METASTASIS TO THE RETROPHARYNGEAL LYMPH NODES IN HEAD AND NECK CANCER

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ABSTRACT
Primary lesions of the retropharyngeal space are rare. The involvement of this space, most commonly, results from direct spread from adjacent sites or metastasis. This review is focused on the characteristics, incidence, imaging and treatment of retropharyngeal lymph node metastasis in head and neck cancer.

KEYWORDS: retropharyngeal lymph node metastasis, imaging prognosis treatment retropharyngeal lymph node metastasis.

INTRODUCTION
Primary lesions of the retropharyngeal space are rare. The involvement of this space, most commonly, results from direct spread from adjacent sites or metastasis. There has been a transcending improvement in the knowledge of the normal anatomy of this space, the common lesions affecting this area and the imaging and biopsy techniques used to evaluate such lesions.

The retropharyngeal lymph nodes (RPLNs) may be affected by metastasis from carcinomas of nasopharynx, oropharynx, hypopharynx, postcricoid region, maxillary sinus and cervical esophagus. Also, tumours of middle ear, Eustachian tube, paranasal sinuses and oral cavity may metastasize to RPLNs. Metastatic involvement of the RPLNs may further extend to involve the skull base, cervical spine and the cranial nerves[1] traversing the adjacent tissues. Increased awareness of this manner of spread is essential for early diagnosis and treatment of the primary as well as metastatic tumour.

ANATOMY OF RETROPHARYNGEAL SPACE AND RETROPHARYNGEAL LYMPH NODES
The anatomy of retropharyngeal space was initially described in relation to retropharyngeal abscess. Grodinsky[2] (1939) discussed the clinical and pathologic anatomy of retropharyngeal space in detail. Rouviere[3] (1938) described the anatomy of retropharyngeal lymph nodes.

The retropharyngeal space (RPS) extends from the clivus above to the upper mediastinum below. It is located posterior to the pharynx and esophagus, and anterior to the prevertebral musculature.[4,5] The space is bounded by the buccopharyngeal fascia and pharyngeal constrictor muscles anteriorly (Fig. 1), the prevertebral fascia posteriorly, and the carotid space laterally. The alar fascia, which is a part of the deep layer of deep cervical fascia, extends from the medial border of the carotid space on one side to the medial border of carotid space on the other side, thus dividing the RPS into two compartments – the anteriorly positioned “true” or “proper” retropharyngeal space and the posteriorly situated “danger” space. The true RPS extends from the clivus above to a variable level between the T1 and T6 vertebrae below, where the alar fascia fuses with the visceral fascia to obliterate the true RPS.[6] The danger space extends farther inferiorly to the posterior mediastinum up to the level of diaphragm, being named as such because it provides a pathway for spread of infection from pharynx to the mediastinum.

The RPS may be further divided into suprahypoid and infrahypoid RPS. Both compartments have different contents. The suprahypoid RPS encloses fat and lymph nodes, while the infrahypoid RPS contains only fat. The infrahypoid compartment can thus be involved by only non-nodal disease. The suprahypoid RPLNs lie medial to the medial aspect of internal carotid artery,[7] at the level of transverse process of atlas. They may be classified into medial and lateral groups. The medial group of lymph nodes is not consistently present and is located anterior to the medial part of longus colli muscles.[4,6] The lateral group, called the nodes of Rouviere, lies ventral to the longus colli muscles.
RPLNs are normally present in children and subsequently exhibit atrophy at puberty. Small nodes may be present in two-thirds of asymptomatic adults, and when present, they may be visible on imaging. Normal RPLNs should be less than 1 cm in diameter.\(^8\)

**CHARACTERISTICS OF NODAL METASTASIS**

The imaging features of RPLN metastasis include focal nodal necrosis, ill-defined margins, or two or more involved nodes on one side of RPS. Zhang et al reported that a minimum axial diameter of 6 mm or more has been reported to have 87.5% accuracy for identification of malignancy in RPLNs from nasopharyngeal carcinoma (NPC).\(^9\) Wang and colleagues\(^{10}\) demonstrated in their study that in NPC, the RPLNs are involved less commonly than level IIb nodes (72.2% vs 86.5%). However, the importance of RPLN metastasis is emphasized by the fact that RPLNs are considered N\(_1\) disease in the 2010 American Joint Committee on Cancer (AJCC) staging system for NPC. This is because the involvement of these nodes increases the risk of distant metastasis and affects prognosis.\(^{11}\) RPLN metastasis is associated with poor treatment outcomes and decreased survival rates because there is decreased control of disease in the neck.\(^{12,13}\)
If apparently malignant nodes are observed in the RPS when there is no known primary tumour, the pharyngeal mucosal space and the nasopharynx should be inspected for submucosal tumour. RPLNs also indicate a poor prognosis for patients with primary tumours originating outside the nasopharynx.

INCIDENCE OF METASTASIS TO RETROPHARYNGEAL LYMPH NODES IN RELATION TO DIFFERENT PRIMARY TUMOUR LOCATIONS

RPLN metastasis has been reported from almost all sites of the head and neck, with nasopharyngeal cancer having the greatest potential. McLaughlin and colleagues designed a retrospective study to assess the frequency of RPLN metastasis in 774 patients with squamous cell carcinoma of nasopharynx, oropharynx, hypopharynx and supraglottis. The enlargement of RPLNs on CT imaging was used as an indicator of the presence of metastasis. The authors found an overall incidence of radiologically positive RPLNs in 9% of the subjects. The highest incidence was reported in patients with cancer of nasopharynx (73.7%) and the pharyngeal walls (19%). The number of cervical nodal groups involved was the most significant factor relating to incidence of RPLN metastasis. The rates of relapse and distant metastasis were significantly higher in patients with RPLN metastasis, while the survival rates were significantly lower. The authors attributed this finding to more aggressive multimodality treatment that these patients receive. They advocated performing RPLN dissection in patients with advanced tumours of oropharynx, hypopharynx and supraglottic larynx.

Liu et al studied the pattern of RPLN involvement in patients with nasopharyngeal carcinoma (NPC) using MRI, in 275 subjects. Any visible nodes in median retropharyngeal group and those of the lateral group, with shortest axial diameter of ≥ 5 mm were considered to be metastatic in addition to nodes with radiological signs of extracapsular spread and necrosis. The authors found RPLN involvement in 63.6% of the subjects, showing a decrease in incidence from level of C1 (62.5% of all positive RPLN) to C3 level (0.8% of positive RPLN). RPLNs were involved less frequently in early stage cancer (T1, N0 and stage I) and correlated with nodal but not with T classification of the disease. Both RPLN and cervical level II nodes were apparently the first-echelon nodes in nasopharyngeal carcinoma.

Ballantyne (1964) conducted a landmark retrospective study, involving 34 patients with squamous cell carcinoma of the pharyngeal wall. All subjects were treated with total pharyngectomy and dissection of RPLNs from the skull base above to esophageal introitus below. Metastasis to RPLNs was detected by microscopic examination in 44.1% (15 of 34) patients with simultaneous involvement in other nodal groups of neck in 13 patients. The involvement of RPLNs was associated with significantly poorer survival. The author also described characteristic severe suboccipital headache as a pathognomonic sign for RPLN metastasis.

Hasegawa and Matsuura (1994) conducted a study involving 24 patients with advanced carcinoma of oropharynx and hypopharynx. The subjects were treated with standard resection and RPLN dissection up to skull base. Postoperative radiotherapy of 50 grays (Gy) was applied to retropharyngeal space if RPLNs were involved pathologically. A total of 50% of subjects had positive RPLNs, 63.2% with pN+ neck and 20% with pN0 neck.

Dirix et al (2006) conducted a study on prognostic influence of RPLN metastasis in oropharyngeal cancer. In a series of 208 patients with oropharyngeal cancer, 16% showed RPLN metastasis after evaluation of pre-treatment CT scans. Patients with RPLN metastasis showed significantly more regional recurrences (45% vs 10%). Also, the disease-specific survival was significantly lower in RPLN positive group. (38% vs 58%). Continuation of this study was reported by Bussels et al (2010) in the same subject population of 208 patients. The RPLNs were most frequently involved in case of posterior pharyngeal wall (38% patients) and soft palate primaries (56% patients).

Yoshimoto et al (2011) conducted a study on 84 patients with base of tongue cancer. In their series, 2 patients showed RPLN metastasis at the time of diagnosis while 2 more developed recurrent cancer in the RPLNs. The incidence of contralateral or RPLN metastasis was low if the tumour neither crossed the midline nor infiltrated the lateral wall.

Kamiyama et al (2012) reported their results of 129 patients with hypopharyngeal cancer. The rate of RPLN metastasis during follow-up period was 13.2%. In this study, the rate of RPLN metastasis was higher in primary hypopharyngeal cancer of the posterior wall / postcriocoid area compared with that of piriform sinus. The authors recommended dissection of RPLNs at the time of treatment of hypopharyngeal cancer, particularly in cases with cancer of posterior wall / postcriocoid area, because RPLN dissection for positive metastasis improved survival. Amatsu et al (2013) published a study of 82 patients who had RPLN dissection for squamous cell carcinoma of hypopharynx and cervical esophagus. RPLN metastasis was positive in 20% of the patients. Posterior pharyngeal wall was involved in 57% of the patients with hypopharyngeal cancer.

Watarai et al (1993) published a study of 25 patients with maxillary sinus cancer. RPLN metastasis was positive in 16% of patients. Similarly, Kimura et al (2025) reported RPLN metastasis in 5 patients with upper gingival and maxillary sinus cancer. Umeda et al (2026) (2009) reported positive RPLN metastasis in 3 patients with cancers of upper gingiva or maxilla.
Robbins and Woodson\(^2\) (1985) published a study on RPLN metastasis from thyroid cancer. Other uncommon site-specific tumours reported were parathyroid carcinoma and esthesioneuroblastoma.\(^{28,29,30}\) The involvement of RPLNs by metastasis has important implications towards prognosis and treatment. Several studies have confirmed that the presence of RPLN metastasis correlates with the rate of occurrence of systemic dissemination and was of prognostic value for predicting the distant metastasis-free survival (DMFS) in patients with nasopharyngeal carcinoma.

**MANAGEMENT OF RETROPHARYNGEAL LYMPH NODE METASTASIS**

A) Radiotherapy

Radiotherapy is the main mode of treatment for nasopharyngeal cancer, with or without chemotherapy. As RPLNs are covered in the treatment field, the additional treatment of nodes is not required. However, to determine the appropriate dose level, it is important to know whether the RPLNs are positive for metastasis.

In many centers, cancers of oropharynx and hypopharynx are also treated with chemoradiation. Taking into consideration the negative impact of RPLN involvement on prognosis of patients with oropharyngeal cancer, Bussels et al\(^20\) recommended that these nodes should be included in clinical target volume, especially in node-positive necks. In node-negative necks, inclusion of RPLN into target volume is advised in posterior pharyngeal wall tumours.

Consensus guidelines of several international radiotherapy groups (Radiotherapy Oncology Group, European Organisation for Research and Treatment of Cancer, National Cancer Institute of Canada, Danish Head and Neck Cancer Group) give detailed description of radiological boundaries for retropharyngeal space.\(^31\) The guidelines identified various criteria for inclusion of RPLNs in the delineation of clinical target volume, such as – in case of N\(_0\) to N\(_1\) neck, for posterior oropharyngeal wall tumours and primaries of nasopharynx, in case of multiple (N\(_b\)) nodal involvement, for primary tumours originating in all three levels of the pharynx.\(^32\) These recommendations were revised in 2006,\(^33\) in the sense that for patients with a positive postoperative neck (including pN\(_1\) cases) from primary tumours of pharynx, the retropharyngeal space should be included in clinical target volume.\(^33\)

B) Surgical Treatment

Surgical management of the RPLNs was first described by Ballantyne\(^17\) (1964) who conducted a study involving 45 patients treated at The University of Texas M.D. Anderson Cancer Center for primary tumours of the pharyngeal wall and other upper aerodigestive tract sites. This landmark article described wide exposure of the retropharyngeal space by a transcervical approach, in which the RPLNs were resected with the primary tumour by en bloc pharyngectomy. For primary tumours of sites other than pharynx, surgical dissection was carried out by retracting the internal carotid artery laterally and the pharynx retracted medially, to gain access to the lymph node-bearing structures up to the base of skull. With passage of time, modifications of the surgical approach to retropharyngeal lymphatic structures were developed such as extended transcervical, transparotid and transmandibular.\(^34\)

Dissection of RPLNs may be performed separately or in continuity with the resection of primary tumour. When performed electively, the surgery is relatively simple and takes only a few minutes. However, when the RPLNs are grossly involved by the tumour, the operation may be difficult and sometimes not feasible. The proximity of the nodes to internal carotid artery and prevertebral structures is such that these structures may be involved once the tumour extends beyond the capsule of lymph nodes. RPLNs can be approached relative ease if a mandibulotomy or a partial / total pharyngectomy is performed. Ozugudek et al\(^35\) (2005) conducted a cadaver dissection study and reported that identification of the alar fascia is the key in the identification and dissection of RPLNs. They described in detail the medial and lateral approaches to retropharyngeal space.

Sometimes, the surgical dissection of RPLNs has to be performed without the advantage of mandibulotomy. This may be done by forward retraction of the posterior belly of digastric and stylohyoid muscles. This technique was described in detail by Vasan and Medina.\(^36\)

Umeda et al\(^37\) published a study involving 72 patients with maxillary cancers. Most of the subjects were treated by surgery and postoperative radiation. The authors reported 5 deaths due to relapse in the RPLNs and advocated en bloc resection of these lymph nodes along with neck dissection and maxillectomy. However, in most paranasal sinus cancers, adjuvant radiotherapy is required, so RPLNs can also be treated electively by postoperative radiotherapy.

RPLN metastasis from differentiated thyroid carcinoma can be managed through transoral approach. Unlike squamous cell carcinoma, RPLN metastasis from well differentiated thyroid cancer is generally small and limited and extracapsular spread is rare. It is thus suited to transoral approach which provides limited and less invasive surgery.\(^34\)

Kamiyama et al\(^22\) (2009) recommended RPLN dissection during initial surgery of patients with hypopharyngeal cancer. The authors reported that, especially in patients with postcricoid or posterior hypopharyngeal wall cancers, a significantly higher number of patients survived 5 years or more. Similarly, Amatsu et al\(^23\) recommended bilateral dissection of RPLNs during initial surgery of carcinoma arising from hypopharynx and cervical esophagus. Although there was no change in cumulative survival, the number of
patients dying of RPLN metastasis was significantly lower in the dissected group.

**DIAGNOSTIC IMAGING**

The retropharyngeal space (RPS) may be evaluated with ultrasonography by placing a transducer in the oral cavity and oropharynx. This technique can be used for fine needle aspiration (FNA) biopsy to evaluate RPS nodes. PET/CT allows detection of disease in the RPS, as well as distant spread of disease throughout the body. Apart from these, MDCT (multidetector CT) and MRI may be used to determine the extent of disease.

**CONFLICT OF INTERESTS**

The author declares that there is no conflict of interests that could influence this work.

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