Head and neck

Cervical metastasis on level IV in laryngeal cancer

Metastasi latero cervicali al livello IV nei carcinomi della laringe

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SUMMARY

The presence of cervical metastasis has substantial negative impact on survival of patients with laryngeal cancer. Bilateral elective selective neck dissection of levels II, III and IV is usually the chosen approach in these patients. However, there is significant morbidity associated with level IV dissection, such as phrenic nerve injury and lymphatic fistula. The objective of the present study was to evaluate the frequency of metastatic nodes in level IV in clinically T3/T4N0 patients with laryngeal cancer. The pathological reports of 77 patients with clinically T3/T4N0 laryngeal squamous cell carcinoma were reviewed. Patients underwent bilateral lateral neck dissection from January 2007 to November 2012. The surgical specimens were subdivided in levels before evaluation. There were 12 patients with neck metastasis (15.58%). In 3 cases (3.89%), there were metastatic lymph nodes in level IV, all T4 and with ipsilateral metastasis. In conclusion, the incidence of level IV metastasis was 3.89%, an in all patients was staged as T4.

KEY WORDS: Laryngeal neoplasms • Neck dissection • Lymphatic metastasis • Squamous cell carcinoma • Neoplasm staging

RIASSUNTO

La presenza di metastasi laterocervicali ha un impatto sostanzialmente negativo sulla sopravvivenza dei pazienti con tumori della laringe. Lo svuotamento laterocervicale elettivo selettivo dei livelli II, III e IV rappresenta di consuetudine l'approccio di scelta in questi pazienti. Tuttavia la morbidità associata allo svuotamento del IV livello non può essere trascurata per il rischio di danno del nervo frenico e di lesione del dotto linfatico. Obbiettivo del nostro studio è stato valutare la frequenza di metastasi linfonodali al livello IV in pazienti clinicamente T3/T4N0 affetti da carcinoma della laringe. Abbiamo esaminato retrospettivamente l'esame istopatologico definitivo di 77 pazienti stadiati clinicamente T3/T4N0 affetti da carcinoma della laringe. I pazienti furono sottoposti a svuotamento latero cervicale bilaterale nel periodo compreso fra il gennaio 2007 e novembre 2012. I pezzi istopatologici furono suddivisi in livelli prima di essere inviati in anatomia patologica. In 12 pazienti sono state riscontrate metastasi latero cervicali (15.58%). In 3 casi (3.89%), fu riscontrato un interessamento del IV livello, tutti i pazienti erano T4 con metastasi laterocervicali ipsilaterali al tumore. In conclusione nei pazienti clinicamente stadiati come T4 l'incidenza di metastasi latero cervicali al IV livello era del 3,89%.

PAROLE CHIAVE: *Neoplasia laringea • Dissezione del collo • Metastasi laterocervicali • Carcinoma a cellule squamose • Stadio della neoplasia*

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Introduction

The presence of cervical metastasis has substantial negative impact on the survival of patients with laryngeal cancer. The appropriate dissection of cervical lymph nodes is important in the surgical approach for determination of pathological staging, indication of adjuvant treatment and definition of prognosis [1].

In patients with squamous cell carcinomas of the larynx clinically staged as N+, the goal of surgical management is the total removal of the primary tumour with therapeutic neck dissection. However, the treatment strategy for clinically N0 patients is still controversial. Bilateral elective selective neck dissections including levels II, III and IV are usually indicated. Nonetheless, there is important morbidity associated with level IV dissection, such as phrenic nerve injury and lymphatic fistula following thoracic duct injury (when the left level IV is involved) [2].

Due to these potential complications, some Authors have analyzed the need for inclusion of level IV in neck dissections in patients with T3/T4N0 laryngeal cancer. It has

been reported that the incidence of level IV metastasis is less than 4% [3-6].

The objective of this study was to evaluate the frequency of metastatic nodes in level IV in patients with clinically T3/T4N0 laryngeal cancers who underwent bilateral elective selective neck dissection of levels II, III and IV.

Methods

This is an observational study of pathological reports of 77 patients with clinically T3/T4N0 laryngeal squamous cell carcinoma. Patients underwent bilateral elective selective lateral neck dissection (levels II, III and IV) over a period of 5 years (January 2007 to November 2012) at Hospital das Clínicas of São Paulo School of Medicine, University of São Paulo (HC-FMUSP) and at Institute of Cancer of São Paulo (ICESP). The exclusion criteria were insufficient clinical information, previous treatment with radiotherapy or chemotherapy and oncologic diagnoses other than squamous cell carcinoma of the larynx.

Surgical specimens were subdivided in levels before being sent to the pathologist. The presence of lymph node metastasis in level IV and in the other dissected levels was studied using H-E stain.

Results

Of the 77 patients, there were 7 (9%) women and 70 men (90%). The average age was 58.8 years, ranging from 38 to 82. Twenty-eight cases were T3 (35.8%) and 50 were T4 (64.2%). The primary tumour subsites were 13 supraglottic (16.8%), 42 glottic (45.5%) and 22 transglottic (28.5%). There were 12 patients with neck metastasis (15.58%). In 3 cases (3.89%), there were metastatic lymph nodes in level IV, 2 from transglottic tumours and one in a case of supraglottic tumour. All 3 cases had T4 tumours and all metastases were ipsilateral to the primary tumour. In one of these, there were simultaneous metastases in level III, ipsilateral to the primary tumour (Table I).

Discussion

Cervical lymph nodes metastases are one of the most significant prognostic factors in patients with laryngeal cancer. The rationale for performing elective selective neck dissections is based on the predictable pattern of lymphatic spread of upper aerodigestive tract tumours [7]. The first echelon of lymphatic drainage should be removed. If it does not harbour metastatic disease, the incidence of metastasis in other levels of the neck is believed to be extremely low. Elective dissection of lymph nodes at levels II-IV is indicated for patients with T3 and T4 laryngeal cancers. However, the need to remove level IV has been questioned. Furthermore, there is a possible risk for associated morbidity [4].

The patterns of cervical metastasis from laryngeal cancer were studied in 262 radical neck dissection specimens from 247 patients. Occult positive adenopathy was found in 37% of patients, mainly on levels II-IV, whereas only rarely were levels I (14%) and V (7%) involved [8].

Selective lateral neck dissection (levels II-IV) was prospectively compared to type III modified radical neck dissection as part of elective treatment for patients with supraglottic and transglottic laryngeal cancer. After a mean follow-up of 42 months, no difference was found in the outcome between patients treated with either modality. It supports the use of lateral neck dissection as an effective treatment for patients with T2/T4 supraglottic and transglottic cancer, which is the elective treatment of choice for patients with laryngeal cancer [9].

Table I. Staging characteristics of patients with neck metastases (n = 12).

Age (years)	Subsite and T staging	Level II	Level III	Level IV
66	Transglottic T4	1 (ipsilateral)	0	0
49	Supraglottic T4	0	0	1 (ipsilateral)
82	Transglottic T4	0	0	1 (ipsilateral)
52	Supraglottic T4	2 (ipsilateral)	1 (ipsilateral)	0
56	Transglottic T4	2 (ipsilateral)	1 (ipsilateral)	0
56	Transglottic T4	2 (ipsilateral)	2 (ipsilateral)	0
49	Glottic T3	1 (contralateral)	1 (contralateral	0
71	Supraglottic T4	1 (contralateral)	0	0
53	Glottic T4	1 (ipsilateral)	2 (1 ipsilateral and 1 contralateral)	0
68	Glottic T3	1 (ipsilateral)	0	0
59	Glottic T3	4 (2 contralateral and 2 ipsilateral)	0	0
69	Transglottic T4	0	1 (ipsilateral)	1 (ipsilateral)

One hundred forty-five selective neck dissections were performed at levels II-III in 79 patients who were surgically treated for laryngeal carcinomas. A more extensive neck dissection that included levels IV-V was performed in all patients with nodal metastasis pathologically demonstrated by intraoperative frozen section analysis. Pathologic assessment of neck dissection specimens revealed nodal metastasis at level IV in 2 patients (2.5%). After a follow-up of at least 24 months, no patients had regional recurrence [10].

Forty-two patients with supraglottic cancers and 29 with transglottic cancers were reviewed. Levels II-IV had been removed in all cases. Of 43 patients who underwent elective lateral neck dissection, one (2.3%) presented level IV metastasis – with simultaneous level II metastases. The authors recommend dissection of level IV as part of therapeutic neck dissection for patients with clinically enlarged lymph nodes. However, they consider the absence of detectable adenopathy a challenge [4].

In a series of 155 N0 patients with supraglottic cancer, whose treatment consisted of an elective neck dissection limited just to level II, 10 patients (6.5%) experienced ipsilateral neck recurrences after a minimum follow-up of 5 years [11].

A prospective study of 142 lateral neck dissections in 73 patients with laryngeal tumour and N0 neck evaluated the incidence of pathological metastases in level IV. Five necks had positive lymph nodes for microscopic metastasis in level IV (3.5%), all of which were ipsilateral. Separate skip metastases in level IV lymph nodes were observed in two cases. Postoperative chylous leakage and phrenic nerve paralysis occurred in 5.5% and 2.7%, respectively [12]. In fact, potential damage to the major lymphatic vessels leading to chylous leakage and phrenic nerve paralysis are the two major complications associated with level IV dissection [5].

The results of our study further support a more selective approach, with dissection limited to levels II-III as the primary elective treatment of a clinically negative neck for patients with supraglottic and transglottic cancers. In spite of this, further prospective studies are necessary to determine its safety in the clinical setting. On the other hand, for patients with clinically positive adenopathy at higher levels (II-III), a more extensive neck dissection (modified radical neck dissection) would appear to be warranted.

The current clinical staging criteria fail to differentiate patients with occult metastases from those without metastases [13]. Molecular markers of metastatic potential could help to indicate treatment of the neck in patients with undetectable disease and to avoid unnecessary approaches. However, since the metastatic process is complex with the involvement of many factors, there are still no genetic biomarkers, and recently published studies are contradictory and of little benefit for routine clinical use [3]. Many investigators are working to identify molecular markers of disease, to improve the understanding of the mechanisms underlying the pathogenesis and development of laryngeal cancer and to improve its clinical staging [13]. The degree of differentiation is the most important histologic factor. Overexpression of EGFR has been associated with poor prognosis, whereas the association with HPV infection is distinguished by better prognosis. p53 mutations and cyclin D1 amplification have also been subject to intensive research [14].

Conclusion

In the present study, the frequency of occult lymph node metastases on level IV in patients with T3-T4 laryngeal cancers was very low (3.89%). No patient with a T3 primary had occult metastases on level IV. Therefore, the results suggest that it is oncologically safe to include only levels II and III in elective neck dissections performed for laryngeal cancer and ipsilateral IV level for T4 tumours. However, prospective studies are necessary to confirm this.

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