Pergamon

Oral Oncol, Eur J Cancer, Vol. 30B, No. 2, pp. 88–92, 1994

0964–1955/94 $6.00 + 0.00

Assessment of Lymph Node Metastases in the Neck

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INTRODUCTION

FOR PATIENTS with oral squamous cell carcinoma, the status of the cervical lymph nodes is the single most important tumour related prognostic factor. Prognosis is roughly diminished by half if lymph node metastases are present at presentation or develop during follow-up [1–4]. Not only the incidence of loco-regional recurrence, but also the risk of distant metastases increases as the tumour burden in the neck increases. Apart from the presence or absence of lymph node metastases, the size, number, level and side relative to the primary tumour are by most authors accepted to influence prognosis. The presence of extranodal tumour spread is generally accepted to be a bad prognostic indicator as well [2–5].

To provide a prognostic scale for tumour patients, TNM classification systems like those of the UICC and AJCC are used. It is important that these classification systems are widely used, not only to guide therapy in a specific patient, but also to enable comparison of treatment results of different treatment centres. In 1988 the last remaining difference between the two classification systems, which regarded the importance attached to laterality, has been smoothed away (Table 1). However, it is unfortunate that these latest revisions have not incorporated the level of involvement of cervical lymph nodes, as it has been shown that the level of involvement has prognostic importance [1, 3]. These levels of the neck that are also used to classify different neck dissections are depicted in Fig. 1, and will be described in the next paragraph. Although the high posterior region is the upper part of level 5, involvement of this region might not be as bad a prognosticator as involvement of the more caudal part of level 5. Both the UICC and the AJCC are not specific and not precise in their recommendations as to the additional procedures for the assessment of the neck. However, it is generally recognised that the validity of any classification system depends on the staging procedures employed. The updated UICC classification recognises an optional additional descripter, the so called C(ertainty)-factor, which reflects the diagnostic method used. The C-factor definitions are: C1: evidence from standard diagnostic means (e.g. physical examination), C2: evidence obtained by special diagnostic means (like CT, MR or US), C3: evidence obtained from histopathological examination of the operating specimen. However, this C-factor is very seldom used.

Pre-treatment assessment of the status of the lymph nodes is essential for optimal treatment planning in head and neck cancer patients. In many institutions, the assessment of the lymph nodes in the neck is still mainly based upon palpation. Palpable nodes are classified as suspect according to their size, consistency and location. However, it is widely accepted that palpation is unreliable for the assessment of the neck. Studies on clinico-pathological correlation have demonstrated that both the false positive rate and the false negative rate of findings at physical examination are unsatisfactorily high [6–8]. Furthermore, the accuracy of palpation with regard to number and size of involved nodes leaves much to be desired [2]. Most of the disagreement on the indications for elective

Table 1. UICC (1987) and AJCC (1988) classification of the neck

Nx	The neck cannot be assessed
N0	No regional lymph node metastases
N1	One ipsilateral metastasis, 3 cm or smaller
N2a	One ipsilateral metastasis larger than 3 cm but smaller than 6 cm
N2b	Multiple ipsilateral metastases smaller than 6 cm
N2c	Contra- or bilateral metastases smaller than 6 cm
N3	Regional metastasis larger than 6 cm

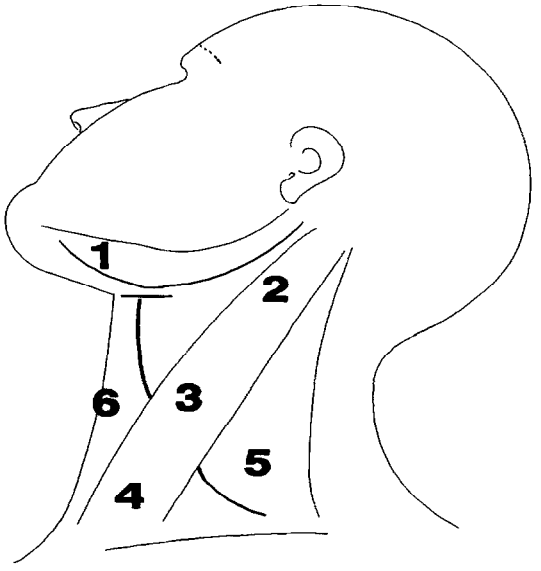

Fig. 1. Six lymph node levels in the neck according to the Memorial Sloan-Kettering Cancer Center [26].

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Received 1 Mar. 1993; provisionally accepted 8 Mar. 1993; revised manuscript received 19 Apr. 1993.

treatment of the neck is based on our inability to accurately stage the neck [9]. Modern imaging techniques, such as computed tomography (CT), magnetic resonance (MR) imaging or ultrasound (US)-guided fine needle aspiration cytology (FNAC) have in recent years proven to be more reliable than palpation. In the light of this improvement in diagnostic accuracy, the indications for neck treatment in general and for elective neck treatment in particular have to be revised.

The management of the neck can be considered as either elective or therapeutic, depending on the findings at preoperative work-up. In patients who have clinical evidence of nodal involvement, comprehensive neck dissection is the most widely accepted treatment. The histopathological examination of the operating specimen can then be used to guide further postoperative radiotherapy [2–5, 9–12]. Clinically occult metastases can be cured in a high percentage with either surgery [9, 11–17] or radiotherapy [18, 19]. In this regard, the efficacy of selective neck dissection, that is currently advocated both as staging and as curative procedure for the N0 neck, has yet to be proven [12, 14, 16, 17]. The choice to treat the N0 neck with either surgery or radiotherapy should mainly depend on the treatment chosen for the primary tumour.

The most important indication for elective treatment of the neck in anterior oral carcinomas, either by surgery or radiotherapy, is a risk of occult metastases higher than 15–20%. The magnitude of the risk of occult metastases, that can occur in both sides of the neck, is estimated on the basis of known prognostic factors of the primary tumour [20–22]. For anterior oral carcinomas, most clinicians tend to treat the neck electively if the primary tumour is larger than 2 cm (T2). If surgery is employed for the primary tumour, elective neck dissection should also be performed when the neck has to be entered for the excision of the primary tumour, as in most posterior oral cavity and oropharyngeal tumours.

ANATOMY OF THE LYMPHATICS IN THE NECK AND PATTERNS OF REGIONAL SPREAD FROM ORAL CARCINOMAS

The neck has the most extensive and variable lymphatic system of the whole body. Of the estimated 800 lymph nodes in the human body, 300 lymph nodes are situated in the neck [23]. The complex anatomy of the cervical lymphatics was originally categorised by Rouvière [24]. Lindberg [25] modified the scheme from Rouvière. He distinguishes the submental, the submandibular (or submaxillary), the jugular chain, the posterior (accessory chain) and the supraclavicular lymph nodes. The jugular chain and the posterior cervical lymph nodes are further divided into, respectively, high-, mid- and low-jugular and high-, mid- and low-posterior lymph nodes. In this classification, the juxtavisceral lymph nodes along the pharynx, larynx and trachea, the superficial nodes along the anterior and external jugular veins, the occipital nodes, the retroauricular nodes, the parotid nodes and the facial nodes are not mentioned.

To simplify this system, surgeons from the Memorial Sloan-Kettering Cancer Center have categorised the neck into six levels [26] (Fig. 1): In this classification system, level 1 corresponds with the submandibular and submental regions. Levels 2, 3 and 4 correspond with the high-, mid- and low-jugular chain nodes and the lymph nodes covered by the sternocleidomastoid muscle. Level 5 are the lymph nodes posterior to the posterior border of the sternocleidomastoid muscle (posterior triangle) and the supraclavicular lymph nodes. Level 6 corresponds with the juxtavisceral lymph nodes.

Although many different pathways and anastomoses of the lymphatics in the neck exist, most primary tumours follow a rather constant route via local lymphatics to the first and further echelons of lymph nodes in the neck [14, 25, 27, 28]. The first and second echelon lymph nodes are at highest risk to harbour occult metastases in early stage head and neck carcinomas. It is important to realise that tumours approaching or crossing the midline, can metastasise to both sides of the neck.

Although advanced oral carcinomas can eventually spread to all sites in the neck, knowledge about the first and second echelons is important for all clinicians dealing with these cancer patients.

In general, anterior oral carcinomas initially spread to the submandibular (or less frequently the submental) lymph nodes or to the high-jugular lymph nodes [28].

In posterior oral cavity and oropharyngeal carcinomas the high- (and mid-) jugular lymph nodes are most frequently involved [27, 28]. Reports on the involvement of retro- and parapharyngeal lymph nodes are sparse.

STAGING OF THE NECK

One of the major problems for optimal treatment planning of the neck in patients with a primary squamous cell carcinoma of the upper aerodigestive tract is the inability to accurately stage the neck by palpation [6–8]. The known fallibility of palpation is a major cause of improper initial treatment of the neck and of delayed identification of recurrences in the neck during follow-up. The resulting treatment controversies are obvious [8, 9].

Although the identification of false positive palpatory findings, that can for example be caused by obstruction of the submandibular duct, can have important therapeutic consequences, the major interest of modern imaging techniques concerns the staging of the clinically negative neck. If any technique is able to decrease the risk of occult metastases below 10–15%, the indications for elective treatment of the neck in these patients would have to be re-evaluated. This radiological technique should idealy be available both for initial work-up and for follow-up.

Although many authors published their data on the accuracy of CT, MR and US for a random head and neck cancer population, the data in literature on the value of modern imaging techniques for the assessment of the N0 neck are relatively sparse. In Table 2 the sensitivity and specificity as found by different authors using different imaging modalities for the N0 neck are shown. The sensitivity reflects the percentage of positive findings in a metastasis containing side of the neck. The specificity is the chance of negative findings in a side of the neck that is free from metastasis. The accuracy is the proportion of overall correct diagnoses. As shown, most authors studied small numbers of patients with N0 necks whereas the incidence of occult metastases varies enormously between different studies. It is thus hard to compare most of the results shown.

Recently in our institution, a prospective study was completed that compared the accuracy of preoperative palpation, CT, MR, US and US-guided FNAC with the histopathological examination for the assessment of the neck in

Table 2. The sensitivity and specificity of different imaging modalities found by several authors for the palpatory N0 neck (electively operated)

Reference	Modality	Number	Sensitivity	Specificity
29	CT	59	38% (6/16)	81% (35/43)
30	CT	16	14% (1/7)	89% (8/9)
	Scintigraph.	16	43% (3/7)	67% (6/9)
31	CT	32	50% (2/4)	86% (24/28)
32	CT	16	83% (5/6)	90% (9/10)
33	CT/MR	19	26% (5/19)	—
34	CT	68	68% (19/28)	90% (36/40)
	MR	16	80% (4/5)	82% (9/11)
35	CT	11	60% (3/5)	83% (5/6)
	MR	8	67% (2/3)	80% (4/5)
36	CT	86	49% (17/35)	78% (40/51)
	MR	83	55% (18/33)	88% (44/50)
37	US-g-FNAC	70	76% (25/33)	100% (37/37)

Table 3. Accuracy of different staging modalities for all (n = 180) *sides of the neck, the clinically positive (N+) sides* (n = 92) *and the clinically negative (N0) sides of the neck* (n = 88) [36]

	Accuracy		
Technique	All	N+	N0
Palpat.	69%	79%	59%
US	75%	86%	68%
USgFNAC	93%	100%	86%
CT	78%	89%	66%
MR	82%	88%	75%

All: 180 sides, 109 positive, 71 negative.
N+: 92 sides, 73 positive, 19 negative.
N0: 88 sides, 36 positive, 52 negative.

patients who all subsequently underwent a neck dissection, either therapeutical or elective, for squamous cell carcinoma of the mucosal lining of the upper aerodigestive tract [36] (Table 3). Before embarking on this study, we first established the optimal MR techniques to depict lymph node metastases in the neck [38] as well as optimal radiological criteria for metastatic cancer in cervical lymph nodes as depicted at CT or MR [39]. These initial studies showed that tumour necrosis in lymph nodes was the most specific criterion for lymph node metastases, and could be visualised at MR with use of Gadolinium-DTPA enhanced T1-weighted gradient echo images. Although the minimal axial diameter proved to be more accurate as size criterion than the so often used maximal axial diameter, all size criteria remain a possible source of false interpretations [37, 39, 40]. The optimal size criteria in our population proved to be 11 mm for subdigastric lymph nodes, and 10 mm for all other nodes. Furthermore, a grouping of three or more borderline lymph nodes (1 or 2 mm smaller) could be used as a criterion as well [39]. One should realise however, that radiological criteria for metastases can never be as accurate as histopathological or cytological criteria [36, 39–41].

In most studies, contrast enhanced CT, as well as MR, are significantly more accurate than palpation (Tables 2 and 3) [8, 29–36, 42, 43]. With both contrast enhanced CT and MR, necrotic tumour foci or keratinising tumour foci larger than 3 mm—both characteristic for metastases—can be depicted reliably. Furthermore, CT and MR can be used simultanously to stage the primary tumour, which is especially important in large posterior oral cavity and oropharyngeal carcinomas. Ultrasound, using a 7.5 MHz transducer, can demonstrate even very small lymph nodes [37, 44–47]. However, as small necrotic foci are not depicted with US, only the size criterion is available for this modality.

By obtaining cytological evidence of metastatic tumour or reactive lymph node tissue, the disadvantages of unreliable radiological criteria for malignancy can be overcome [37, 41, 47]. Furthermore, US-guided FNAC has proved to be a safe, quick and inexpensive technique, that can be used for follow-up as well. Our results furthermore show that in the hands of experienced clinicians this technique is the most accurate staging technique for the neck [36, 37]. One must realise however, that the accuracy fully depends on the skill of the ultrasonographer and the cytopathologist. The US examination of the neck should be performed with the use of a 7.5 or 10 MHz linear array transducer. Whereas the scanning plane for level 1 can be either frontal or sagittal, all other levels are preferably scanned in an axial plane. By using this plane along the jugular chain lymphatics, lymph nodes can be optimally distinguished from the surrounding tissues, as lymph nodes appear and disappear from the screen by gently moving the transducer in a craniocaudal or caudocranial direction. This is the best method to distinguish lymph nodes from vessels and muscles, which can be particularly difficult in level 2. In almost all necks, lymph nodes are depicted. For US guided aspiration it is essential to select the lymph nodes that most likely harbour metastasis. In this respect, it is essential to have knowledge about the site and extent of the primary tumour and its first and second echelon of metastases. For oral carcinomas, level 1 and 2 are the most likely sites of early metastases, and can be affected in both sides of the neck. In general, the larger the lymph node, the greater are the chances that it will be a metastatic lymph node. However, level 2 lymph nodes are often somewhat larger than other lymph nodes in the neck. To obtain a high sensitivity with US-guided aspiration cytology, lymph nodes with a minimal diameter of 5 mm or more in level 2 should be aspirated whereas in the rest of the neck lymph nodes with a minimal diameter of 4 mm or more should already be aspirated.

As some 12% of all tumour positive neck dissection specimens harbour only micrometastases [33, 48], one should

realise that it will be very hard to increase the sensitivity of any preoperative staging technique over 88%. Although unlikely, PET scan or immunoimaging with use of radiolabelled monoclonal antibodies against surface antigens of squamous cell carcinoma cells, might in future be able to detect even these very small metastases [49, 50].

Preoperative staging techniques are less accurate in the assessment of the number of nodal metastases in the neck and the number of levels involved [8], as relatively large detectable metastases are very often accompanied by small undetectable micrometastases [48]. With US-guided FNAC it seems unpractical and certainly poorly tolerable for the patient to aspirate from more than two or three lymph nodes on one side of the neck. Furthermore, the therapeutical implications of assessing the exact number of metastases in the neck are minimal for most patients. Preoperative assessment of extranodal tumour spread and tumour infiltration in, for example, the carotid artery can have important therapeutic implications. In this respect, Som [40] reports an estimated sensitivity of 100% for CT. However, Close *et al.* [42] reports that CT could only identify extranodal spread in large nodes. Only Carvalho *et al.* [51] studied the value of CT in detecting extranodal spread and found a sensitivity of 63% and a specificity of 60%. In our opinion only major macroscopic extranodal spread (infiltration) can be detected with some accuracy by preoperative staging techniques. The assessment of microscopic extranodal spread, which occurs much more often in small lymph nodes, can never be done accurately, preoperatively as even the microscopic evaluation of this feature on paraffin sections often gives rise to disagreement among histopathologists. So far, the accuracy of most imaging techniques has been disappointing in detecting tumour invasion into the great vessels of the neck [52–54].

IMPACT OF RADIOLOGICAL STAGING ON TREATMENT OF THE NECK

If the neck is treated electively because the primary tumour is exposed through the neck, the therapeutical implications of accurate staging techniques are minimal for the treatment of the ipsilateral neck. However, if the neck is treated electively because of a high likelihood of occult lymph node metastasis, as in small anterior oral carcinomas, an accurate imaging technique can certainly influence the treatment policy by decreasing this risk of occult metastases. In case of an initial risk of occult lymph node metastasis of 40%, as is the case in many T2 oral carcinomas, imaging techniques that can detect 75% of these metastases, like US-guided FNAC [36, 37, 47], can reduce this risk to 10% ($25\% \times 40\% = 10\%$). In this respect, it is widely accepted that an estimated risk of occult metastasis lower than 10–15% justifies a watchful "wait and see" policy. Another comparable but even more frequent problem poses the contralateral neck in tumours approaching or crossing the midline. As bilateral treatment of the neck greatly increases patient morbidity, the possibility of a watchful "wait and see" policy for this side of the neck is even more important for the patient. Although the indications for elective radiotherapy differ slightly from those of elective surgery, to a certain degree the same philosophy can be used.

Patients with a low risk of occult metastases, like those with small lip or palatal carcinomas, are usually not treated electively on behalf of the neck. The same holds true for the contralateral neck in patients with strictly unilateral tumours. However, in a small percentage of these patients, occult metastases are present of which the great majority can be detected preoperatively as well. For these patients, postponement of neck treatment can be overcome by US-guided FNAC.

The clinically positive neck, in which slightly enlarged lymph nodes or an indistinguishable swollen submandibular gland are palpated poses another major problem, as false positive findings at palpation occur in 20–40% [6–8, 36]. Our study has shown that these false positive cases can be reliably excluded with use of US-guided FNAC (Table 2). Therefore, it seems reasonable to rely on the US-guided FNAC findings in these patients as well. However, it must be recognised that most head and neck surgeons will at least perform a staging neck dissection in case of conflicting findings at palpation and US-guided FNAC.

CONCLUSIONS

It is fortunate that since 1988 both the UICC and the AJC use the same classification system for the neck, and that there is a growing consensus about the nomenclature of the anatomy in the world. Unfortunately, the level of nodal involvement is not incorporated in the current staging systems. Although palpation has proved to be unreliable in detecting or excluding nodal metastases, there are no clear recommendations by the UICC as to whether modern imaging techniques should be used routinely for initial staging purposes.

The currently available imaging techniques, especially US-guided FNAC, have improved our ability to detect small lymph node metastases in the neck, and can thus decrease the incidence of occult metastases. As a consequence, the need for elective neck treatment on the basis of high likelihood of occult metastases, as in small anterior oral carcinomas, will diminish. However, as the reliability of any staging technique depends on the skill of the clinician performing these techniques, it is wise to assess the accuracy "in your own hands" before changing elective treatment to a "wait and see" policy.

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