Do Pathologic and Molecular Analyses of Neck Dissection Specimens Justify the Preservation of Level IV for Laryngeal Squamous Carcinoma with Clinically Negative Neck?

Mohamed N Elsheikh, MD, Alfio Ferlito, MD, DLO, DPath, FRCs, Alessandra Rinaldo, MD, Ashok R Shaha, MD, FACS, Avi Khafif, MD, H Hakan Coskun, MD, Luiz P Kowalski, MD, Jesus E Medina, MD, FACS

Since the first detailed description by Franciszek Jawdyński in 1888,1-4 there have been many variations and modifications of the radical neck dissection procedure. These include modified radical neck dissection (also called functional neck dissection) and various selective neck dissections.5-6

Analysis of the distribution of lymph node metastases in patients with squamous carcinoma of the larynx reveals a marked preference for levels II, III, and IV; levels I and V are rarely involved.7-9 Based on these observations, lateral neck dissection has been recommended in patients with necks staged as N0 or N1.10 This means removing the upper jugular lymph nodes (level II), middle jugular lymph nodes (level III), and lower jugular lymph nodes (level IV). Lateral neck dissection is also described as jugular node dissection by many surgeons.

The need for routine dissection at level IV has recently been questioned.11 This article discusses whether sparing level IV lymph nodes is justified on the strength of pathologic and molecular studies on the pattern of nodal metastasis in patients with squamous carcinoma of the larynx. In other words, dare we perform a selective neck dissection involving levels IIA and III for N0 neck laryngeal cancer to avoid potential complications such as chylous fistula or phrenic nerve injury?

Anatomy of level IV
The lymph nodes of level IV are located around the lower third of the internal jugular vein. According to the updated classification of neck dissections by the American Head and Neck Society and the American Academy of Otolaryngology-Head and Neck Surgery,12 the boundaries of level IV extend from the inferior border of the cricoid cartilage superiorly to the clavicle inferiorly. The anterior (medial) boundary of level IV is the lateral border of the sternohyoid muscle and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle or the sensory branches of the cervical plexus. The horizontal plane defined by the inferior border of the cricoid cartilage separates level III from level IV.12

Pathologic and molecular analysis of neck dissection specimens
In 1996, Ambrosch and colleagues13 mentioned that Steiner advocates performing “limited” selective neck dissection, clearing only levels II and III, for cancer of the larynx. In 2001, a retrospective study was published by Steiner’s group14 and the authors believed that dissecting levels II and III was sufficient when no metastases were suspected during operation to level IV (a type of operation they had been performing routinely since 1979).
In 1999, in a prospective nonrandomized study, Tu suggested that a very limited neck dissection, called upper neck (level II) dissection, could be considered diagnostic and therapeutic for N0 neck supraglottic cancer. In the case of subclinical metastases being detected on frozen sections, a level III neck dissection was also performed.

In the same year, prospective randomized study from the Brazilian Head and Neck Cancer Study Group demonstrated that level IV metastases were extremely rare in patients with supraglottic tumors. Only patients with transglottic tumors involving the subglottis had metastatic lymph nodes at level IV too.

In 2004, Coskun and associates prospectively evaluated the incidence of metastatic nodal involvement in 71 patients with squamous carcinoma of the larynx and a clinically N0 neck. None of the 113 neck dissection specimens revealed metastases at level IIB or IV. This would provide an oncologic basis for safely leaving these lymph nodes in place. Fifty-five patients had follow-up of more than 12 months (mean 29 months), and no recurrence developed in the operated neck in any of these.

In the same year, Khafif and coworkers retrospectively analyzed 71 patients with squamous carcinoma of the larynx (42 supraglottic and 29 glottic). Levels II to IV had been removed in all of them, and their neck specimens were pathologically examined. Of 43 patients who underwent elective lateral neck dissection, only 1 (2.3%) with level IV metastases also showed metastases at level II. Nine (32%) of the other 28 patients with clinical adenopathy had level IV metastases. The authors concluded that dissection of this level might not always be necessary in patients with cancer of the larynx and a clinically N0 neck, although they advocated dissecting level IV as part of a therapeutic neck dissection for supraglottic and transglottic squamous carcinoma in patients with clinically enlarged lymph nodes.

In 2005, Lim and colleagues prospectively reported 73 consecutive previously untreated patients with clinically N0 laryngeal squamous carcinoma and analyzed the incidence of level IV lymph node metastases in 142 elective lateral neck dissections. Ipsilateral level IV metastatic involvement was present in 3.5% (5 of 142 neck specimens) and none in the contralateral level IV side. Separate skip metastasis in level IV lymph nodes was observed in 1.4% (2 of 142 necks). The authors concluded that dissection of level IV may not be necessary in the management of laryngeal squamous carcinoma, in particular considering the ipsilateral neck of early T-staged tumors or the contralateral neck.

These prospective and retrospective studies were not supported by immunohistochemical and molecular investigations.

In the same year, Elsheikh and associates prospectively examined 31 consecutive previously untreated patients with squamous carcinoma of the larynx (14 supraglottic, 8 glottic, and 9 transglottic). The incidence of metastases to level IV after elective selective neck dissection (II to IV) was evaluated by nested reverse transcriptase-polymerase chain reaction for cytokeratin 19 and cytokeratin 20, and by pathologic examination. Based on the two molecular markers, the incidence of occult positive lymph node metastases was 29% (9 of 31), and level IV was involved in 1 of the 9 patients. This metastasis was detected by both pathologic and molecular analyses. The overall incidence of metastases to level IV was consequently 3.2% (1 of 31). The patient with a positive level IV had a T3N0 transglottic cancer. In this patient, an isolated metastasis to this level occurred without any involvement of the other lymph nodes in the selective neck dissection specimen. This might mean that skip metastases to level IV are a potential problem.

On the other hand, many surgeons prefer to include level IV when performing an elective selective neck dissection for laryngeal squamous carcinoma. Redaelli de Zinis and coauthors performed a retrospective review of 402 consecutive patients with supraglottic squamous carcinoma. They found that lymph node metastases occurred in a sizable percentage of patients (40%), emphasizing the need for elective neck dissection. The repetitive pattern of distribution, which mainly involved levels II, III, and IV, suggested that the treatment of choice for T2 to T4N0 supraglottic cancer is a lateral neck dissection, which has the advantage over comprehensive neck dissection of shorter operative time and reduced morbidity. These authors suggested performing a selective neck dissection, including levels II to V, whenever there is clinical, radiologic, or intraoperative evidence of metastases to any level, though metastases to level IV occurred only in association with metastases to levels II to III.

Pinilla and associates retrospectively examined 295 patients with laryngeal cancer and N0 neck, 124 of them with supraglottic tumors. In their experience, routine bilateral functional neck dissection in supraglottic cancers,
regardless of the size of the tumor, proved to be the most beneficial approach for patients in terms of survival.

Buckley and MacLennan\textsuperscript{22} prospectively analyzed the prevalence and distribution of histologic cervical node metastases in 100 consecutive patients whose neck dissection was part of their primary treatment for laryngeal and hypopharyngeal cancer. For these tumors, the authors recommended elective dissection of node levels II to IV for the N0 neck and suggested including level VI nodes for tumors invading the subglottis, pyriform fossa apex, and postcricoid region. The prevalence of contralateral metastases indicates bilateral neck dissection in midline or bilateral tumors.

Jia and colleagues\textsuperscript{23} suggested that lateral neck dissection (levels II, III, and IV) may be suitable for treating laryngeal carcinoma patients staged as T2 to T4cN0.

Here again, the previously-mentioned studies were not supported by immunohistochemistry or molecular analysis.

Discussion

Neck metastases are the major cause of failure after operations for cancer of the head and neck. Inadequately managed, these positive lymph nodes can be fatal even if the primary tumor has been controlled. The mortality generally increases by 50\% in patients with neck node metastases. Recognition of this fact prompted the early attempts at radical removal of cervical lymph nodes actually or potentially involved by cancer along with resection of the primary tumor. To prevent the severe long-term morbidity of radical neck dissection, including shoulder dysfunction, cosmetic deformity, cutaneous paresthesia, and chronic neck and shoulder pain, Suárez\textsuperscript{24} developed a “functional” neck dissection in 1952. Though he is often forgotten in the English-language literature, Suárez is truly the “father” of functional neck dissection.\textsuperscript{25}

More recently, selective neck dissections (removing only the lymph nodes at the levels at greatest risk of metastasis from the primary tumor at various sites) have become accepted practice for elective and, in some instances, therapeutic treatment of the neck.\textsuperscript{26,27} Pathologic and molecular analyses of neck dissection specimens support the use of selective neck dissection (levels II to IV), sparing sublevel IIB in cases of laryngeal squamous carcinoma with clinically negative neck.

The need to routinely dissect level IV has recently been questioned. Some investigators suggest preserving this particular group because of the very low rate of positive metastases. Others stress that this group should be included, weighing the risk of occult metastases against the low potential morbidity associated with this resection, and emphasizing the limited accuracy of traditional pathologic methods, which might miss isolated neoplastic cells, micrometastases, extracapsular spread, or soft tissue metastases in neck dissection specimens. Although more accurate molecular analysis has identified a low incidence of involvement, concern has been voiced about skip metastases to this particular level.

To avoid additional confusion on this issue, the question should be not whether to preserve or remove the level IV lymph nodes, but whether there is some common ground between the two points of view.

All studies mentioned previously reported very few, isolated, or no level IV metastases, so more studies are warranted on the real incidence of metastases to level IV and the consequent need to dissect these nodes. The chylous fistula rate can be as high as 5.8\%, depending on the surgeon’s experience,\textsuperscript{28} but even more important than its incidence is the morbidity associated with chylous fistula. Delay in return to oral feeding, loss of important body fluids, wound complications that can lead to major vessel blow-outs, the need for reoperation to close the fistula, and the delay in adjuvant radiotherapy are the main adverse effects of chylous fistula.

The previously mentioned studies lack some important information. Though it is well known that the lymphatic drainage patterns of supraglottic, glottic, and subglottic tumors differ considerably, most studies considered all primary tumors at different sites in the same group. Neck treatment should be customized according to the site of the primary tumor. Our knowledge of lymphatic drainage of the larynx provides a basis for developing such a customized neck dissection system. Lymphatic collectors of the supraglottic and glottic larynx drain primarily into level II and secondarily into level III cervical lymph nodes; the lymphatic vessels of the subglottis drain primarily into level IV lymph nodes.\textsuperscript{29} So, level IV dissection may not be necessary for supraglottic and glottic tumors in N0 necks. But transglottic and primary subglottic tumors may well require level IV dissection.

In conclusion, although data from several pathologic and molecular analyses on neck dissection specimens from patients with laryngeal squamous carcinoma and a clinically N0 neck have demonstrated a low incidence of positive nodes at level IV, this is not enough to justify a
standardized selective neck dissection (levels IIA and III). Using immunohistochemistry and in addition developing the genetic diagnosis of occult metastases, we shall probably discover that selective neck dissection (IIA, III) is justified for patients with supraglottic and glottic squamous carcinoma with a clinically N0 neck, and transglottic and primary subglottic tumors will also require level IV dissection. Additional prospective studies are needed.

REFERENCES