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Cervical node metastases in oropharyngeal squamous cell carcinoma: prospective analysis of prevalence and distribution

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Abstract

The treatment of cervical lymph node metastases is an important part of the management of oropharyngeal squamous cell cancer. Metastases are already clinically present in 61 per cent (+ or −2.6 per cent) of patients at presentation. Previous studies concerning the prevalence and distribution of neck node metastases in oropharyngeal carcinoma have been retrospective, and little or no information is available about the histopathological methods used.

This study has prospectively analysed 85 neck dissection specimens in 72 consecutive patients with squamous cell carcinoma of the oropharynx, both with clinically N_0 and N+ve necks, to identify the prevalence and distribution of cervical metastases. We have used a technique to separate the neck dissection into nodal levels per-operatively, and then embedded the entire specimen for histological examination to avoid missing metastatic disease in small lymph nodes (<3 mm diameter).

Key words: Carcinoma, Squamous Cell; Lymphatic Metastasis; Oropharyngeal Neoplasms

Introduction

The treatment of cervical lymph node metastases is an important part of the management of oropharyngeal squamous cell cancer. Metastases are already clinically present in 61 per cent (+ or −2.6 per cent) of patients at presentation.[1–5] Histopathlogical metastases are present in 69 per cent (+ or −5 per cent) of all patients,[2,4–6] and in 29 per cent (+ or −9.3 per cent) of patients with clinically N_0 disease.[2,4,5,7]

Surgical treatment of the cervical lymph nodes in oropharyngeal cancer is based on clinical,[8] and pathological studies[2,4,5] of the distribution of metastases to the lateral cervical lymph nodes. All of these studies classify lymph node levels according to the Memorial Sloan Kettering Cancer Center scheme.[9] Metastases occurred most frequently to levels II, III, and IV, and less frequently to levels I and V.

Previous studies have, however, been retrospective, and little or no information is available about the histopathological methods used. It is likely that the reported studies used the standard technique of macroscopically identifying lymph nodes and dissecting them from the specimen.[6] This technique limits the evaluation to nodes of greater than 3 mm diameter, which may lead to an underestimation of the true disease prevalence. Our department in a previous study has demonstrated that approximately one-third of metastases occurred in nodes of less than 3 mm diameter.[10]

This study has prospectively analysed 85 neck dissection specimens in 72 consecutive patients with squamous cell carcinoma of the oropharynx, both with clinically N_0 and N+ve necks, to identify the prevalence and distribution of cervical metastases. A technique was used to separate the neck dissection into nodal levels pre-operatively and the entire specimen was embedded for histological examination to avoid missing metastatic disease in small lymph nodes (<3 mm in diameter).

Materials and methods

Between January 1996 and October 2000, 72 consecutive patients with oropharyngeal squamous cell carcinoma had neck dissections performed and prospectively analysed. All 72 had ipsilateral dissections, 13 also had contralateral dissections for either midline or bilateral disease. It is our policy to carry out neck treatment on oropharyngeal tumours of all stages. Patients were treated with selective, modified radical or radical neck dissections, depending on the extent of the disease, and invasion of non-lymphatic structures. Sixty-one patients had combined surgery to both the neck and primary site, nine were treated

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TABLE I
STUDY POPULATION CLASSIFIED BY THEIR TUMOUR AND NODAL STAGING

	T1	T2	T3	T4	Total
N_0	1	3	10	8	22
N_1	0	4	8	6	18
N_{2a}	4	6	4	1	15
N_{2b}	1	1	2	1	5
N_{2c}	0	1	3	1	5
N_3	0	2	3	2	7
Total	6	17	30	19	72

with neck dissection followed by brachytherapy or external beam radiotherapy to the primary site.

Tumours were classified into five subsites according to mucosal distribution. These were:

(1) lateral wall (including tonsil);
(2) soft palate;
(3) posterior wall;
(4) tongue base;
(5) vallecula

Most tumours involved more than one subsite. Tumours that extended into adjacent sites were included provided that extension was not beyond the immediately adjacent subsite. Epiglottic invasion, for example, would be included whereas vocal fold or ventricular extension would not. Tumours were staged using clinical examination, endoscopy and axial computerized tomography with sagittal magnetic resonance imaging for tongue base tumours. Twenty-two patients were clinically N_0, and 50 N+ve (Table I). Bilateral neck dissections were performed in seven N_0 and six N+ve patients.

The neck dissections were separated into node levels per-operatively, using landmarks suggested by Robbins *et al.*[11] The node levels were marked with steel clips and separated immediately after resection. The node levels were fixed in formalin and sent as separately labelled specimens. Each node level was cut into two mm thick blocks and all the tissue was embedded in paraffin wax. These blocks were then sectioned at six μm thickness, and each section was stained with haematoxylin and eosin. Lymph nodes were defined as an aggregate of encapsulated lymphoid tissue of any size, that had a peripheral sinus. This method allows the examination of lymph nodes down to 0.5 mm diameter.

Fisher's Exact test was used to test for associations between each subsite and presence of nodal involvement, extensions to neighbouring sites and presence of nodal involvement and tumour stage and presence of nodal involvement.

TABLE III
ASSOCIATION OF TUMOUR STAGE AND CLINICAL NECK NODE STATUS

Tumour stage	N_0	N+ve	% +ve	Overall *p*-value for Fisher's exact test of association
T_1	1	5	83%	
T_2	3	14	82%	
T_3	10	20	67%	0.42
T_4	8	11	58%	
Overall	22	50	69%	

Results

Eighty-five neck dissections were prospectively analysed from 72 patients between January 1996 and October 2000. The staging of this population is shown in Table I. The mean node yield from the neck dissections was 62 (range 21–126). Overall, 56 of the 85 neck dissections (65.9 per cent) had histological metastases. Fifty of the 72 (71.4 per cent) ipsilateral, and six of the 13 (46.2 per cent) contralateral dissections had metastases (Table II). Of the 22 clinically N_0 patients, eight (33.3 per cent) of the ipsilateral neck dissections were pathologically positive. Seven patients who were clinically N_0 had contralateral neck dissections, two (28.6 per cent) of these were positive (Table II). With the 50 clinically N+ve patients, 42 (91.3 per cent) had metastatic disease in the ipsilateral neck dissections, and four out of six (66.7 per cent) of the contralateral neck dissections were positive (Table II).

Metastases occurred predominantly in levels II to IV, the prevalence in levels I and V was low, even in the clinically N+ve group (Table II). 'Skip metastases' to levels IV or V occurred in six patients, five on the ipsilateral side, and one on the contralateral side (seven per cent). Fisher's Exact test did not reveal any statistical association between the subsite and presence of nodal involvement, extensions to neighbouring sites and presence of nodal involvement, or tumour stage and presence of nodal involvement (Tables III and IV).

Discussion

Previous studies of cervical lymph node metastases from oropharyngeal squamous cell carcinoma show considerable variations in practice as well as reporting of data.[2,4–6] Since these studies are retrospective, there is little or no information on study methods, and data from ipsilateral and contralateral dissections is often combined. The method used to identify

TABLE II
DISTRIBUTION OF CERVICAL LYMPH NODE METASTASES

Neck dissections	N_0 ipsilateral	N_0 contralateral	N+ve ipsilateral	N+ve contralateral	Total
Total dissections	24	7	46	6	85
Number positive	8	2	42	4	56
Level I positive	2	0	3	0	5
Level II positive	7	1	39	3	50
Level III positive	0	1	16	0	17
Level IV positive	0	0	10	1	11
Level V positive	0	0	3	1	4

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TABLE IV
ASSOCIATION BETWEEN (A) OROPHARYNGEAL SUBSITES, (B) EXTENSION TO ADJACENT SITES AND CLINICAL NECK STATUS

Tumour stage	N_0	N+ve	% +ve	*p*-value for Fisher's exact test of association
(a) Subsite				
Soft palate	12	23	66%	0.61
Lateral wall	14	40	74%	0.15
Posterior wall	4	6	60%	0.48
Tongue base	16	29	64%	0.30
Vallecula	4	12	75%	0.76
(b) Adjacent sites				
Oral cavity	9	10	53%	0.08
Nasopharynx	4	2	33%	0.07
Hypopharynx	4	8	67%	1.00
Larynx	3	10	77%	0.74
Overall	22	50	69%	

nodal metastases in different levels in the neck may have a bearing on the reported prevalence. Reliable identification of the node levels in the pathology laboratory is difficult due to the distortion of the specimen in formalin,[12] and the absence of operative landmarks.[11] With traditional pathological methods, the pathologist usually examines one or two sections of tissue from each lymph node found macroscopically in the neck dissection. Consequently, the vast majority of tissue is never examined and micrometastases (defined as tumour deposits that are <3 mm in diameter) are missed. The number of micrometastases detected also depends on the skill and commitment of the pathologist as well as the number of sections examined.[13] The technique we have employed involves separation of the nodal groups at the time of surgery.[10] The individual levels were sliced at 2 mm and these slices were then sectioned at six μm intervals to avoid missing metastases in small nodes. The conventional method of analysis of neck dissections is limited to nodes of 3 mm or greater,[6] and is therefore likely to underestimate the prevalence of metastatic disease.

In this study, the overall prevalence and distribution of metastases is similar to the combined data from historical studies.[2,4–6] The true prevalence of nodal disease, however, is uncertain, as the study group is pre-selected. The prevalence in any study group is dependent on the selection criteria for neck dissection, and the treatment policy for oropharyngeal tumours.

The site prevalence of metastatic disease at different nodal levels in our study supports the use of selective neck dissection for clinically N_0 patients.[14] Our data indicates that levels I to IV should be dissected, as the pattern of metastatic disease is not always sequential, with 'skip metastases' occuring in six cases (seven per cent). Bilateral neck dissection is indicated in midline or bilateral tumours. With N+ve disease, dissection of levels I to IV may be an adequate therapeutic strategy with limited disease, otherwise our preferred treatment is modified radical neck dissection if this is technically possible.

In addition to the technique of lymph node examination used in this study, immunohistochemistry[15] and molecular analysis[16] have been used by others in an attempt to increase the detection rate of micrometastases in head and neck cancers. However, unless the entire neck dissection specimen is examined instead of picking apparent lymph nodes, micrometastases and soft tissue deposits will be missed as they are left behind in the unexamined tissue. The fate of micrometastases is uncertain; some may have been destined for destruction or dormancy while others may provide a niche for the evolution of tumour cells with a phenotype conducive to development of extracapsular spread or distant metastases.[13] The challenge faced is to find ways of detecting micrometastases with phenotypic and genotypic characterics that support such progression, thereby affecting prognosis.

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