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Current thinking of the management of abnormal retropharyngeal nodes in patients with oral, oropharyngeal and nasopharyngeal squamous cell carcinomas-a structured review

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Key words: retropharyngeal nodes, squamous cell carcinoma, oral, oropharyngeal, nasopharyngeal cancer

Abstract

Introduction

The management of enlarged retropharyngeal lymph nodes (RLN) in a patient with a confirmed oral, oropharyngeal and nasopharyngeal squamous cell carcinoma is a challenge for the clinical teams and have prognostic relevance. There is no consensus in the clinical management or the radiographic evaluation. The aim of this work is to present the current thinking in the management of RLNs. This may be helpful to clinical teams and could improve the outcome of patients.

Materials and methods

A search of several online databases was devised using the following key terms: retropharyngeal node, oral cancer, head and neck cancer, oropharyngeal cancer, nasopharyngeal cancer, nasopharynx, oral cavity, oropharynx, TORS, radiotherapy.

Results

1024 papers were screened, of which 32 articles eligible; There is no consensus amongst the clinical teams for the management of RLN.

Discussion

There is a lack of randomised studies and hence conclusions in most papers are coherent arguments. We recommend direct sampling where appropriate. This will be a step closer to provide tailored care that may affect the clinical outcome.

Introduction

The retropharyngeal lymph nodes (RLN) lie within a fat pad in retropharyngeal space (RPS). This is one of the deep neck compartments which extends from the clivus to the upper mediastinum, and is located anterior to the prevertebral fascia and muscles, posterior to the pharyngeal mucosa space, anteromedial to the carotid space and posteromedial to the parapharyngeal space and is in close relationship to the cervical sympathetic trunk and ganglion. The fat pad per se extends from about the level of the carotid bifurcation to just below the skull base (1).

The RPS divided into the suprahyoid and infrahyoid RPS. The suprahyoid RPS contains fat and lymph nodes, whereas the infrahyoid RPS contains only fat and, thus, can be involved only by non-nodal disease. The RLN are divided into the medial and two lateral groups. The medial group of nodes lies behind the pharyngeal midline, anterior to the medial parts of the longus colli muscles, at a level between the first and fourth cervical vertebrae. They are very small and are rarely present in adults. The lateral group, better known as the nodes of Rouviere, are clinically most significant. They are contained within a sliver of fatty tissue located immediately medial to the internal carotid artery, anterior to the lateral masses of the atlas and ventral to the longus colli muscles (1,2). They usually are 1-3 and size between 2-5 mm in adults (3).

They mainly receive afferents from nasopharynx, oropharynx (especially lateral and posterior pharyngeal walls) and hypopharynx. Nevertheless, metastastic 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 RLN involvement was pointed out as early as 1964 by A. J. Ballantyne from the University of Texas, M.D. Anderson (6). He presented 34 patients with squamous cell carcinoma of the pharyngeal wall, who were treated with total pharyngectomy and dissection of the RPLNs from the base of the skull to the oesophageal introitus. The patients with RLN metastases had dismal prognosis.

In general, there is great variability in reported rates of RLN metastasis in head and neck cancer and subsites due to the lack of consensus in diagnostic approach and treatment (3). The aim of

this review is the evaluation of current practice and evidence-based understanding of the management of abnormal RLN in NPC, OPSCC and OSCC in order to provide insight to clinical teams.

Materials and Methods

A search strategy was devised using the following key terms: retropharyngeal node, oral cancer, head and neck cancer, oropharyngeal cancer, nasopharyngeal cancer, nasopharynx, oral cavity, oropharynx, TORS, radiotherapy. The following databases were examined: PubMed, Handle-on-qol, Medline, Ebase (Excerpta Medica), Science Citation, Index/Social Sciences Citation Index, Ovid Evidence-Based Medicine databases. Only manuscripts written in English were included. All instruments included in PRISMA guidance were considered in the search and presentation of the results (7). A total of 1024 papers were identified. From an evaluation of the abstracts and available full text, 32 pertinent papers were scrutinized (Figure 1). Data gleaned pertained to the topic of the paper, sample size, primary tumour site, diagnostic method, treatment modality and outcomes.

Results

The authors found 32, which satisfied our criteria (Figure 1). The vast majority was retrospective in nature. A detailed description is tabulated in Table 1. The prevalence of RTN involves NPC, OPSCC and OSCC in descending order. We have noticed diversity in diagnostic methods and treatment protocols. In almost most of the cases positive nodes were radiologically confirmed by means of CT, MRI and/or PET/FDG.

There were differences in discriminating positive nodes between centres in US vs Far East countries in the axial dimension of lateral lymph nodes (>10mm vs >5mm; latter applied to NPC cases). Other criteria included any nodes with cystic/central necrosis, any nodes with ill-defined margins suggesting extracapsular spread, any nodes with hyper-enhancement on post-contrast images as compared to the adjacent musculature, groups of 2 or more lymph nodes in the ipsilateral retropharyngeal space and any finding of a medial RLN, FDG-avid CT/PET with anatomical correlation <1cm. The sensitivities and specificities are shown in table 1.

Discussion

There is variation in RLN involvement depending on the studied head & neck subsites. It is more common in NPC with orderly level involvement, followed by OPC and OSCC. Moreover, RLN involvement in nasopharyngeal carcinoma (NPC) and varies between 29.1% and 88.6% (3). Tang et al reviewed data of 749 patients with non-metastatic NPC which were mainly treated with radiotherapy. The incidence of RLN metastasis was 64.2% (481/749). Significant differences were observed in the 5-year disease free survival (DFS; 70.6% vs. 85.4%, P<.001) and distant metastasis-free survival (DMFS; 79.2% vs. 90.1%, P<.001) rates of patients with and without RLN metastasis (12).

On the contrary, data regarding the OSCC with RLN metastasis is scant (4). Boeve at al. retrospectively evaluated data from SLNB studies in 11 patients with maxillary malignancies (10/11 OSCC) and found that even the anterior part of the maxilla may drain to RLN (5). In addition, Tsang et al reported outcomes in 2678 patients with OSCC from 2007-2011. Only 38 patients with RLN radiologically positive nodes (CT/PET, MRI/CT). 2 patients were excluded. Most of their cases (26/36) represented RLN relapse, the remainder (10/36) being primary RLN metastases. The 2-year DSS and DFS rates of untreated patients with RLN involvement were 20% and 24% retrospectively. Patients with relapsed RLN fared even worse (the 2-year DSS and DFS rates from the relapse day were 12.8% and 9.6%, respectively) (37).

Similarly, Gunn et al reported that the overall incidence of radiologically abnormal RLN in 981 patients with oropharyngeal squamous cell carcinoma (OPSCC) was 10%. However, tumour extension to the lateral pharyngeal walls was associated with 23% risk of RLN metastasis (9). RLN involvement was associated with poorer 5-year outcomes on univariate analysis (P<.001 for all) for local control (79% vs 92%), nodal control (80% vs 93%), recurrence-free survival (51% vs 81%), distant metastases-free survival (66% vs 89%), and overall survival (52% vs 82%) and maintained significance on multivariate analysis for local control (P<.023), recurrence-free survival (P<.001), distant metastases-free survival (P<.003), and overall survival (P<.001). Nevertheless, the importance of HPV status and de-escalation treatment in this clinical setting have yet to be concluded. Taken together, it is clear that patients with RLN metastasis fare worse and therefore adjuvant treatment is mandatory (13).

There is a lack of consensus relating to the management of enlarged RLN. One of the reasons was the difficulty relating to access. Often multidisciplinary teams decided in favour of serial imaging in order to confidently define malignant involvement. This may be helpful in terms of

diagnosis but can have adverse prognostic implications. New technological advances may change the diagnostic pathway and lead to early intervention potentially affecting survival. Several retrospective studies have used CT, MRI and PET/CT as diagnosis tools, setting different diagnostic criteria. Although these methods help to diagnosis and planning radiotherapy fields for this relatively inaccessible area, it seems that they lack sensitivity and NPV. Chung et al. recently compared the radiological and pathological RLN status after surgically treating 54 patients with OPC. The authors concluded that CT, MRI and PET-CT had a sensitivity of 66.7%, specificity 87.5%, and negative prognostic value of 87.5% (20).

Given that we are now able to safely sample RLN by means of transoral US-guided FNA, lip-split mandibulotomy or transcervical approach with division of the posterior belly of digastric muscle, or more recently transoral dissection (TORS), we think that this is the indicative pathway at least in equivocal cases in surgically fit patients (1, 3, 8-11). The rationale for tailored approach is that some patients may be spared unnecessary chemo-radiotherapy toxicities and have better quality of life, whereas others can benefit from early adjuvant treatment as the presence of metastatic RLN portends dismal prognosis.

Safer conclusions regarding RLN management in the HPV OPC era and generally in head and neck cancer should be drawn with future randomised clinical trials.

Conflict of interest: The authors have no conflict of interest to declare

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Figure 1 Search results included in the review

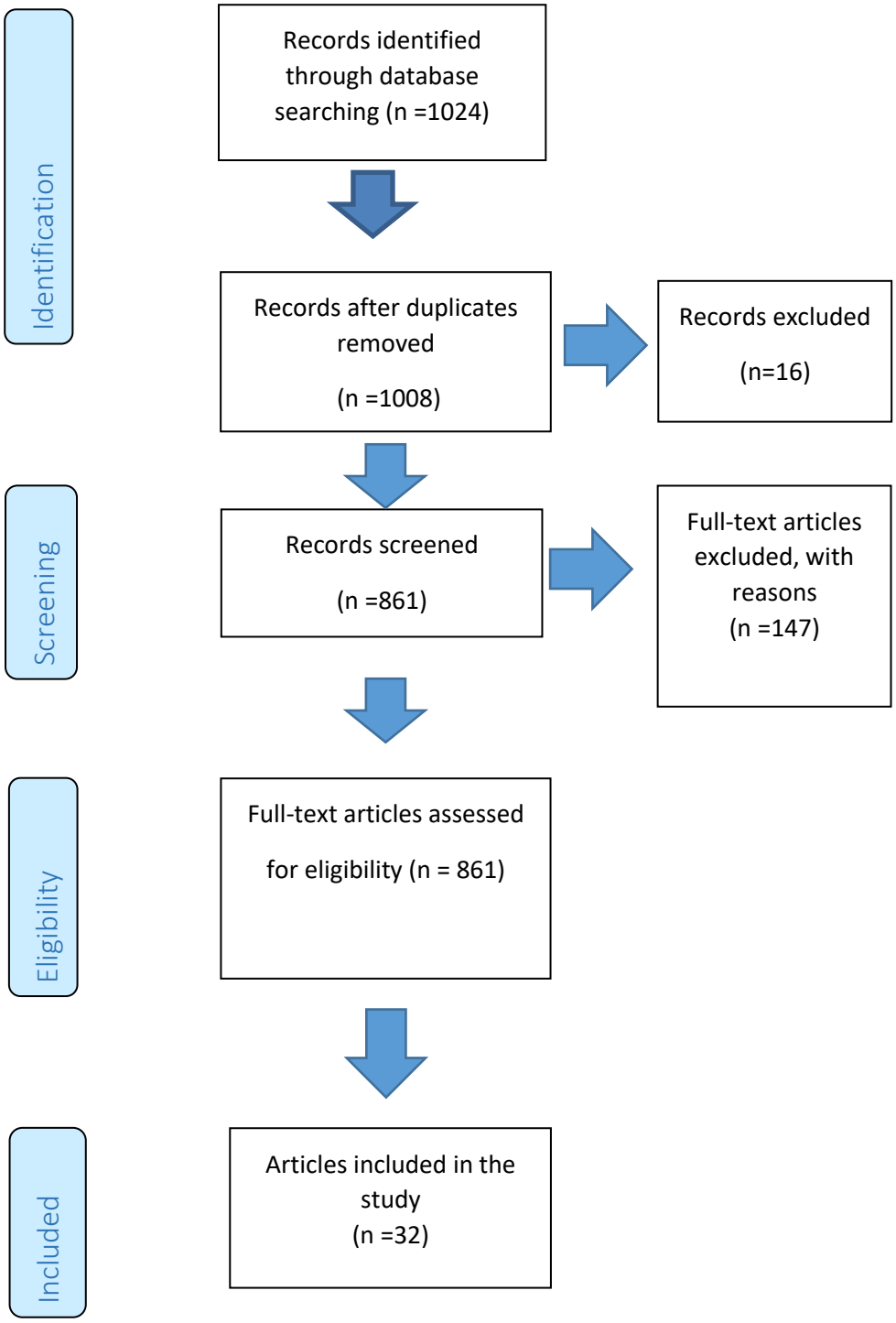

Table 1: Details from papers used in this structured review

Authors	Study Type	Sample Size	Type of Primaries	Surveillance Study	Treatment	Outcome	Survival rates	Main conclusions	Ref
Ballantyne AJ et al. 1964	Retrospective & case studies	34	'"Pharyngeal wall cancer" (N=34), Oropharynx and hypopharynx (N=11)	N/A	Surgical resection of primary ±ND including RLNs.		Follow up < 3-y, 16 out of 19 with RLN (-) group alive, 10 out of 15 RLN(+) alive	RLN involvement was present in 44% of the 34 cases of pharyngeal-wall cancer. RLNs may be significantly involved in spread of oro- and hypopharygeal malignancies (data not shown). The removal of positive RLNs may aid survival in such cancers. RLN involvement may induce a pain complex.	Ref 6
Baxter M et al.2015	Retrospective	165	Oropharyngeal SCC - HPV associated	PET or CT	Radiotherapy (IMRT ot IGRT) or concurrent chemohterapy. Neoadjuvant chemotherapy was used in 18.2% of patients.	RLNs were involved in 16 patients (9.70%). No significant association between RLN status and recurrence free survival was identified after T and N stage were adjusted for.	Average follow up was 2 years. In patients positive for RLN pretreatment, odds for recurrence or death were 5.2-times greater (31.3% vs. 8.1%, p=0.004).	The PET/CT combination is useful in identifying RLNs. Further studies are required to determine the sensitivity and specificity of PET/CT for detecting RLNs, and the impact of RLNs on HPV-associated OPSCC treatment and outcomes.	Ref 14
Boeve K et al. 2016	Retrospective	11	Oral maxillary cancer (10/11 SCC, 1/11 melanoma)	Histopathology	SLN +/- SND, MRND (3 out of 11 had previous treament for OSCC)	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 parapharyn geal. 8/11 (73%) of patients only had 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.	Ref 5
Chan JY et al. 2012	Prospective analysis	82	Nasopharyngeal carcinoma (with persistent or recurrent RLN involvement after previous treatment.)	MRI	Radiotherapy or chemoradiotherapy	Mean follow-up was 38 months. The mean size of RLN on MRI was 1.6 cm, the mean standardize d uptake value maximum (SUVmax) on PET scan was 6.8. RLNs were resected via	5-year actuarial tumor control rates and the overall DFS after resection of isolated RLN were 79.6% and 59% respectively.	PET scans may be useful for diagnosis of persistent or recurrent RLNs after previous radiotherapy for NPC. The maxillary swing technique facillitates resection with clear margins.	Ref 15

						the maxillary swing approach, 87.8% contained viable malignant cells. The rate of microscopic extracapsular spread was 30.6%.			
Chan JYW et al. 2018	Retrospective	145	Nasopharyngeal carcinoma (recurrent) - with RLN metastasis (group I), - with parapharyngeal space (PPS) invasion (group II) - with internal carotid artery (ICA) encasement (group III).			Local tumor recurrence rate was significantly higher in groups II and III. Systemic metastasis rate & 5-year OS were significantly worse in group III.	5-year OS for groups I, II and III were 81.2%, 68.4%, 48.5% respectively.	Upstaging of recurrent NPC encasing the ICA to T3 may be warranted given its worse prognosis.	Ref 16
Chen KW et al. 2011	Retrospective	181	Nasopharyngeal carcinoma (no distant metastases, stage III/IV diseases in 95.6%)	MRI	All received neoadjuvant chemotherapy followed by radiotherapy; 17/181 reveived concurrent chemotherapy.	The pre-treatment RLN volume (RNV) was greater in patients who developed distant failure than those without distant failue (p=0.0536). DMFFS correlated with N-stage, gender and RNV.	7-year DMFFS in patients with RNV >4.68 and ≤4.68 cm3 were 66.4% and 83.5% (p=0.0043) respectively.	In patients with advanced NPC, RNV measured by MRI is a potential predictor of distant metastasis.	Ref 17
Chua DT et al. 1997	Retrospective	364	Nasopharyngeal carcinoma	CT	All received radiotherapy, 87 also received neoadjuvant chemotherapy for locally advanced disease.	RLN incidence was 29.1%. Identification of RLNs on CT in NPC did not show a statisitcally significant correlation with prognostic parameters. Involvement of RLNs on CT in N0 disease was not deemed adequate evidence for an N1 classification.	Differences in survival rates were not statistically significant. 5 year relapse free survival rate for patients with RLN(+) was less than for those RLN(-) (54% v 64%, p=0.05). 5 year distant metastasis free rates were also reduced in RLN(+) (74% v 77%, p=0.30).		Ref 18
Chung EJ et al. 2011	Retrospective	76	Tonsillar SCC (advanced in 81.6% (stage III&IV))	CT, MRI, or PET-CT	Surgery alone (16/76 patients), surgery with postoperative radiotherapy (38/76), surgery with chemoradiation (22/76). RLN dissection (34/76).		DSS was significantly different RLN(-) vs with RLN(+) (82.1% vs 55.6% p=0.021).	RLN metastasis was significantly associated with positive pre-operative image, posterior pharyngeal wall invasion, > N2 stage, contralateral node metastasis, or ipsilateral multilevel involvement. Primary lesions proximal to the midline or advanced ipsilateral nodal disease necesitate bilateral neck dissection. Elective RLN dissection should be considered for advanced neck and primary tumor, especially in the	Ref 19

								presence of posterior pharyngeal wall invasion.	
Chung EJ et al. 2015	Retrospective	54	Oropharyngeal squamous cell carcinoma	MRI, PET-CT or CT	Surgical resection of primary with RLN dissection - all patients. Surgery alone (14/54 patients), postoperative radiotherapy (14/54) and chemoradiation (26/54). HPV genotyping 52/54	RLN metastasis was confirmed in 22 patients. High-risk HPV+ status did not correlate significantly with RLN metastasis.	The overall 5-year DFS and OS were both 66.7 %. RLN(+) conferred worse DSS and OS rate (DSS; 54.5 vs 75 %; p=0.05, OS; 50 vs 78.1 %). In the 14 patients, who could not receive postoperative adjuvant treatment overall 5-year DFS and OS rates were both 53.8 %.	Elective RLN dissection should be considered for advanced neck and primary tumors, especially in posterior pharyngeal wall invasion.	Ref 20
Dirix P et al. 2006	Cohort	208	Oropharyngeal SCC	CT	Radiotherapy alone in 84.1% of patients, by surgery with postoperative radiotherapy in 11.5%, and by concomitant chemoradiotherapy in 4.4%.		5 year overall survival was 45%. There was no significant difference between RLN(+) and RLN(-) groups (36% vs. 46%, p=0.3), but 23% (46/201) died of other cause. DSS was lower in the RLN(+) group (38% vs. 58%, p = 0.03).	At 5 years, regional recurrence was greater in patients with RLN involvement was increased (45% vs. 10%, p = 0.004). RLN involvement can predict regional recurrence.	Ref 21
Gunn GB et al. 2013	Retrospective	981	Oropharyngeal cancer (base of the tongue (47%), tonsil (46%)	CT was used in 96% of patients. 26 (3%) underwent MRI, 13 (2%) underwent PET ± CT.	IMRT in 77% of patients, systemic therapy in 58% of patients.	Median follow-up was 69 months. Incidence of RLN involvement was 10%; greatest in pharyngeal wall primaries (23%) and lowest for tongue-base (6%). RLN involvement was associated with poorer local control, recurrence-free survival, DMFS and OS on multivariate analysis.	5-year actuarial OS was higher for patients without radiological RLN involvement than with RLN involvement (82% v 52%, p<0.001) respectively.	RLN involvement in OPC was identified in 10% of patients and is associated with detrimental effects on disease recurrence, distant relapse, and survival.	Ref 22
King AD et al. 2000	Retrospective	150	Nasopharyngeal carcinoma	MRI	Radiotherapy	Retropharyngeal lymph node involvement (RLN) (94%) was more frequent than nonretropharyngeal lymph node involvement(NRLN) (76%) in 115 patients. NRLN involvement in the absence of RLN involvement was seen in only 6% of all patients.	No evidence of nodal disease at long term follow up (6-42 months, N=71)	Retropharyngeal nodes are involved in the majority of initial metastases. RLNs are involved at the orophrayngeal level more frequently than previously believed.	Ref 23
Leeman JE et al. 2017	Retrospective	102	Oropharyngeal carcinoma (unilateral, cN0-N2b)	Info not available from abstract	IMRT ± concurrent chemotherapy	There were no failures in treated ipsilateral RLN nodes or spared contralateral high RLN nodes in any patient.	Median follow-up was 26.9 months. 2-year rates of the p16+ sub-group and the entire cohort for overall survival 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.	Ref 24
Liao XB et al. 2008	Retrospective	420	Nasopharyngeal carcinoma	CT, MRI	N/A	MRI demonstrated RLN involvemen	N/A	MRI resulted in different clinical and T-stages and is preferable	Ref 25

						t in a greater percentage of cases compared to CT (MRI, 69% vs CT, 52.1%).		to CT staging of NPC.	
Liu LZ et al. 2006	Retrospective	275	Nasopharyngeal carcinoma	MRI	N/A	Incidence of metastatic lateral RLNs decreases gradually between levels C1-3 In NPC the first echelon nodes include both RLNs and cervical Level II nodes, the incidence of involvement was equal (81.4% v 81.4%)	N/A		Ref 26
Ma J et al. 2007	Retrospective	749	Nasopharyngeal carcinoma	MRI	Radiotherapy	RLN metastasis incidence was 51.5%. RLN metastasis shows a detrimental effect on DMFS rates in NPC and the prognosis of N0 disease.	5 year survival rates were both better in patients without RLN metastasis; OS (58.7% v 72.2%, P < 0.001) and DMFS (75.0% v 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.	Ref 27
Ng WT et al. 2007	Retrospective	202	Nasopharyngeal carcinoma	MRI	3D conformal radiotherapy - all patients. 41% of patients recieved additional chemotherapy.	Nodal involvement was high in NPC (96% of patients) Nodal involvement primarily occurred at II (94%), III (85%) and RLN (80%). RLN involvement only affected the N-category in 3.5% of patients; RLN impact on tumor control was not significant. Replacing supraclavicular fossa (SCF) with Levels IV and Vb (LL) as one of the criteria for defining N3 is predictive for distant control and overall survival - 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.		Ref 28
Ou X et al. 2012	Retrospective	119	Nasopharyngeal carcinoma (with RLN metastasis only)	MRI	Definitive radiotherapy - 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 were detected between nodal recurrence in elective neck irradiation and whole neck	Median follow-up was 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, however, further confirmation is required. IMRT was associated with improved regional control. The prophylactic radiation dose of the upper	Ref 29

						irradiation. IMRT and 3D conformal radiotherapy improved regional control, compared with convention al 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 demonstrated by multivariate analysis.		neck region in patients with RLNs metastasis may need to be increased.	
Samuels SE et al. 2015	Retrospective	185	Oropharyngeal Cancer (HPV+)	Histology	Radiotherapy (IMRT) and concurrent chemotherapy	29 (16%) of the HPV+ patients had RLN involvement. Median follow-up was 49 months. No RLN recurrences were observed. 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 vs patients without RLN involvement were 57% vs. 81% (p=0.02), 63% vs 80% (p=0.015) and 70% vs 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 treatment de-intensification.	Ref 30
Shi Q et al. 2014	Retrospective	142	Nasopharyngeal carcinoma (N1, M0)	MRI	Radiotherapy ± chemotherapy	Median follow-up was 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 statistically significant for LRFS (p=0.051).	The 5-year local recurrence-free survival (LFS), nodal recurrence-free survival (NFS), local regional recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), progression free survival (PFS), and overall survival (OS) of the whole group were 82.3%, 83.0%, 81.0%, 82.1%, 75.3% and 89.8%, respectively.	In NPC, N1, RLN and CLN involvement may be a prognositc factor for distant metastasis and disease progression.	Ref 31
Shimizu K et al. 2006	Retrospective	77	Oropharyngeal cancer	Histopathology	Resection - neck dissection	RLN metastasis was present in 29% of patients with primaries of the lateral or posterior wall. No RLN metastasis was identified in patients with anterior or superior wall primaries. Survival rate with <2 positive LNs was better than >3 positive LNs, survival rates were associated	5-year OS of all patients was 54%. 5-year OS in stage II, stage III and stage IV lesions were 100%, 69%, and 43%, respectively.	RLN involvement must be considered in oropharyngeal cancer, especially when of lateral or posterior wall origin. Intensified adjuvant therapy is necessary for multiple nodal involvement especially in the presence of extracasular spread.	Ref 32

						with extracapsular spread were also poorer than those for LN metastasis alone (both p<0.05).			
Spector ME et al. 2016	Retrospective	205	Oropharyngeal SCC (previously untreated, advanced stage (III, IV))	CT or CT/PET	Radiotherapy and concurrent chemotherapy	RLN involvement was 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 the posterior tonsillar pillar. In patients with advanced OPSCC there is no clear algorithm for treatment de-intensification (exclusion of the retropharyngeal site) based on pre-treatment imaging.	Ref 33
Tang C et al. 2013	Retrospective	165	Oropharyngeal carcinoma	MRI, PET-CT or CT	Radiotherapy		2-year OS and EFS rates were poorer with RLN involvement than without (OS; 71% v 89%, EFS; 71% v 81%); the statisitcal difference was not significant.	RLN involvement was associated with stage N2c-3 and N2b disease with either advanced T-stage, ≥3 involved cervical LNs, and ≥1 involved contralateral LN, or lateral/posterior subsites.	Ref 34
Tang LL et al. 2014	Retrospective	749	Nasopharyngeal carcinoma (non-metastatic)	MRI	IMRT - all patients, additional chemotherapy was given to 86.2% (424/492) of the patients with stage III or IV disease.	RLN metastasis incidence was 64.2% (481/749).	5 year DFS and DMFS were significantly poorer in RLN metastasis (DFS; 70.6% vs. 85.4%, p=0.001, DMFS; 79.2% vs. 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.	Ref 35
Tauzin M et al. 2010	Retrospective	101	Oropharyngeal SCC -biopsy proven	Histopathology and PET-CT	IMRT - all patients. 47 (88.7%) received concurrent chemotherapy, 3(5.7%) also underwent neoadjuvant chemotherapy, and 1 (1.9%) also received post radiation chemotherapy. 5 patients (9.4%) did not receive any chemotherapy.	RLN involvement frequency 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 compared to N0-1 patients.	N/A	Pre-treatment 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 in the literature.	Ref 8
Tham IW et al. 2009	Retrospective	395	Nasopharyngeal carcinoma T2-4 N0-N1 only included	CT	All received radiotherapy, 1 also received 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 overall survival rates (%), N0: 71.4, N1: 58.8, RLN metastasis negative: 68.3, RLN Positive: 57.8. (Rates reported seperately). Kaplan-meier curves: demonstrate better DMFS and OS rates in N0 compared with N1. RLN positive N0 patients were more than twice as likely to experience distant metastases or death compared with RLN negative patients.		Ref 36
Troob S et al. 2017	Retrospective, case-control	30 + 37	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 postoperativeradiotherapy or adjuvant chemotherapy. RPLND was performed after resection of primary tumour.	RLNs metastasis was identified in 20% (6/30) of subjects undergoing RPLND. No difference was observed between	N/A	RPLND is not associated with poorer comlpciation rates including swallowing outcomes. RPLND may aid staging and selection of appropriate adjuvant treatment.	Ref 11

						groups in in length of stay, length of feeding tube dependence, net change in perioperative weight, or rates of hemorrhage and postoperative complications. RPLND altered adjuvant treatment recommendations in 1 of 30 patients.			
Tseng JR et al. 2013	Retrospective	36	Oral cavity SCC (with RLN metastases (N=10) or RLN relapse (N=26))	FDG-PET/CT	Surgical resection of primary tumour. For clinically positive neck nodes - classical radical or modified neck dissections. For clinically negative neck nodes - supra-omohyoid neck dissections. ± postoperative radiotherapy.	Median follow-up time was 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 therapy yielded the greatest survival benefit in patients without N2c disease and ipsilateral RLN involvement alone (p=0.005).	2-year DSS and DFS rates of untreated patients with RLN involvement were 20% and 24%, respectively. 2-year DSS and DFS rates for patients treated for relapse were 12.8% and 9.6%, respectively. All patients presenting with neck lymph node involvement of 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.	Ref 37
Umeda M et al. 2005	Retrospective & case studies	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 underwent maxillectoma ± adjuvant radiotherapy, 4 had combination treatment and 1 had intracavity irradiation. Antral carcinoma: 9 underwent maxillectomy, 13 had a combination of external irradiation, maxillary sinus excision, and regional intra-arterial infusion chemotherapy Posteriorly invasive maxillary carcinoma: 5 underwent en bloc resection	All 5 patients undergoing en bloc resection remain alive without recurrence.	5-year survival rate: 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.	Ref 38
Umeda M et al. 2009	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 post-operative radiotherapy.	No posterior invasion was present but all developed lateral RLN involvement.	Only patient 1 remains alive with no evidence of tumor 14 months after the last surgery.	Treatment of lateral RLN metastasis in oral cancer is challenging; best outcomes may be yielded by early detection and treatment.	Ref 4
Wang XS et al. 2009	Retrospective	618	Nasopharyngeal carcinoma	MRI	Radiotherapy alone 205 (33.2%) Combined chemoradiotherapy 413 (66.8%)	Incidence of metastatic RLNs decreases gradually between levels C1-3. In NPC the first echeclon nodes appear to be level IIb nodes rather than RLNs, the incidence of RLN involvement was less than level IIb nodes (72.2% v 86.5%). RLN	N/A		Ref 39

						involvement correlates with involvement of the parapharyngeal space and Level II, III, IV, and/or V nodes but not T stage.			
Wang XS et al. 2014	Prospective	3100	NPC - (Previously untreated)	MRI	N/A	RLNs were involved in 2679/3100 (86.4%) cases.	N/A	Involved RLNs mainly belonged to the lateral rather than the medial group. All metastasis to the medial RLN was accompanied with involvement of other nodes. Only one medial RLN can be identified in a patient, whereas the enlarged lateral RLNs per affected side could be multiple. The lateral RLNs were larger in size than the average medial RLN.	Ref 40

Abbreviations:
N/A - information not documented or not relevant to study
RLN - retropharyndeal lymph node
SCC - squamous cell carcinoma
OSCC - Oral cavity SCC
HNSCC - head and neck SCC
NPC - nasopharyngeal carcinoma
Intensity-modulated radiotherapy (IMRT)
Image-guided radiotherapy (IGRT)
Human Papillomavirus (HPV)
Superior cervical sympathetic ganglion (SCGs)
Overall survival (OS)
Failure-free survival (FFS)
Distant failure-free survival (DFFS)
Regional relapse free survival (RFS),
Distant metastasis free survival (DMFS)
Progression-free survival (PFS)
Distant metastasis failure-free survival (DMFFS)
Event free survival (EFS)
Disease-specific survival (DSS)
Disease-free sur