23%.[9] In their study of the role of RLN in 981 patients with oropharyngeal SCC, Gunn et al reported a 10% overall incidence of radiologically abnormal nodes.[9] However, tumour extension to the lateral pharyngeal walls was associated with a 23% risk of metastasis to the RLN. On univariate analysis, involvement of the RLN was associated with poorer five-year outcomes (p < 0.001 for all) for local control (79% compared with 92%), nodal control (80% compared with 93%), recurrence-free survival (51% compared with 81%), distant metastases-free survival (66% compared with 89%), and OS (52% compared with 82%). On multivariate analysis, significance was maintained for local control (p < 0.023), recurrence-free survival (p < 0.001), distant metastases-free survival (p < 0.003), and overall survival (p < 0.001). Similar findings have been reported,[14,17–19] but the management of RLN varied. Chung et al proposed that elective dissection of the nodes should be considered for advanced neck and primary tumours, particularly when the posterior pharyngeal wall is invaded,[18] and Troob et al stated that there is a role for transoral robotic surgery (TORS) given the safety and good functional outcomes of the procedure.[10] Overall, involvement of the posterior pharyngeal wall warrants surgical intervention if patients are surgically fit.

There is still uncertainty about the management of patients with the human papillomavirus (HPV). In their report of dissections of the RLN in 54 patients with oropharyngeal SCC, Chung et al found positive nodes in 22 cases, but the high-risk HPV strains did not correlate with metastasis to the RLN.[18] However, in a study of 185 HPV-positive cases of oropharyngeal SCC, Samuels et al found that involvement of the RLN was an independent prognosticator for distant failure, corresponding with worse OS. In these cases a de-escalation of treatment may not be suitable.[27]

The management of patients with oropharyngeal cancer and metastasis to the RLN is still equivocal because of the lack of robust correlations between radiological and pathological findings, discrepancies in the definitions of radiologically-pathological nodes between East and West, and difficulty of access. Patients with involved nodes fare worse, so adjuvant treatment is essential.[9,18]

Finally, data on patients with oropharyngeal SCC and metastasis to the RLN are scarce.[4] Boeve at al retrospectively evaluated data from sentinel lymph node biopsy examinations in 11 patients with maxillary cancers (10/11 with oropharyngeal SCC) and found that even the anterior part of the maxilla may drain to the RLN.[5] Tseng et al reported outcomes in 2678 patients with oropharyngeal SCC from 2007-2011.[33] Only 38 had radiologically positive nodes (CT/PET, MRI/CT), and two patients were excluded. Most (26/36) had RLN relapse, the remainder (10/36) were primary RLN metastases. Two-

year disease-specific survival (DSS) and DFS of untreated patients with involved nodes was 20% and 24%, respectively. Patients with relapsed nodes fared even worse (the two-year DSS and DFS from the day of relapse was 12.8% and 9.6%, respectively).[33] Involvement of the RLN therefore has a dismal prognosis in most cases.

The management of patients with nasopharyngeal and non-nasopharyngeal tumours varies. The RLN seem to be a high-risk group in cases of NPC, and most pertinent reports suggest that they are almost always involved. Given that primary treatment is chemoradiotherapy, patients would benefit if these nodes were included when fields are planned. On the other hand, there is no consensus about non-NPC tumours, partly because access is difficult. Multidisciplinary teams often choose serial imaging (which may help in terms of diagnosis) to define malignant involvement confidently, but it can have adverse prognostic implications. New technological advances may change the diagnostic pathway, lead to early intervention, and potentially improve survival.

Several retrospective studies have reported the use of CT, MRI, and PET/CT as diagnostic tools, with different criteria. Although they aid diagnosis and the planning of radiotherapy fields, they seem to lack sensitivity and negative prognostic value. Chung et al compared the radiological and pathological status of the RLN after the surgical treatment of 54 patients with oropharyngeal carcinomas. The authors concluded that CT, MRI and PET-CT had a sensitivity of 66.7%, a specificity of 87.5%, and NPV of 87.5%. Nevertheless, multivariate analysis showed that frank RLN metastasis correlated with preoperative radiographically-positive retropharyngeal nodes (p = 0.012; OR 53.920) and invasion of the posterior pharyngeal wall (p = 0.021; OR 33.014).[18] Based on these findings they recommended dissection of the RLN particularly when the posterior pharyngeal wall was involved.

Given that we can now safely sample the RLN by means of transoral ultrasound-guided fine needle aspiration (FNA) or TORS, we think that this is the indicative pathway in equivocal cases when patients are surgically fit.[1,3,8–10,37,39] A tailored approach (based on overall fitness, and clinical, pathological, and radiological correlation) can spare some patients unnecessary treatment (and enable them to have a better quality of life) and allow others to benefit from early adjuvant treatment. Safer conclusions may be drawn about the management of RLN in HPV oropharyngeal cancer in particular, as well as head and neck cancer in general, in future randomised trials that include sampling of these nodes.

## Conflict of interest

We have no conflicts of interest.

## Ethics statement/confirmation of patients' permission

Not applicable.

## References

1. Vasan NR, Medina JE. Retropharyngeal node dissection. *Oper Tech Otolaryngol* 2004;**15**:180–3.
2. Debnam JM, Guha-Thakurta N. Retropharyngeal and prevertebral spaces: anatomic imaging and diagnosis. *Otolaryngol Clin North Am* 2012;**45**:1293–310.
3. Coskun HH, Ferlito A, Medina JE, et al. Retropharyngeal lymph node metastases in head and neck malignancies. *Head Neck* 2011;**33**:1520–9.
4. Umeda M, Shigeta T, Takahashi H, et al. Metastasis to the lateral retropharyngeal lymph node from squamous cell carcinoma of the oral cavity: report of three cases. *Int J Oral Maxillofac Surg* 2009;**38**:1004–8.
5. Boeve K, Schepman KP, Vegt BV, et al. Lymphatic drainage patterns of oral maxillary tumors: approachable locations of sentinel lymphnodes mainly at the cervical neck level. *Head Neck* 2017;**39**:486–91.
6. Ballantyne AJ. Significance of retropharyngeal nodes in cancer of the head and neck. *Am J Surg* 1964;**108**:500–4.
7. Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**:e1000097.
8. Tauzin M, Rabalais A, Hagan JL, et al. 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.
9. Gunn GB, Debnam JM, Fuller CD, et al. The impact of radiographic retropharyngeal adenopathy in oropharyngeal cancer. *Cancer* 2013;**119**:3162–9.
10. Troob S, Givi B, Hodgson M, et al. Transoral robotic retropharyngeal node dissection in oropharyngeal squamous cell carcinoma: patterns of metastasis and functional outcomes. *Head Neck* 2017;**39**:1969–75.
11. Tang LL, Guo R, Zhou G, et al. Prognostic value and staging classification of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy. *PLoS One* 2014;**9**:e108375.
12. Baxter M, Chan JY, Mydlarz WK, et al. Retropharyngeal lymph node involvement in human papillomavirus-associated oropharyngeal squamous cell carcinoma. *Laryngoscope* 2015;**125**:2503–8.
13. Chan JY, Chow VL, Wong ST, et al. Surgical salvage for recurrent retropharyngeal lymph node metastasis in nasopharyngeal carcinoma. *Head Neck* 2013;**35**:1726–31.
14. Chan JY, Wong ST, Wei WI. Stage II recurrent nasopharyngeal carcinoma: prognostic significance of retropharyngeal nodal metastasis, parapharyngeal invasion, and carotid encasement. *Head Neck* 2018;**40**:103–10.
15. Chen KW, Wang WY, Liang WM, et al. The volume of retropharyngeal nodes predicts distant metastasis in patients with advanced nasopharyngeal carcinoma. *Oral Oncol* 2011;**47**:1171–5.
16. Chua DT, Sham JS, Kwong DL, et al. Retropharyngeal lymphadenopathy in patients with nasopharyngeal carcinoma: a computed tomography-based study. *Cancer* 1997;**79**:869–77.
17. Chung EJ, Oh JI, Choi KY, et al. Pattern of cervical lymph node metastasis in tonsil cancer: predictive factor analysis of contralateral and retropharyngeal lymph node metastasis. *Oral Oncol* 2011;**47**:758–62.
18. Chung EJ, Kim GW, Cho BK, et al. Retropharyngeal lymph node metastasis in 54 patients with oropharyngeal squamous cell carcinoma who underwent surgery-based treatment. *Ann Surg Oncol* 2015;**22**:3049–54.
19. Dirix P, Nuyts S, Bussels B, et al. Prognostic influence of retropharyngeal lymph node metastasis in squamous cell carcinoma of the oropharynx. *Int J Radiat Oncol Biol Phys* 2006;**65**:739–44.
20. King AD, Ahuja AT, Leung SF, et al. Neck node metastases from nasopharyngeal carcinoma: MR imaging of patterns of disease. *Head Neck* 2000;**22**:275–81.
21. Leeman JE, Gutiontov S, Romesser P, 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.

22. Liao XB, Mao YP, Liu LZ, 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.

23. Liu LZ, Zhang GY, Xie CM, et al. Magnetic resonance imaging of retropharyngeal lymph node metastasis in nasopharyngeal carcinoma: patterns of spread. *Int J Radiat Oncol Biol Phys* 2006;**66**:721–30.

24. Ma J, Liu L, Tang L, et al. Retropharyngeal lymph node metastasis in nasopharyngeal carcinoma: prognostic value and staging categories. *Clin Cancer Res* 2007;**13**:1445–52.

25. Ng WT, Lee AW, Kan WK, et al. N-staging by magnetic resonance imaging for patients with nasopharyngeal carcinoma: pattern of nodal involvement by radiological levels. *Radiother Oncol* 2007;**82**:70–5.

26. Ou X, Shen C, Kong L, et al. Treatment outcome of nasopharyngeal carcinoma with retropharyngeal lymph nodes metastasis only and the feasibility of elective neck irradiation. *Oral Oncol* 2012;**48**:1045–50.

27. Samuels SE, Vainshtein J, Spector ME, et al. Impact of retropharyngeal adenopathy on distant control and survival in HPV-related oropharyngeal cancer treated with chemoradiotherapy. *Radiother Oncol* 2015;**116**:75–81.

28. Shi Q, Shen C, Kong L, et al. Involvement of both cervical lymph nodes and retropharyngeal lymph nodes has prognostic value for N1 patients with nasopharyngeal carcinoma. *Radiat Oncol* 2014;**9**:7.

29. Shimizu K, Inoue H, Saitoh M, et al. Distribution and impact of lymph node metastases in oropharyngeal cancer. *Acta Otolaryngol* 2006;**126**:872–7.

30. Spector ME, Chinn SB, Bellile E, et al. Subsite, T class, and N class cannot be used to exclude the retropharyngeal nodes from treatment de-intensification in advanced oropharyngeal squamous cell carcinoma. *JAMA Otolaryngol Head Neck Surg* 2016;**142**:313–8.

31. Tang C, Komakula S, Chan C. Radiologic assessment of retropharyngeal node involvement in oropharyngeal carcinomas stratified by HPV status. *Radiother Oncol* 2013;**109**:293–6.

32. Tham IW, Hee SW, Yap SP, et al. Retropharyngeal nodal metastasis related to higher rate of distant metastasis in patients with N0 and N1 nasopharyngeal cancer. *Head Neck* 2009;**31**:468–74.

33. Tseng JR, Ho TY, Lin CY, et al. Clinical outcomes of patients with oral cavity squamous cell carcinoma and retropharyngeal lymph node metastasis identified by FDG PET/CT. *PLoS One* 2013;**8**:e79766.

34. Umeda M, Minamikawa T, Komatsubara H, et al. En bloc resection of the primary tumour and cervical lymph nodes through the parapharyngeal space in patients with squamous cell carcinoma of the maxilla: a preliminary study. *Br J Oral Maxillofac Surg* 2005;**43**:17–22.

35. Wang XS, Hu CS, Ying HM, et al. Patterns of retropharyngeal node metastasis in nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2009;**73**:194–201.

36. Wang X, Hu C, Ying H, et al. Patterns of lymph node metastasis from nasopharyngeal carcinoma based on the 2013 updated consensus guidelines for neck node levels. *Radiother Oncol* 2015;(115):41–5.

37. McLaughlin MP, Mendenhall WM, Mancuso AA, et al. Retropharyngeal adenopathy as a predictor of outcome in squamous cell carcinoma of the head and neck. *Head Neck* 1995;**17**:190–8.

38. Wang XS, Yan C, Hu CS, et al. Study of the medial group retropharyngeal node metastasis from nasopharyngeal carcinoma based on 3100 newly diagnosed cases. *Oral Oncol* 2014;**50**:1109–13.

39. Fornage BD, Edeiken BS, Clayman GL. Use of transoral sonography with an endocavitary transducer in diagnosis, fine-needle aspiration biopsy, and intraoperative localization of retropharyngeal masses. *AJR Am J Roentgenol* 2014;**202**:W481–486.