ASSESSMENT OF LYMPH NODE METASTASES IN THE NECK

a radiological and histopathological study

Michiel van den Brekel

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aan mijn ouders

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CONTENT

GENERAL INTRODUCTION

Squamous cell carcinoma is the most frequently occurring tumour of the upper aerodigestive tract, and can occur anywhere in the mucous membranes. Head and neck carcinomas have a proclivity to metastasize to the regional lymph nodes rather than to spread hematogenously. Distant metastases occur almost exclusively after spread to the regional lymph nodes.

It is well known that the histopathological presence and extent of lymph node metastasis in the neck is the most important prognosticator, not only in terms of loco-regional recurrence, but also in terms of distant metastasis. If lymph nodes are present at initial treatment or develop in the course of the disease, cure rates decrease roughly by half.

The incidence of lymph node metastasis is highly correlated to the size, site and other characteristics of the primary tumour, varying from as low as 1% for early glottic carcinoma to as high as 80% for nasopharyngeal cancer. For most oral and pharyngeal carcinomas this risk is in the range of 30-60%. In general it holds true that the more advanced and the deeper the infiltration of the primary tumour, the higher the risk of cervical metastasis.

The assessment of the status of the cervical lymph nodes in patients with a squamous cell carcinoma of the head and neck is still one of the most challenging diagnostic problems. Palpation is still the mainstay, and often the only method used to stage the neck at initial presentation and during follow up. The palpability of a lymph node metastasis mainly depends on its size and consistency and on its location in the neck. The type of neck and previous surgery or radiotherapy play an important role as well. Whereas superficially located lymph nodes as small as 5 mm can be palpable in a thin neck, lymph nodes as large as 2 cm can be missed if they are located deep in a short and fat neck. One must realize however that not all enlarged nodes contain metastatic deposits. It is therefore not surprising that many authors have shown that palpation is inaccurate in a large percentage (20-50%) of patients.

Because of the prognostic significance of the status of the neck and the known inaccuracy of palpation to assess it, in many institutions the neck is treated in the absence of palpable lymph nodes if the risk of occult metastasis is estimated higher than 15-20%. Consequently, elective neck dissection or irradiation is often carried out in the absence of metastases in the neck. On the other hand, if the risk of occult metastasis is low, the neck will not be treated prophylactically. In a small percentage of these patients metastasis will become apparent during follow-up.

It is evident that an accurate staging technique, that is able to reliably detect or exclude metastasis in the neck can better select patients who should, and patients who should not be treated on behalf of their neck. If for example an initial risk of occult metastases of 30% can be diminished below 10%, elective treatment of the neck can no longer be defended on the basis of a high likelihood of occult metastasis. Furthermore, an accurate staging technique might also enable detection of the great majority of occult metastases in patients who in general are not treated electively, thus preventing treatment delay.

The *main question* that this study attempts to answer is whether *modern imaging techniques* such as ultrasound (US), computed tomography (CT), magnetic resonance (MR) imaging or US-guided fine needle aspiration cytology (FNAC) *can do better than palpation*, and which of these techniques is superior for the assessment of the status of the neck. In the past, most experience has been gained with CT and US. In most studies it is reported that these techniques are more accurate than palpation in assessing the presence, size and number of metastases. Relevant data in the literature on MR imaging and US-guided FNAC of the neck were sparse when this study was initiated. In chapter 2 different MR imaging techniques for assessing the status of the neck are compared. This thesis describes the first large *prospective study* in which all these modalities are compared in a large group of patients. This part of the study is described in chapters 4, 5 and 6. The *radiological criteria for metastatic lymph nodes in the neck* as depicted by CT, MR or US, are studied in chapter 3 in this thesis.

In view of the problems encountered with the clinical assessment (palpation) of the neck nodes, it is not surprising that retrospective clinico-pathologic analyses of patients treated with a neck dissection, have demonstrated that histopathological prognostic parameters of neck node metastases are more reliable than clinical parameters. Extranodal spread, the number and the level of positive nodes are the most important prognostic indicators. In this respect, it is unlikely that preoperative imaging techniques can be as accurate as histopathological examinations. This emphasizes the importance of neck dissection as a staging technique, apart from its therapeutical effect.

In this study all patients underwent a neck dissection. The histopathological findings of the specimens were used as "gold standard" to assess the accuracy of the radiological techniques employed. However, as the sampling and sectioning techniques of lymph nodes in neck dissection specimens differ between institutions, the average number of metastases detected will vary as well. In chapter 7, we therefore assessed the number of *micrometastases* detected using routine histopathological examination of the specimens, as well as the number of additional micrometastases detected using immunostaining and additional sectioning.

The introductory chapter 1 describes the anatomy of the lymphatic system in the neck and the patterns of lymphatic spread of head and neck cancers. The prognostic and therapeutical significance of neck staging is discussed in this chapter as well. Furthermore, the currently available diagnostic tools are reviewed, and some statistical measures are explained. In chapter 8 the results obtained in this study as well as their practical implications are discussed.

Chapter 1

ASSESSMENT OF THE NECK IN HEAD AND NECK CANCER

1.1. INTRODUCTION

Lymphatic metastasis is the most important mechanism in the spread of head-and neck squamous cell carcinomas. The mechanism of lymphatic spread is largely unknown. After penetration of the basement membrane of the epithelium, cancer cells enter the lymphatics partly by active movement, partly by hydrostatic pressure. These cells then pass up the lymphatic trunc and settle in the subcapsular sinus of the first echelon of lymph nodes. After local proliferation and infiltration into the lymph node and/or the lymph node capsule, the lymph node is ultimately destroyed. The tumour often stimulates the appearance of an encapsulating stroma (desmoplastic reaction). Occasionally, tumour emboli are seen in the extracapsular afferent lymphatics. These emboli may block the lymph vessels and give rise to extranodal masses (1). In general lymph nodes are rather poor barriers to tumour cells (2), and clinical practice has learnt that lymph nodes quite often appear to be a fertile soil for tumour growth. However, the destruction of small numbers of tumour cells in lymph nodes has been described (3). A metastatic node can itself act as a focus for further dissimination into the surrounding lymphatics or the blood stream. The rate of metastasis probably reflects the aggressiveness of the primary tumour.

This chapter gives an overview of the anatomy of the lymphatics in the neck and the patterns of lymphatic spread of carcinomas at various sites within the head and neck. The prognostic and therapeutical significance of lymph node staging will be outlined. Furthermore, some principles and practical aspects of computed tomography (CT), ultrasound (US), US-guided fine needle aspiration cytology (FNAC), magnetic resonance (MR), lymphography, lymphoscintigraphy, immunoscintigraphy and positron emission tomography (PET) will be discussed.

1.2. ANATOMY OF THE LYMPHATIC SYSTEM

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 (4). The complex anatomy of the cervical lymphatics was originally categorized by Rouvière (5), who named lymph node clusters according to their location relative to other structures in the neck. The classification system of Lindberg (6), who modified the scheme of Rouvière is depicted in figure 1.1. Most authors who described the anatomy of the lymphatic system in the neck, derived their data from anatomical studies or studies on patients who underwent a neck dissection. It is therefore not always easy to use these classifications in the axial images obtained at CT or MR imaging, and it might sometimes even be impossible to use these classifications in the histopathological examination of neck dissection specimens.

The classification described herein is derived from Lindberg (6), as depicted in figure 1.1. However, the anatomy of the different regions and the topographical landmarks are described for use in axial images from CT and MR especially.

The first two regions are the submental and submandibular (or submaxillary) regions or triangles. The submental regions {1} are situated between the anterior bellies of the digastric muscles, below the mylohyoid muscle. Lateral to each submental region lies the submandibular lymph node region {2}. The lymph nodes in this region are situated around the submandibular glands medial to the mandible and lateral to the anterior bellies of the digastric muscles. The posterior border of both regions is ill-defined to the high-jugular region and lies just dorsal to the submandibular gland in the frontal plane of the body of the hyoid bone.

The three most important lymph nodes regions in the neck involve the deep cervical or jugular chain lymph nodes along the internal jugular vein. Three seperate regions can be distinguished: the high-, mid- and low-jugular nodes. The high-jugular chain nodes {3} lie between the base of skull and the axial level of the hyoid bone and contains the subdigastric or jugulodigastric lymph nodes. Below this region, between the level of the hyoid bone and the cricothyroid junction lies the mid-jugular region {4}. The jugulo-omohyoid nodes, at the junction of the internal jugular vein and the omohyoid muscle constitute the most caudal nodes of this region. The low-jugular region {5} lies between the level of the cricothyroid junction and the clavicle.

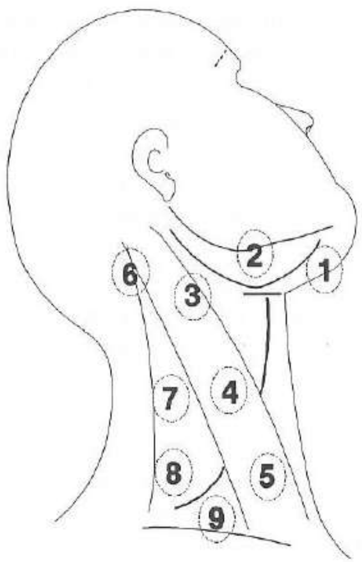

Figure 1.1. Nine lymph node regions of the neck according to Lindberg[6]. See text for explanation of figures.

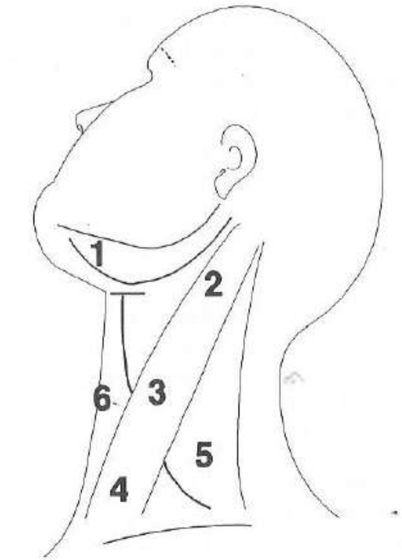

Figure 1.2. Six lymph node levels in the neck according to the Memorial Sloan-Kettering Cancer Center[7]. See text for explanation.

The posterior (triangle) cervical lymph nodes are more or less concentrated along the accessory nerve anterior to the trapezius muscle and are also called accessory chain nodes. Again three groups (high- {6}, mid- {7} and low-posterior {8}) can be distinguished. The bounderies between these three groups are in the same axial plane as those of the jugular chain nodes.

The supraclavicular lymph nodes {9} lie along the transverse cervical vessels just cranial to the clavicle. Apart from the caudal border (the clavicle) no distinct anatomical boundery is defined.

In this classification, the juxtavisceral lymph nodes along the pharynx, larynx and trachea are not mentioned. Other lymph nodes that are not mentioned in this classification, but were recognized by Rouvière, are the superficial nodes along the anterior and external jugular veins, the occipital nodes, the retroauricular nodes, the parotid nodes and the facial nodes.

As lymph nodes can be situated everywhere in the neck, in axial images it is not always easy to classify them as being part of one of the above mentioned regions. This is caused by the fact that the borders between most regions are not marked by landmarks that are visible at CT, US or MR imaging. For example, submandibular lymph nodes situated just dorsal to the submandibular gland can be misinterpreted as high-jugular chain nodes, whereas lymph nodes located under the sternocleidomastoid muscle, but not adjacent to the great vessels can arbitrarily be classified as jugular chain or posterior cervical lymph nodes.

As many of the anatomical landmarks described above are missing or displaced in neck dissection specimens, the pathological classification of lymph nodes can give rise to problems. To partially overcome this problem, surgeons from the Memorial Sloan-Kettering Cancer Center have categorized the neck into six levels (7) (Figure 1.2):
In this classification system, level 1 corresponds to the submandibular and submental regions. Level 2, 3 and 4 correspond to the jugular chain nodes (high-, mid- and low-jugular). The posterior border is now defined by the posterior border of the sternocleidomastoid muscle, whereas the three levels are equal in size. Level 5 are the lymph nodes posterior to the posterior border of the sternocleidomastoid muscle (posterior triangle) and the supraclavicular lymph nodes. The posterior border of this level if formed by the trapezius muscle. Level 6 corresponds to the juxtavisceral lymph nodes. In this thesis, both the classification per region (6) and per level (7) are used. Because metastases in level 6 (juxtavisceral) occur rarely, in some chapters these metastases are not mentioned separately.

1.3. PATTERNS OF LYMPHATIC SPREAD

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 deep lymphatic system of the neck. Many studies on this subject have been published, some deriving their data from -unreliable- clinical findings (8), others from the pathological reports obtained from therapeutical (6,9) or elective (10-15) neck dissections. From the pathological studies on the specimens obtained from therapeutical neck dissections (6,9) can be derived that all primary carcinomas can eventually spread to all levels of the neck, necessitating a comprehensive neck dissection for all clinically positive necks. The pathological studies performed on specimens from elective neck dissections give clues about the *first and second echelon lymph nodes* that are at highest risk to harbour occult metastases from the various sites of primary tumours within the mucous membranes of the

head and neck. The knowledge of these patterns of metastases is important for radiologists, head and neck surgeons and radiotherapists. For the radiologist, it is important to look for lymph nodes especially in these first and second echelon regions, and, if guided FNAC is used, to preferrably aspirate from lymph nodes in these regions. The therapeutical importance of these patterns has been emphasized by Byers and Shah and co-workers (10-14) in a series of articles on prophylactical selective neck dissections. A summary of the most important initial patterns of metastases, as found in these studies will be described. It is important to realize that tumours approaching or extending over the midline, can metastasize to both sides of the neck.

Oral carcinomas can roughly be split in two groups: anterior and posterior oral cavity. Anterior oral cavity carcinomas, especially anterior floor of mouth, buccal mucosa and alveolar process carcinomas initially spread to the submandibular lymph nodes or to the high-jugular lymph nodes. Although submental lymph nodes can be affected initially, this occurs preferrably in carcinomas of the lower lip or anterior alveolar proces. Mid- and low-jugular lymph nodes are mostly affected secondly. Posterior oral cavity carcinomas, like posterior floor of mouth, retromolar trigone and most mobile tongue carcinomas, less frequently spread to the submandibular lymph nodes. For these tumours, the high- and mid-jugular chain nodes are the most important echelons. Although isolated (skip) metastases in low-jugular nodes do occur, these are extremely rare.

Oropharyngeal tumours behave more or less like posterior oral cavity carcinomas. However, whereas submandibular nodes are more seldom involved, high-posterior metastases occur more frequently than in posterior oral carcinomas. The most important regions however, are the high- and mid-jugular regions. Histopathological reports on the involvement of retro- and parapharyngeal lymph nodes are sparse.

Hypopharyngeal carcinomas also spread preferrably to the jugular chain nodes. All three levels can be involved, although the high- and mid-jugular nodes are involved most often. As with laryngeal carcinomas, isolated involvement of the submandibular or posterior nodes occurs rarely.

Small laryngeal carcinomas, confined to the vocal cords very seldom spread to the regional lymphatics. However, tumours originating from or extending into other sites in the larynx, have a tendency to spread to the high- or mid-jugular chain nodes primarily. The low-jugular lymph nodes are the second echelon. Although (large supraglottic) laryngeal carcinomas can spread primarily to the submandibular nodes, this occurs in only 1% to 5% of cases (6,14,15). The prelaryngeal and paratracheal lymph nodes are very seldom the only involved lymph nodes in glottic and subglottic tumours (10,16,17).

Nasopharyngeal carcinomas have a high propensity to metastasize.The high-jugular and the high-posterior lymph nodes make up the first echelons.

Nasal cavity and maxillary sinus carcinomas initially spread to the high-jugular lymph nodes or to the submandibular lymph nodes. However, initial invasion of the parotid lymph nodes might occur.

The patterns of metastases from skin (18) and thyroid carcinomas will not be discussed here.

1.4. PROGNOSTIC RELEVANCE OF NECK NODE STAGING

Prognostic data are important to guide therapy in cancer patients. The prognosis of any patient with cancer is determined by three types of factors: those determined by the tumour, those determined by the host and those determined by the treatment. For head and neck cancer patients, the status of the cervical lymph nodes is the single most important tumour related prognostic factor. Although some older studies and radiotherapeutical studies have derived their data from clinical information on the status of the neck (19,20), it is generally accepted that histopathological parameters of cervical lymph node metastases are more accurate and reliable (21-26). In this respect, the prognostic information obtained from radiological staging has never been assessed.

Prognosis is roughly diminished by half if lymph node metastases are present at presentation or develop during follow-up (21-32). Not only the incidence of loco-regional recurrence, but also the risk of distant metastases increases as the tumour burden in the neck increases. It is generally accepted that prognosis worsens as the number of metastases in the neck increases (22-29). However, some authors could not confirm this finding (30,33). Of those who studied the importance of the size of metastasis, some found no significant differences in prognosis (22,25), whereas others found that metastases larger than 2-3 cm were a bad prognostic sign (21,26).

Not only the number and size, but also the involved side of the neck relative to the primary tumour is important if the tumour is located strictly unilateral (22). Then, prognosis worsens in case contralateral or bilateral metastases are present (21,22). The level in the neck to which metastatic nodes extend (19-

21,23,25,28,32,34) and the presence of microscopic extranodal tumour spread (22-26,28,32-38) are genarally accepted to be important prognostic factors. Nodal fixation (equivalent to macroscopic extranodal spread) is considered to be a bad prognostic indicator as well (21-23,39,40), although again one author could not confirm this finding (25).

As lymph nodes might play an important role in tumour rejection, or as a temporary barrier for further dissimination (1,2,41,42), some authors tried to define prognostic histopathological features like lymphatic reaction patterns (43-48). However, these reaction patterns have not found acceptance as prognostic factors (24,35) and are not generally used.

Although lymph node metastases are the most important prognostic indicators, features of the primary tumour like site, size, extent, depth and pattern of infiltration, perineural or intravascular growth, differentiation and other parameters have been proven to influence prognosis. Although some of these features are subjective or difficult to assess, they can be used to assess the likelihood of occult lymph node metastases in the neck (24,25,29,31,49-57). Other factors, like ploidy or DNA content and amplification of different oncogenes, have not yet proven to be reliable prognosticators (58-61).

Prognostic factors that are not tumour related include patient related prognostic factors like sex, age and immunologic competence of the patient, and of course treatment related prognostic factors (19,25,27,31,62,63).

1.5. THERAPEUTICAL RELEVANCE OF NECK NODE STAGING

1.5.1. Treatment of lymph node metastasis.

In patients who have clinical evidence of nodal involvement, neck dissection is the most widely accepted treatment. However, it has been recognised that the incidence of recurrence in the neck after neck dissection is high in patients with histopathological evidence of extranodal spread or multiple involved nodes (22,26). In an attempt to increase the cure rate, a combination of radiotherapy and surgery - first described by Martin in 1941 (64) - gained popularity in the 1960's. Nowadays, a combination of surgery and postoperative radiotherapy is generally accepted to increase the effectiveness of therapy in patients at high risk to develop loco-regional recurrence (22,25,26,32,34, 37,39,65-67). In the last two decades, several modifications of the classical radical neck dissection have been described. First of all there has been an increasing trend to preserve the spinal accessory nerve and/or the internal jugular vein and/or the sternocleidomastoid muscle, whereas all lymph node groups are removed (i.e. modified radical neck dissections, comprehensive neck dissections). The reasons for these modifications were functional and cosmetical, while oncological safety was preserved. More recently the concept of selective neck dissection has been introduced (6,10). In selective neck dissections only those groups of lymph nodes are removed, which depending upon the location of the primary tumour are most likely to contain metastasis.

Small (often clinically occult) metastasis can be cured in a high percentage of cases with either surgery or radiotherapy (10,66,68-73). In this regard, the efficacy of selective neck dissection (or in line with this, partial neck irradiation), that is currently advocated both as staging and as curative procedure for the N0 neck, has yet to be proven (10,66,69-73). The choice to treat the N0 neck with either surgery or radiotherapy should mainly depend on the treatment chosen for the primary tumour.

1.5.2. Management of the N0 neck.

In principle the neck needs no treatment if no metastases are present. One of the major problems for optimal treatment planning of the neck is the inability to accurately stage the neck by palpation (74). The known fallibility of palpation is a major cause of improper treatment of the neck and delayed identification of recurrences in the neck. The resulting treatment controversies will be discussed.

Because palpation is inaccurate in detecting early metastasis in the neck, many institutions employ prophylactic neck treatment if the risk of occult metastasis is estimated to be higher than 15% to 20%. As indicated in the paragraph 1.4, this risk is estimated on the basis of known prognostic factors of the primary tumour (20,28,49-56) (Table 1.1, see also Tables 4.1 and 6.1).
A further indication for prophylactic neck dissection exists when the primary tumour is treated by excision via the lateral neck, as in most pharyngeal and posterior oral cavity tumours. There are several reasons for this policy. First of all, sectioning of the lymphatics of the neck during the excision of the primary tumour may cause spill of tumour cells in the neck and can change the pattern of metastases if occult metastases are left behind. Furthermore, in case of a bulky reconstruction, using for example a pectoralis major flap, the neck dissection can provide the necessary space in the neck. In our institution the neck is treated electively in all carcinomas, except for sino-nasal, T1-2 laryngeal and T1 oral carcinomas.

Primary Tumor	T-Stage	Metastases %
Oral tongue[75]	T1	18
Oral tongue[75]	T2	33
Oral tongue[75]	T3	60
Floor of mouth[76]	T1	38
Floor of mouth[76]	T2	65
Floor of mouth[76]	T3	71
Subglottic[77]	Tx	19
Supraglottic[77]	Tx	33
Supraglottic[78]	T1-3	22
Supraglottic[78]	T4	44
Transglottic[77]	Tx	52
Hypopharynx[79]	T2	63
Hypopharynx[79]	T3	68
Hypopharynx[79]	T4	100

Table 1.1. Percentage lymph node metastases versus primary tumor site and stage.

The most important advantage of prophylactic treatment is that occult metastases are treated in an early stage, ensuring a low incidence of multiple metastatic nodes and extranodal tumour spread (66,80). Proponents of elective treatment maintain that treatment delay is unacceptable because during this delay the histopathological stage of the disease in the neck and the risk of distant metastases can increase. Furthermore, histopathological examination of the obtained specimen reveals important prognostic information and can direct further treatment at an early stage (19,22,25,32). However, the most important disadvantage of elective treatment of the neck is that many patients are treated in the absence of lymph node metastases. In these patients the risk of postoperative complications and functional or esthetic impairment is unnecessarily increased.

The major question in this respect concerns the influence of delayed versus prophylactic treatment on prognosis. Although a delay of treatment will almost certainly have an adverse effect on survival, this has not been proven yet, and will probably depend upon the duration of the treatment delay. Although most studies on this subject found a benefit of elective neck dissection over therapeutical neck dissection on survival (11,81-87), only the study by Fakih et al. (82) was a randomized prospective one, and showed no significant difference in survival. Moreover, other studies did not demonstrate a difference in prognosis between delayed neck dissection and prophylactic neck dissection (76,80,88). However, again only one of these studies - by VandenBrouck et al. (80) - was randomized prospective. Nahum et al. (89) gave a comprehensive overview over literature, in which arguments pro and contra elective treatment are analyzed.

To avoid overtreatment, a "wait and see" policy for clinically negative sides of the neck that do not have to be entered for primary tumour excision can be propagated. Apart from avoiding morbidity of overtreatment, this policy avoids disruption of the normal lymphatic pathways in the neck thus preserving the possible barrier function of lymph nodes to future local recurrences or second primaries. The most important drawback of this "wait and see" policy, is that undertreatment necessitates therapeutical rescue neck treatment in too many patients. Therefore, this policy is less popular.

The third option, that is becoming more and more popular, entails a more accurate assessment of the status of the cervical lymph nodes. This can be done by a (selective) staging neck dissection using peroperative frozen section biopsy, or by modern radiological or scintigrafical imaging techniques. An accurate radiological technique that detects occult metastasis would be ideal to select patients who should, and who should not be treated on behalf of their neck, if the risk of occult metastases can be brough below 10-15%. This technique should idealy be available both for initial work-up and follow-up. The imaging modalities that are at our disposal to stage the neck will be discussed in the next paragraphs and chapters.

The major advantage of a selective staging neck dissection over radiological techniques is that histopathological evidence of metastasis is more reliable than radiological evidence (66,90). However, small metastases can be missed using fresh frozen biopsies as well, and peroperative sampling of the wrong nodes for frozen biopsy is a major problem, causing 10-17% false negative reports (66,90). The major disadvantage however, is that this technique is not without morbidity. Furthermore, a false negative frozen section examination can even increase morbidity, because it necessitates postoperative radiotherapy, that would have been avoided if the metastasis was detected earlier and some type of comprehensive neck dissection would have been carried out. On the other hand there is a tendency to refrain from postoperative radiotherapy if only one or two metastases are found in a selective neck dissection specimen (10,73). This policy however, has not proven to be effective on the long range. A further restriction of staging neck dissections, that does not apply to radiological screening for occult metastases, is that staging neck dissections will not be carried out in patients with primary tumours that carry only limited risk of occult metastases.

1.5.3. Management of the N+ neck.

Palpatory evidence of metastasis in the neck is almost as unreliable as negative palpatory findings on the neck (74) (see also table 6.1). The great number of overtreated sides by treating all palpatory positive sides of the neck can again only be reduced by an accurate preoperative staging technique. This is especially the case for sides of the neck in which borderline nodes are palpated. However,

most head and neck surgeons tend to rely on their findings at palpation and will perform at least a selective neck dissection in case of conflicting findings at palpation and radiology.

Another problem in the preoperative assessment of the neck concerns the extent of large metastasis. Although preoperative imaging techniques might play a role in determining invasion of vital structures, as the vertebral bodies or the (internal) carotid artery, most reports on this issue show that CT, MR or US can only exclude invasion with relative certainty (91-93). In this thesis, preoperative imaging for these indications is not studied.

1.6. ASSESSMENT OF CERVICAL LYMPH NODE METASTASES

Assessment of the neck is still mainly based upon palpation. Palpable nodes are classified as suspect according to their size, consistency and location. Until 1987, the UICC and the AJCC used different classifications for neck lymph node involvement. In 1988 the last remaining difference between the two classification systems, which regarded the importance to be attached to laterality, has been smoothed away (Table 1.2). The validity of any classification depends on the staging procedure employed. In this regard, the updated UICC and the AJCC classifications for the neck, although incorporating a "certainty factor", do not insist on additional staging procedures to be used for the neck. It is unfortunate

Nx :	the neck can not 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 in largest dimension

Table 1.2. UICC (1987) and AJCC (1988) classification of the neck.

that the recent revisions of the classification have not incorporated level of involvement of cervical lymph nodes, which has been proven to be prognostically important (19-21,23,25,28,32,34).

Studies on clinico-pathological correlation have demonstrated that both the false positive rate and the false negative rate of the palpatory findings are unsatisfactorily high (74,94) (see also tables 4.1 and 6.1). Furthermore, the accuracy of palpation with regard to number and size of involved nodes leaves much to be desired. The consequences of this inaccuracy of palpation for treatment policy have been discussed above.

The main question this thesis attempts to answer is whether modern imaging techniques can do better than palpation for neck node staging. The following paragraphs give an overview of recent and previously used imaging techniques of cervical lymph nodes.

1.6.1. Computed tomography.

The advent of large computer systems in the 1970's allowed digital image reconstruction as used in CT scanning. The CT image is made up of a series of points in a matrix (256-1024 lines per axis), each point representing the absorption value to an x-ray beam. Third generation scanners, like the one we used in this study, are characterized by a smooth moving x-ray tube that moves around the patient opposed to multiple detectors, enabling acquisition times of 10 seconds or less.
Since the late 1970's CT examinations have gained widespread popularity in staging cancer of the head and neck. From 1981 until we started this study (95-99) and since 1989 (100-102) many studies showed the advantages of CT over palpation. However, other authors found CT to be comparable or slightly less accurate than palpation, and consequently did not recommend this technique for staging purposes of the neck (103,104). It remains difficult however to reliably compare different studies on this subject as often different criteria for malignancy were used, whereas the older studies used low resolution CT scans and slice thicknesses of 1 cm or more. None of these studies described the exact histopathological procedures used to detect (micro)metastases in the neck dissection specimen, which might be a reason for underestimating the incidence of these metastases. Furthermore, in none of the above cited studies CT was compared to other imaging techniques.

High resolution CT scanning gives excellent anatomical information. To reliably discriminate between lymph nodes, vessels, muscles and salivary glands, intravenous administration of an iodine containing contrast agent is neccessary. Window level and width settings are critical in evaluating the enhancement patterns inside these nodes, and should be adjusted as much as possible on an individual basis. On contrast enhanced CT scans, lymph nodes and viable tumour metastases are depicted with intermediate density, mostly inbetween the density

of muscle and vessels, very similar to salivary glands. Although the use of dynamic contrast studies, making images after different time intervals after contrast injection, has been recommended to differentiate between benign and malignant nodes (105), this technique is unpractical and has not proven its value.

The enhancement pattern seen in cervical lymph node metastases is often characteristic, showing an irregular enhancing rim of viable tumour and/or lymph node tissue surrounding a low density center of tumour necrosis. In this respect, fat tissue inside lymph nodes can cause false positive results at CT. It remains striking, but unexplained that this typical pattern of enhancement seen in neck lymph nodes that are partially occupied with necrotic tumour tissue is not frequently encountered in lymph node metastases from squamous cell carcinomas elsewhere in the body, and is consequently not used as a criterion elsewhere in the body (106).

Apart from necrosis that is used by most authors as a criterion for malignancy of lymph nodes, many different criteria concerning size, grouping and obliteration of fat planes are described in the literature (see chapter 3).

Comparing the results of recent studies to older ones shows that thin ($\leq$ 5-6 mm) slices are more reliable than thick slices, as small necrotic foci are depicted more reliably and lymph node size can be measured more precisely. However, our own findings have shown that if very thin slices (3 mm) are used, unexplained irregular enhancement patterns inside lymph nodes can occur, causing false interpretation of tumour necrosis.

Apart from its value for staging the neck, CT scans can be used simultanously to stage the primary tumour. Furthermore, the CT scan can be of value as a permanent document than can be reviewed during follow-up or used as a guide for radiotherapy planning. The depiction of infiltration of tumour into the wall of the carotid artery, although not always reliable, might be useful as well (91,92). However, disadvantages of CT scanning are the risk of adverse reactions to iodine contrast agents and exposure to ionizing radiation.
In our study, we tried to define optimal CT criteria for malignancy, and prospectively compared the accuracy of CT with other radiological modalities.

1.6.2. Ultrasound and US-guided FNAC.

Ultrasound (US) uses the reflected high frequency sound waves, that are intermittantly generated and detected by piezoelectric crystals in a transducer as a signal

(107). By electric transformation and (frequently) computerized processing, the reflected sound waves are transformed into a two dimensional image. In B-mode scans a tomogram deep to the transducer is depicted, in which the amount of reflected sound is depicted by the brightness of a dot on the image. Differences in acoustic impedance between tissues and the homogenity of the tissues determine the amount of reflected sound waves. For the neck, 7.5 - 10 MHz linear array, real-time B-mode transducers are optimal, although sector or phase-array transducers can be used as well. The resolving power of an US system is proportional to both the duration and frequency of the sound pulse (axial resolution) and the focusing of the transducer (lateral resolution) (108,109). For 7.5 MHz tranducers the axial (depth) resolution is in the range of 0.5 mm, whereas the lateral resolution at focus distance is in the range of 0.7 mm. On the other hand, the depth of infiltration of the sound waves decreases as the transducer frequency increases. Systems that use 7.5 MHz transducers are designed to image a depth of approximately 3 to 4 cm. The detectability of a lesion also depends on its contrast to the surroundings and the noise of the system (108,109).
Although freeze-frame mechanisms allow permanent recording on a film, the lack of dynamic information and topographical landmarks on the image make the US examination unsuitable for retrospective evaluation. This limitation puts great stress on the skill and motivation of the ultrasonographer.

Tissue characterisation with use of US has been studied (110), but reliable differentiation between malignant and benign lesions was never accomplished. Lymph nodes that are reactively enlarged are depicted as low- to anechogenic well circumscribed masses, sometimes resembling cysts. However, solid metastases can not be reliably differentiated from these reactive lymph nodes on the basis of their reflection pattern. Tumour necrosis mostly reflects more sound waves, whereas keratin in tumours has a hyperechogenic appearance at the images. Fat tissue is depicted as a hyperechogenic area as well, reflecting more sound than muscle tissue. Salivary glands are depicted with a very regular pattern of hyperechogenic spots, very similar to thyroid tissue. Because bone (mandible) and air interfaces reflect all sound waves, no signal from underlying structures can be visualized.

In the older reports, in which 2.0, 3.5 or 5.0 MHz transducers were used, resolution was relatively poor, and the authors concluded that US was fit only for evaluating size, extent and number of nodes (111-114). Although later studies using 7.5 MHz, 10 MHz or broad-band transducers showed the efficacy of US in detecting even small cervical lymph nodes, the size of the nodes remained the most important criterion to differentiate between malignant and reactively enlarged nodes (115-121). Although some authors studied other sonographic criteria

(117,118), none of these has proved its value in discriminating metastatic from reactively enlarged nodes (121,122). Ultrasound has proved to be relatively reliable in assessing the absence of tumour infiltration into the internal jugular vein or the carotid artery (wall) (91,115,116,119) and was useful to detect early regional recurrences according to one author (115). In our study, the accuracy of different size criteria for US were evaluated.

Since 1988 some important studies on US-guided FNAC were published (123-129). The great advantage of obtaining cytologic material from lymph nodes visualized at US, is that descriptive radiological criteria for malignancy, that can give rise to false results, are replaced by more accurate "tissue diagnoses" from aspirates. Furthermore, it has proved to be a safe, quick and inexpensive technique, that can be used for follow-up. A major shortcoming of the above cited studies is that none addressed the accuracy of the US-guided FNAC examination for previously untreated clinically negative necks. Furthermore, histopathological examination was not always performed to confirm negative cytologic results.

In this thesis we focussed on the accuracy of this technique for clinically negative sides of the neck (chapters 5 and 6), and tried to formulate guidelines to select the most suspicious lymph nodes for aspiration. Furthermore, this technique was prospectively compared to the other radiological techniques.

1.6.4. Magnetic resonance imaging.

Magnetic resonance (MR) imaging is based on the principle of nuclear magnetic resonance (NMR). In 1946, E.M.Purcell (130) and F.M.Bloch (131) independently revealed their findings on NMR. The idea of NMR resulted from the observation that energy is absorbed and subsequently released by nuclei following excitation by electromagnetic waves of a specific resonant frequency. Since its inception, NMR-spectroscopy has become a powerful analytical tool for chemists and physicists. However, all measurements were averaged over the entire sample until 1973, when P.C.Lauterbur published the first spatially differentiated NMR measurements (132). Since that time, progress has been very rapid and has enabled the adoption of MR imaging as a standard procedure in medical diagnosis. The nuclei of many atoms (e.g. ^{1}H, ^{13}C, ^{31}P) have magnetic dipole moments and thus act as small bar magnets with different resonant frequencies. Because of the high concentration of protons (H) in the human body, and their relatively large magnetic moments, MR imaging uses these protons to emit a signal. By

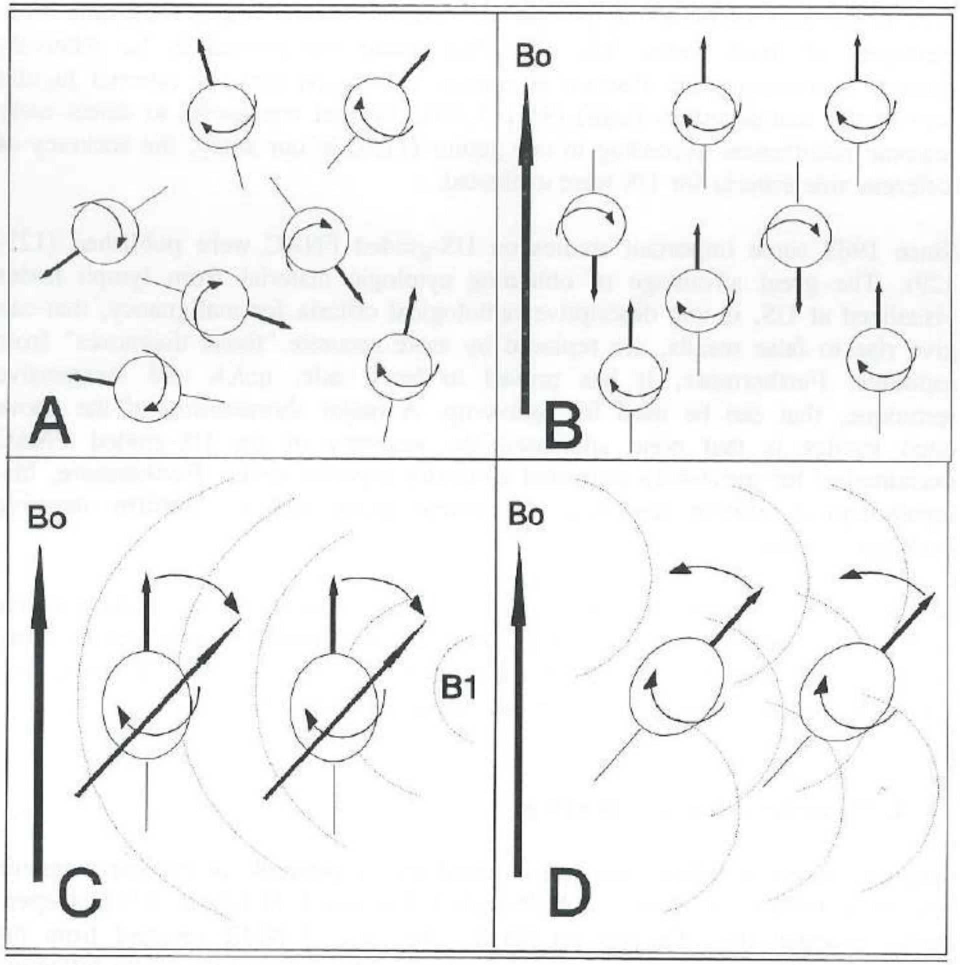

Figure 1.3. States of proton magnetisation. A. No external magnetic field, random magnetic dipole moments. B. External magnetic field (Bo) causing alignment of the dipole moments parallel or antiparallel to this field. C. Excitation by a electromagnetic pulse (B1) causing the magnetic dipole moments to flip over an angle. D. After cessation of the electromagnetic pulse the dipole moments the dipole moments re-align to the external field while emitting electromagnetic waves that can be detected.

applying a strong magnetic field (0.5 - 2 Tesla in commercial MR systems), the magnetic moments of spinning nuclei tend to align parallel (majority) or antiparallel (minority) to this field, giving rise to a macroscopic vector (sum of magnetic moments) parallel to the external field (figure 1.3).

By applying an external perpendicular force to the nuclei with use of an electromagnetic wave of resonant frequency (radiofrequency pulse), the net magnetisation vector can be tipped to any angle in the magnetic field, depending on the strength and duration of this electromagnetic wave. After cessation of the radiofrequency pulse, the vector will return to its equilibrium position. The rate at which equilibrium is restored is determined by the T1 and T2 relaxation times, that are tissue dependant. During this relaxation, the nuclei emit the absorbed energy in the form of electromagnetic waves. These electromagnetic waves that have the energy of radiofrequency waves as well, can be detected by coils (133,134).

To obtain tomographic images at any plane of the body, gradient magnetic fields are applied to manipulate the resonant frequencies and phase angles of different sites within the imaged object. By modulating the interval between (TE,TR,TI) radiofrequency waves and different gradients, different tissue characteristics can be highlighted. Essentially, all tissues are characterized by four parameters (133): a specific hydrogen density, a T1 relaxation time and a T2 relaxation time. Furthermore, flow (movement) has specific signal characteristics, that are based on the fact that the imaged volume does not correspond to the excited volume.

The depiction of a lesion in MR imaging depends on the signal to noise ratio, the spatial resolution and the contrast of the lesion to its environment (135,136). All these parameters can be influenced by the equipment and imaging techniques used. Because partial volume and surface coils increase the signal to noise ratio and the spatial resolution, these coils are essential for head and neck imaging (137,138). Of the multiple MR imaging artifacts that can occur in the neck region, movement artifacts by swallowing and respiratory movements are the most disturbing. To overcome motion artefacts, recently developed motion compensating techniques such as pulse gating and refocussing gradients are promising, but have not proven their value for swallowing artifacts. As yet, patient instruction and short acquisition times are essential to minimize motion. However, shortening imaging time is often accompanied by a decrease in contrast/signal to noise ratio (139).

Many techniques are possible for the depiction of head and neck lesions, but all have advantages and disadvantages (140,141). The MR imaging techniques in most common use, are the spin echo and gradient refocussed echo techniques.

The spin echo technique is the most useful for most parts of the body. In this technique, both T1- and T2 relaxation times contribute to signal intensity and thus to contrast. Several milliseconds (TE or echo-time/2) after the initial excitation (90^0 pulse), a second pulse is applied which is strong enough to tip the spin through 180^0. The spin echo signal can be recorded at TE/2 ms after this 180^0 pulse. Additional echoes can be elicted by repeatedly applying 180^0 pulses. The sequence can be repeated at different time intervals (TR). MR images can be T1-weighted, T2-weighted, proton density weighted or anything in between. For most tissues T1-weighting can be obtained by a short repetition time (TR $< \approx$ 650 ms) and a short echo time (TE $< \approx$ 30), whereas T2 weighting increases as both TE and TR are lengthened. T1-weighted images demonstrate normal anatomical structures with optimal detail. Squamous cell carcinoma is depicted with low to intermediate signal intensity on T1-weighted images, whereas the signal intensity relative to muscle and fat tissue increasesin T2-weighted images. The advent of paramagnetic contrast agents like Gadolinium-DTPA, that shorten the spin-lattice relaxation time (T1), has further increased the soft tissue discrimination potentials of MR imaging, by selective enhancement of mucosal linings, tumour tissue and inflammatory lesions (142, 143).

The great potential of MR in discriminating soft tissues was the most important incentive for this study. Rapidly increasing imaging possibilities with MR, due to the development of partial volume coils (surface coils), more sophisticated software for faster imaging (e.g. gradient refocussed echo) and the introduction of Gadolinium-DTPA as a paramagnetic contrast agent, motivated us to define the value of MR for cervical lymph node imaging. Although some studies on MR imaging of neck node metastases and some comparative radiological studies have been published during the period of this study (see chapter 6), none of these prospectively compared all modern radiological techniques, nor did they study a large group of patients.

In this thesis we compared several imaging techniques, such as spin echo and gradient refocussed echo with or without gadolinium-DTPA, to assess the optimal imaging techniques for neck node depiction. Furthermore, the accuracy of MR imaging was compared to that of other imaging modalities.

1.6.5. Other imaging modalities.

Some techniques were not evaluated in this study. Among these are lymphography, lymphoscintigraphy, immunoscintigraphy and proton emission tomography (PET).

In line with lymphographic studies of pelvic lymph node disease, in the past some authors studied lymphography of lymph node metastases in the neck using intralymphatic injection of contrast (144,145). This technique has never become very popular because of time consuming procedures and serious problems with criteria for malignancy of depicted nodes.

Although ^{99}Tc-lymphoscintigraphy, using local or intravenous injection of technetium that is not labelled to antibodies, can depict the anatomy of the lymphatic drainage pathways and assess the radicality of neck dissections, these techniques have no role in detecting early nodal metastasis in the neck (146, 147). Immunoimaging uses the scintigraphic detection (plain images or SPECT scans) of radiolabelled monoclonal antibodies targetted against squamous cell carcinoma of the head and neck. The great theoretical advantage of this technique over all other imaging modalities is the very specific binding of the monoclonal antibody to the tumour. Recently, our head and neck oncology research group has started a study in which technetium labelled E48 (148) is used to detect regional and distant metastases of head and neck carcinomas. Although the first results are very encouraging, a number of practical problems still have to be resolved.

PET uses metabolic imaging agents that are positron emittors. Examples of such emittors are isotopes such as ^{11}carbon or ^{15}oxygen that can easily be built in metabolic substances. The greatest potential of this technique relates to its potential in evaluating metabolic activity (and maybe also cell proliferation rates?) of any site in the body. No studies on this technique and neck node metastases have yet been published. Currently, the radiological department at UCLA in the USA, is studying this technique in relation to neck node metastasis (personal communication).

1.7. STATISTICAL ANALYSIS

To compare different radiological modalities or different criteria for malignancy, different statistical measures can be used. The sensitivity is defined as the chance of positive findings with a certain criterion (or test) in a metastasis containing side (or node), while the specificity is the chance for negative findings when no tumour is found in the specimen (or node). The accuracy is the proportion of all test results that are correct, whereas the overall error expresses the chance that test results are incorrect. The positive predictive value is defined as the probability of having metastasis, given a positive test result, whereas the negative predictive value is the probability of not having metastasis if the test results are negative. The false positive rate is the probability of not having metastasis, given a positive test, whereas the false negative rate is the chance of having metastasis if the test results are negative.

Estimations of the values of currently used statistical measures can be derived from the following scheme.

		METASTASES	
		Present	Absent
TEST	Positive	a true positive	b false positive
	Negative	c false negative	d true negative

Prevalence of metastasis	$= (a + c) / (a + b + c + d)$
Sensitivity of the test	$= a / (a + c)$
Specificity of the test	$= d / (b + d)$
Accuracy of the test	$= (a + d) / (a + b + c + d)$
Overall error of the test	$= (c + b) / (a + b + c + d)$
Positive predictive value	$= a / (a + b)$
Negative predictive value	$= d / (c + d)$
False negative rate	$= c / (c + d)$
False positive rate	$= b / (a + b)$

A few remarks on these statistical measures should be made. Because sensitivity and specificity express the relation between test findings to the pathological outcome (gold standard), these measures are generally accepted to be characteristics of a certain test and thus independent of the population studied (i.e. the prevalence of nodal metastases). However, this is not entirely true. On can imagine that if the prevalence of neck node metastases is very low (as in a random non-head and neck patient population, but also when looking at all nodes in this study), the specificity remains relatively high over a large range of sensitivity values. On the other hand, if almost all patients studied do have metastases, the sensitivity will stay relatively high over a large range of different specificity values.

Measures such as accuracy and overall error (i.e. 1 - accuracy), are even more dependent on the patient population studied. Mathematically this can be shown by the following formula: accuracy = (sensitivity x prevalence) + (specificity x (1 - prevalence)). The same holds true for the positive and negative predictive value and the false positive and negative rate, as these measures compare test data with other test data. Mathematically this can be shown by the following formula: Positive predictive value = (prevalence x sensitivity) / ((sensitivity x prevalence) + ((1 - specificity) x (1 - prevalence))).

Because head and neck cancer populations differ in each center, in this thesis we will work as much as possible with sensitivity and specificity, that are relatively independant of the patient population.

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Chapter 2

DETECTION AND CHARACTERIZATION OF METASTATIC CERVICAL ADENOPATHY BY MR IMAGING: COMPARISON OF DIFFERENT MR TECHNIQUES

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Thirty-five patients scheduled to undergo a neck dissection for squamous cell carcinoma of the head and neck, were evaluated preoperatively by Magnetic Resonance (MR) imaging. Axial, and occasionally sagittal and coronal images were obtained.
To define the most reliable technique to detect cervical lymph node metastasis, we compared several MR pulse sequences with and without Gadiolinium (Gd)-diethylenetriaminepantaacetic acid (DTPA) administration to histopathologic findings in the neck dissection specimens.

T1-weighted spin echo (SE) combined with T2-weighted gradient refocussed echo (GE) sequences were found to be more useful than any other combination of pulse sequences in localizing lymph nodes. On T2-weighted GE images, lymph nodes were depicted with intermediate to high signal intensity in contrast to low signal muscular and fatty tissue. Gadolinium-DTPA enhanced T1-weighted GE images reliably depict central lymph node necrosis, the most specific criterion for lymph node metastasis.

2.1. INTRODUCTION

Assessment of the status of the neck in patients with squamous cell carcinoma of the head and neck remains a problem. Although one recent study still doubts its value (1), computed tomography (CT) has proven its ability to upstage clinically negative necks (2-5).
Enlarged cervical lymph nodes are reliably shown by magnetic resonance (MR) imaging (6-12). However, MR has not yet proven its accuracy in demonstrating tumor necrosis in lymph nodes.
The potential of recently developed imaging techniques, such as T1- and T2-weighted gradient refocussed echo (GE) and the potential of Gd-DTPA enhanced T1-weighted spin echo (SE) and GE images, for imaging neck nodes have not been explored.

In a previous study we showed the value of a surface (partial volume) coil for neck imaging (13). In the present study we used this coil to compare the appearance of cervical lymph node and their contrast to surrounding tissues with various MR techniques, to establish an optimal imaging protocol for neck node imaging and staging.

2.2. MATERIALS AND METHODS

Thirty-five patients scheduled for a therapeutic or elective neck dissection for squamous cell carcinoma of the upper air and food passages, were examined preoperatively with MR. The treatment of the neck was not influenced by the MR staging of the neck, and depended fully of the site and extension of the primary tumor and the clinical (palpatory) status of the neck.

The study population consisted of 11 women and 24 men, 25-78 years of age. Fourteen patients had oral carcinoma, 13 patients had pharyngeal carcinoma, and 8 patients had laryngeal carcinoma. Twenty patients underwent unilateral and 15 bilateral neck dissections, usually in continuity with the excision of the primary tumor. Of the 35 patients studied, 22 proved to have unilateral and 4 bilateral lymph node metastasis on histopathologic examination. In nine patients the pathologist found no cancer in the neck dissection specimens (Table 2.1).

Images were made on a 0.6 T Teslacon MR system (Technicare, General Electric), using a semi-saddle-shaped surface (partial volume) coil. Section thickness was 5 mm with 50 % interslice gap. Field of view was kept as small as

Patient	Staging R\L		Neck	Metast.	Necros.	MR
sex,age	Cinical	MR	treatm	R\L	R\L	Techn.
1(m,34)	-\-	-\-	1	1\-	0\-	1,3,4
2(m,52)	++\+	++\+	1	25\-	1\-	1,3,4
3(f,41)	+\+	++\++	2	8\6	1\1	1,2,3
4(m,56)	-\++	-\++	1	-\4	-\1	1,2,5
5(m,62)	-\-	Nx	2	2\0	1\0	1,2,3
6(f,25)	-\+	-\+	2	0\1	0\1	2,3,5,6
7(m,58)	-\++	±\++	1	-\1	-\1	1,2
8(m,53)	-\++	-\±	2	0\1	0\1	1,2,5,6
9(m,52)	-\-	-\±	2	0\2	0\0	1,5,6
10(m,71)	-\+	+\+	2	1\0	0\0	1,3,6
11(m,53)	+\-	++\-	1	13\-	1\-	1,3,6
12(m,56)	-\-	++\-	1	4\-	1\-	3,4,5
13(m,59)	-\+	-\+	2	0\1	0\1	1,3,5
14(f,66)	-\+	-\-	2	0\0	0\0	3,4,5
15(m,69)	++\-	++\-	1	5\-	1\-	3,4,5
16(f,47)	-\+	Nx	2	0\2	0\0	1,3
17(f,54)	-\-	-\-	1	0\-	0\-	3,5
18(f,54)	+\-	++\++	2	3\2	1\0	2,3
19(f,75)	+\-	++\-	1	3\-	1\-	3,5
20(m,61)	-\-	-\-	1	0\-	0\-	1,3
21(m,38)	+\-	+\-	1	2\-	1\-	3
22(f,64)	+\-	+\-	1	2\-	1\-	3,5
23(m,54)	++\+	++\+	2	11\8	1\1	1,3,6
24(m,78)	-\+	-\+	1	-\3	-\1	3,5
25(m,58)	-\-	-\+	2	0\1	-\1	3,5
26(m,46)	+\+	++\++	2	7\9	1\1	3,5
27(m,68)	-\-	-\-	1	0\-	0\-	3
28(m,64)	-\-	-\-	1	-\0	-\0	3,5
29(f,59)	-\-	-\+	1	-\0	-\0	3,5
30(m,76)	-\+	-\+	1	-\3	-\1	3,5
31(m,64)	-\++	-\±	2	0\0	0\0	3,4,5
32(m,75)	-\++	-\+	1	-\1	-\1	3,4,5
33(f,56)	+\-	+\-	1	2\-	1\-	3,4,5
34(m,56)	-\-	-\-	1	-\0	-\0	1,3,6
35(f,60)	-\-	-\-	2	0\0	0\0	1

Table 2.1. The first two columns show the clinical and MR staging of both sides of the neck (-= no suspect nodes, += one suspect node, ++= 2 or more suspect nodes, ±= borderline node(s), Nx= insufficient data to stage the neck). The third column indicates the treatment of the neck (1= unilateral neck dissection, 2= bilateral neck dissection. The fourth and fifth columns show the number of positive nodes in the specimen, and the presence (1) or absence (0) of considerable (≥ 3mm) tumor necrosis (-= no neck dissection on that side). The last column shows the variable MR techniques used (1=axial proton density and T2-weighted SE, 2=axial T1-weighted GE, 3=axial T2-weighted GE, 4=axial Gd-DTPA enhanced T1-weighted SE, 5=axial Gd-DTPA enhanced T1-weighted GE, 6=coronal T1-weighted SE).

possible (220 x 180 mm) and acquisition matrixwas 256 x 160-192. After a sagittal T1-weighted SE series (SE 250ms/22ms, 4 excitations, 7 slices) as a scout scan, axial T1-weighted SE images (SE 595 ms/20 ms, 4 excitations, 17 slices) were made in each patient. The T2-weighted and proton density SE images (SE 2000 ms/64 ms; 2000 ms/32 ms, 2 excitations, 17 slices) were obtained in 16 patients. In 31 patients T2-weighted GE images (GE 280 ms/32 ms, flip angle 8^0-12^0, 6 excitations, 3 - 5 slices), and in 7 patients non-enhanced T1-weighted GE images were made.

In 23 patients Gadoliniumd-DTPA (Magnevist, Schering) (8 mg/20 ml i.v. bolus injection) was administered, and T1-weighted SE (SE 595 ms/20 ms, 4 excitations, 17 slices) and/or T1-weighted GE images (GE 125 ms/15 ms, flip angle 45^0, 6-8 excitations, 3 x 3 slices) were obtained post injection. In 7 patients additional coronal T1-weighted SE images were obtained.

All MR scans were thoroughly examined by two observers (MWMvdB and JAC), who compared the scans with the histopathologic outcome. The signal intensities of metastatic and reactively enlarged nodes, muscle tissue, fat and salivary gland tissue were measured in all patients with measurable nodes (Fig 2.1). Because of the use of a partial volume coil, the signal intensities had to be measured, as far as possible, in the same coronal plane. This enabled us to compare relative signal intensities of the above mentioned tissues with different techniques.

To reliably compare histopathologic examination and the images, a radiograph of all neck dissection specimens was obtained using a Philips mammodiagnost U-M. For this purpose the specimens were immersed in 96% ethanol (14). Next, the specimens were fixed in formaldehyde 4% for 48 hours and all lymph nodes were examined histopathologically. Not only the presence of tumor, but also the size of the nodes, and the amount of necrosis were recorded. We retrospectively compared the location and size of each lymph node seen on MR images with the location and size of the node on the specimen radiograph and the histopathologic outcome.

2.3. RESULTS

Figure 2.1 presents the signal intensities of different tissues relative to muscle tissue. It clearly shows that reactively enlarged as well as metastatic lymph nodes are not characterized by a specific signal intensity in any pulse sequence with or without Gd-DTPA. Contrast between lymph nodes and fat or muscle tissue is optimal in the T2-weighted GE technique.

In two patients (Cases 5 and 16) none of the images could be interpreted due to movement artifacts (Nx). Six representative cases out of a series of 35 have been selected to show the value of T1-weighted SE, T2-weighted GE and Gd-DTPA enhanced T1-weighted GE images (Figs 2.2-2.7).

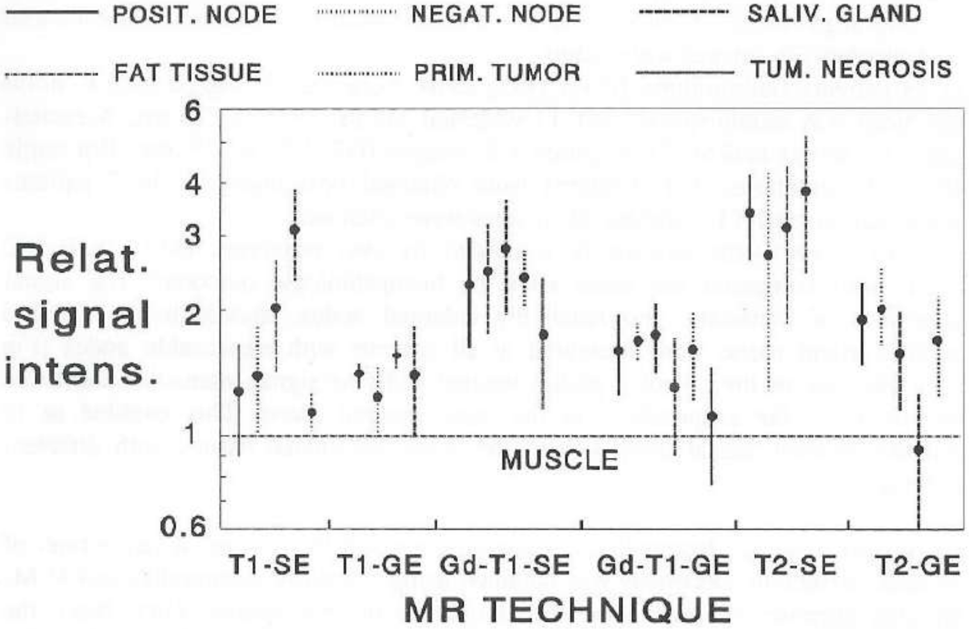

Figure 2.1. Plots (mean ± SD) of the relative signal intensities of some tissues in different imaging techniques with and without Gd-DTPA, measured on screen in all enlarged lymph nodes of which the histology was certain. All signal intensities were normalized relative to that of muscle tissue signal intensity (=1), as much as possible in the same coronal plane. The black points indicate the mean values, while the lines indicate one SD to both sides. The large spread and overlap of signal intensities can be partially explained by the use of a surface (partial volume) coil.

2.3.1. Techniques.

Axial T1-weighted SE images were found to be the most reliable for detecting cervical lymph nodes in most patients. Lymph nodes tended to have a slightly

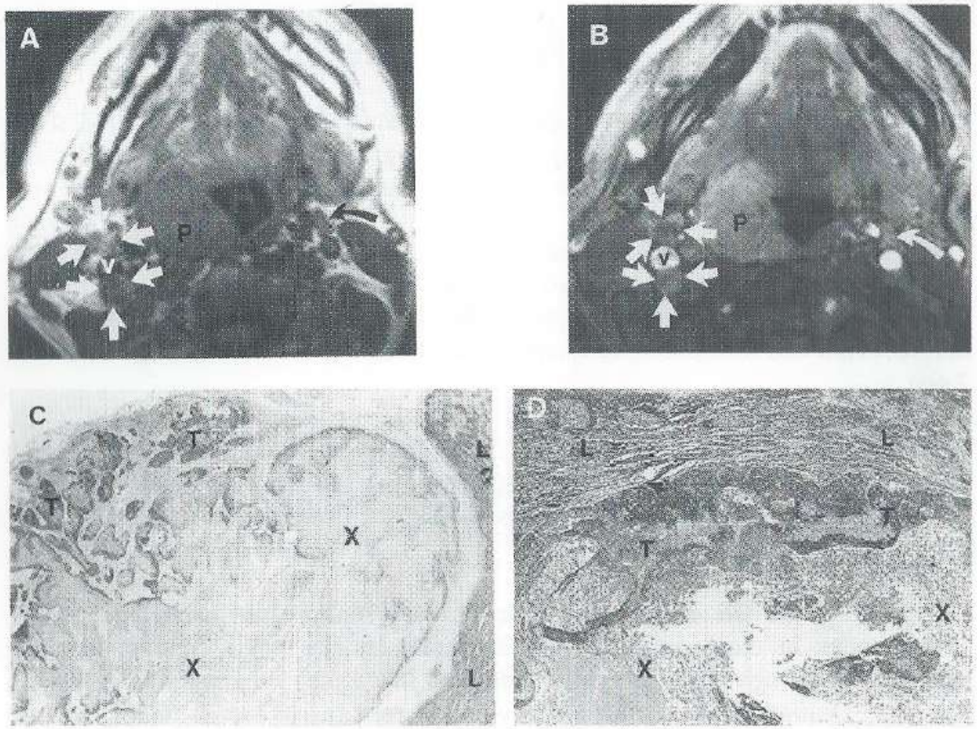

Figure 2.2. A. T1-weighted SE image of case 12: T4N0 oropharyngeal carcinoma. Ventral and dorsal to the internal jugular vein (v), two borderline subdigastric nodes can be seen (arrows) with the same signal intensity as muscle. The carotid artery lies between the primary tumor (P) and the internal jugular vein (v). On the left side a small node is depicted (curved arrow). B: Gd-DTPA enhanced T1-weighted GE image. The tumor and the metastatic nodes are depicted with intermediate signal intensity. Both nodes on the right side show a low signal intensity center, depicting central necrosis. Curved arrow = small reactive lymph node with distinct Gd-DTPA enhancement. Fat tissue is depicted with low to intermediate signal intensity. C and D. Microscopic slides of both subdigastric nodes (C=anterior, D=posterior lymph node), showing the tumor necrosis (X). L = preexistent lymphatic tissue, T = viable tumor cells.

higher signal intensity than muscle and the primary tumor, and a lower signal intensity than salivary gland tissue and fat in these images (Figs 2.1, 2.2a, 2.3a and 2.5a). However, owing to a lack of contrast between lymph nodes and surrounding muscles and blood in vessels, it is not always possible to localize borderline lymph nodes, especially in the subdigastric region. Indeed, in 5 of the 35 patients (Cases 1,6, 12,21 and 25) these nodes were not distinguishable (Fig 2.2a). In spite of the varying flow related enhancement artifacts, vessels could be identified by following them in serial slices. Coronal and sagittal T1-weighted SE images, performed in 7 patients, gave no relevant additional information above that provided by axial T1-weighted SE images for staging of the neck.

Unenhanced T1-weighted GE images (performed in 7 patients) exhibited slight fat suppressive properties (Fig 2.1). However, contrast between lymph nodes and other tissues was less than with the other techniques.

The T2-weighted SE images depicted lymph nodes with intermediate to high signal intensity. However, contrast between lymph nodes and fat or salivary glands was minimal (Figs 2.1, 2.4a, 2.6b). Consequently, in 6 patients (Cases 8,9,10,11,34 and 35) enlarged lymph nodes were not visualized (Figs 2.4a and 2.6b).

On more heavily T2-weighted images (echo time 96 ms) contrast between lymph nodes and surrounding fat or salivary gland tissue remained minimal. However, T2-weighted SE images reliably demonstrated blood flow in most patients.

The T2-weighted GE images proved to be very sensitive in localizing cervical lymph nodes in most patients. This is caused by the sharp contrast between intermediate to high signal intensity nodes and low signal intensity muscle and fat (Fig 2.1). Variations in signal intensity, often seen inside lymph nodes, had no relation to lymph node malignancy (Figs 2.4b and 2.6a). Only large, fluid filled, cystically degenerated tumor tissue was depicted reliably as a very high signal intensity area inside a node (Fig 2.3b). In all 12 patients in whom both T2-weighted SE and T2-weighted GE images were obtained, T2-weighted GE images showed more contrast between lymph nodes and surrounding muscle, fat and salivary glands. In 6 out of these 12 patients (Cases 8, 9,10,11,34 and 35) lymph nodes that were not recognizable in T2-weighted SE images, were shown clearly in T2-weighted GE images (Figs 2.4b and 2.6a). Because of the flow related enhancement in the GE images, blood in vessels is depicted with varying signal intensities, sometimes resembling lymph nodes. In 4 out of 31 patients (Cases 19,20,27 and 28) part of the T2-weighted GE images were of no diagnostic value, due to motion and/or susceptibility artifacts, whereas T1-weighted SE images of these patients could still be interpreted.

In only 5 out of 25 sides (in 22 patients) with necrotic nodes did unenhanced T2-weighted images (SE or GE) depict necrosis with high signal intensity (Cases 4,7,21,22 and 24). Histopathologic examination of these nodes showed fluid containing cystically degenerated tumor tissue (Fig 2.3d).

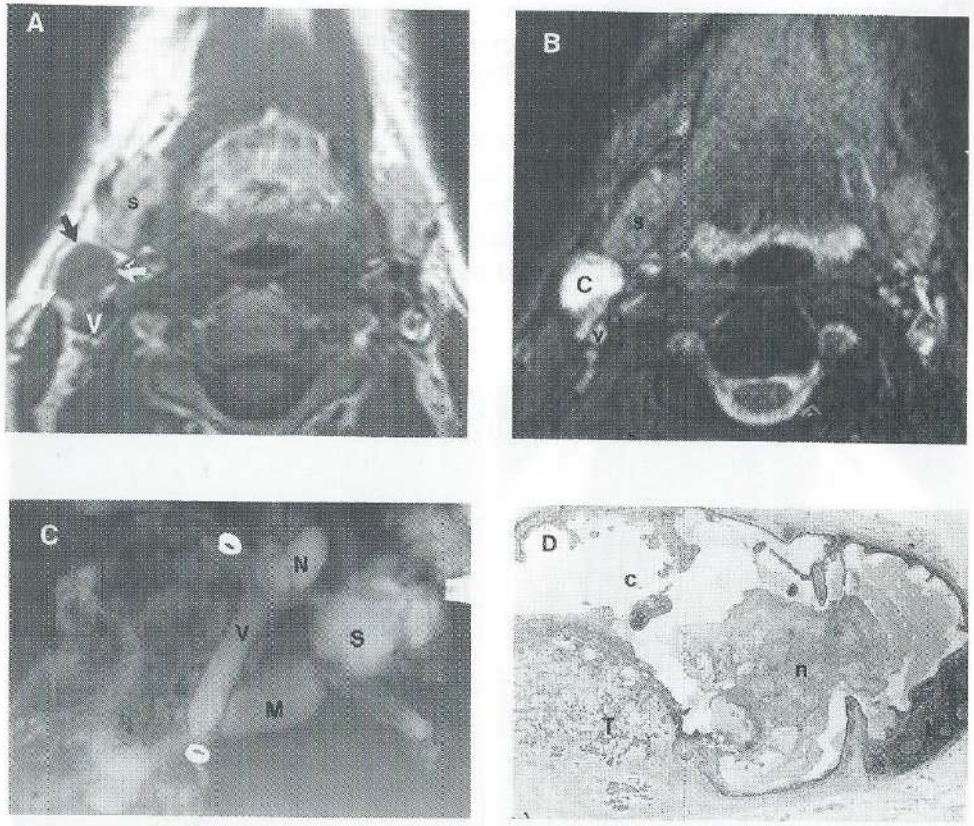

Figure 2.3. A. T1-weighted SE image of case 21: T3N1 oropharyngeal carcinoma. At the right subdigastric level, the metastatic lymph node (arrows) is depicted ventral to the sternocleidomastoid muscle and the internal jugular vein (v). It is depicted with intermediate signal intensity (s= submandibular gland). B. T2-weighted GE image. The subdigastric node is depicted with a high signal intensity center (C), depicting cystically degenerated tumor tissue. C. Specimen radiograph clearly depicts the internal jugular vein (v), labeled with two iron rings, the submandibular gland (s), the metastatic subdigastric node (N) and the omohyoid muscle (M). D. Microscopic detail of the metastatic node showing the cystic tumor degeneration (c) and necrosis (n). L = preexisting lymphatic tissue, T = viable tumor.

2.3.2. Gadolinium-DTPA.

Dynamic Gd-DTPA studies were made in 4 cases. Unenhanced T1-weighted GE images were obtained followed by Gd-DTPA injection. Next, 4 short series of

T1-weighted GE images were made at 1, 3, 6 and 9 minutes. In these four dynamic studies, enhancement was maximal and thus the demarcation of necrosis was best seen ± 3 minutes after Gd-DTPA injection.

Gadolinium-DTPA enhanced T1-weighted GE images demonstrated tumor necrosis in lymph nodes in all 14 neck sides in which considerable necrosis (i.e. 3 mm or larger) was present histopathologically (Figs. 2.2b, 2.5b and 2.7a; Table 2.1) and in which Gd-DTPA was used. Figure 2.1 shows the signal intensity differences between enhancing viable tumor and necrosis in lymph nodes. Owing to

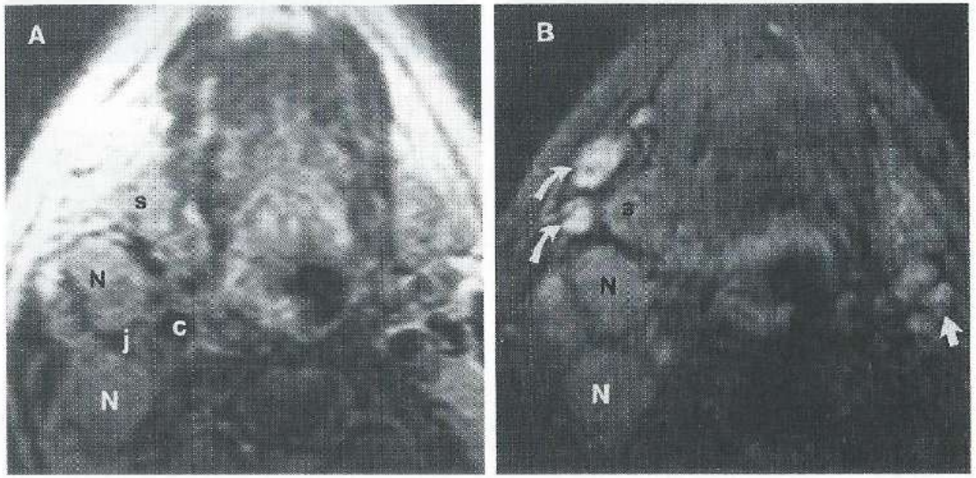

Figure 2.4. A. T2-weighted SE image of case 11: T1N2a piriform sinus carcinoma. On the right side two large subdigastric nodes (N) with intermediate signal intensity, compressing the internal jugular vein (j) are clearly shown. In spite of careful window setting, two submandibular nodes are obscured by fat tissue. s = submandibular gland, c = carotid artery. B. T2-weighted GE image. Besides the clearly depicted subdigastric nodes (N) two enlarged submandibular nodes (curved arrows) with high signal intensity become apparent on the right side. In spite of the irregular signal intensity of these nodes, they proved to be reactively enlarged on histopathological examination. Arrow indicates small reactive lymph node on the left side.

better tumor delineation, in 3 patients (Cases 2,25 and 32) additional nodes adjacent to the primary tumor, and not seen with other techniques, were found after Gd-DTPA administration. Macroscopic extranodular tumor extension also was sometimes demonstrated after Gd-DTPA administration (Fig 2.5b).

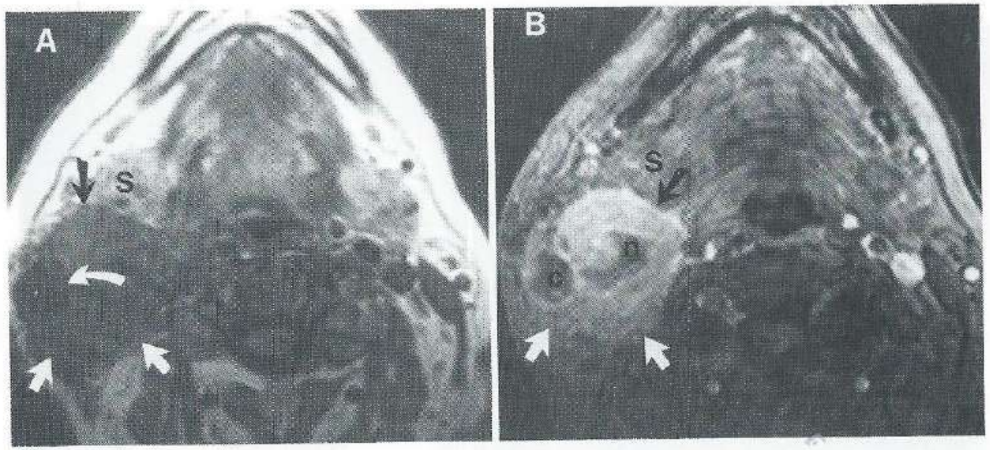

Figure 2.5. A. T1-weighted SE image of case 22: Right T1N2a tonsillar carcinoma. A 5 cm tumorous mass (straight arrows) in the subdigastric region on the right side is depicted with the same signal intensity as surrounding muscles and peripharyngeal tissues. A low signal intensity zone in the mass on the right side is suspected, depicting fluid containing cystic tumor degeneration (curved arrow), S = submandibular gland. B. Gd-DTPA enhanced T1-weighted GE image. The mass (arrows) shows Gd-DTPA uptake and can now be delineated from all surrounding tissues. Two low signal intensity areas in the mass have become apparent. n = necrotic part, c = fluid containing cystic tumor degeneration.

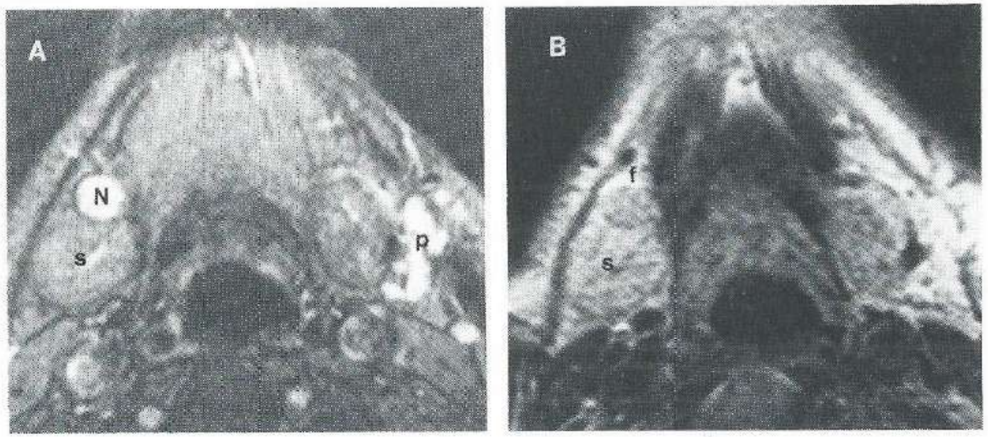

Figure 2.6. A. T2-weighted GE image of case 10: T2N1 floor of mouth carcinoma. A metastatic submandibular node (N) on the right side is depicted with high signal intensity, in high contrast to all surrounding tissues. The signal of the node is not fully homogenous. The high signal intensity lesion on the left side (p), although never proven, could very well be a parotid tumor. s = submandibular gland. B. T2-weighted SE image. Submandibular gland, fat (f) and the nodal metastasis are now depicted with intermediate to high signal intensity and minimal contrast.

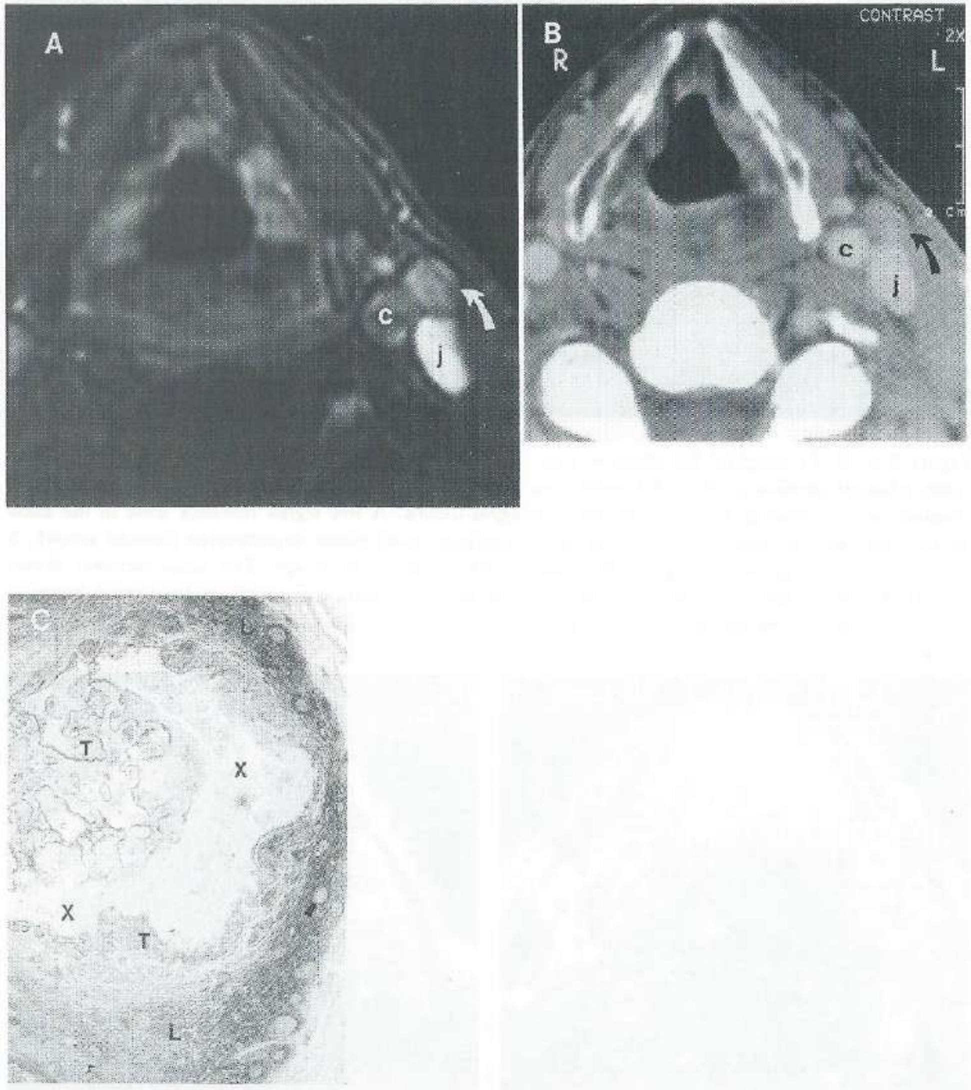

Figure 2.7. A. Gd-DTPA enhanced T1-weighted GE image of case 25: Right T3N0 pharyngeal carcinoma. A 1 cm, right sided, midjugular lymph node is depicted with intermediate signal intensity (curved arrow). Inside the node the irregular enhancement pattern can clearly be seen. c = common carotid artery, j = internal jugular vein. B. Contrast enhanced CT scan (Philips 350 Tomoscan, 6 mm slice thickness) at the same level. Although the node is clearly depicted on this scan, it has a homogenous density, not depicting any necrosis. C. Microscopic detail of the metastatic midjugular node. The pattern of tumor necrosis (x) that was seen in the Gd-DTPA enhanced MR image, can be recognized in the node. L = preexistent lymphatic tissue, T = viable squamous cell carcinoma.

In five of six patients Gd-DTPA enhanced T1-weighted GE images showed more contrast between nodes and surrounding tissues, and more accurately showed the intranodular enhancement pattern than Gd-DTPA enhanced T1-weighted SE images did.

2.4. DISCUSSION

Although palpation has a high percentage of false positive and false negative results (15,16), so far no imaging modality has found general acceptance for staging of the neck. Even in patients with a high probability of occult cervical metastasis, most head and neck surgeons do not ask for additional imaging prior to elective neck treatment (17). Several reasons may account for this. Aside from practical objections and cost, the accuracy and clarity of the imaging method are important factors. So far MR has not been definitely shown to detect occult cervical lymph node metastasis accurately (7,8).

Our results reiterate previous demonstrations of the relative merits of T1-, proton density, and T2-weighted SE pulse sequences for the display of lymph nodes. However, to our knowledge, the appearance of cervical lymph nodes on T2-weighted GE images, and the depiction of necrosis on Gd-DTPA enhanced T1-weighted GE images has not been previously explored.

Several authors have shown that in T1-weighted SE images, lymph nodes are depicted with intermediate signal intensity, similar to muscular signal intensity (7,11) and bloodstream. Consequently lymph nodes have to be identified by the presence of mass effect or by characteristics of location and shape (Figs 2.2a, 2.3a and 2.5a). This may be difficult in the high jugular region where many vessels and thin craniocaudally oriented muscles may mimic or obscure lymph nodes. Coronal and sagittal T1-weighted SE images may sometimes clarify the anatomy. However, the diameters of lymph nodes in the axial plane, as depicted on axial scans, provide a more reliable criterion for evaluating the nodal status than the longitudinal diameter.

In proton density and T2-weighted SE images lymph nodes are clearly differentiated from muscle and bloodvessels (9,11,18), but not from fat and salivary glands (Figs 2.1, 2.4a and 2.6b) on the basis of signal intensity.

Our experience with T2-weighted GE images demonstrates that for the imaging of cervical lymph nodes, they combine desirable features of both the T1- and the T2-weighted SE scans as the nodes contrast well with both fat and muscle. The

T2-weighted GE images demonstrate cervical lymph nodes with high to intermediate signal intensity; muscle and fat are depicted with low signal intensity (Figs 2.1, 2.3b, 2.4b and 2.6a). Vessels are variable in appearance because of varying flow related enhancement artifacts. Our experience has shown that T2-weighted GE images are more reliable for lymph node imaging than T2-weighted SE images. Signal intensity variations within lymph nodes do not necessarily evidence metastasis (Figs 2.3b, 2.4b and 2.6a). However, T2-weighted GE images are characterized by a low signal-to- noise ratio. The technique is very sensitive to susceptibility and motion artifacts. The combined use of T1-weighted SE and T2-weighted GE imaging enabled us to localize even small lymph nodes.

Considerable areas ($\geq$ 3 mm) of tumor necrosis, cystic tumor degeneration or tumor keratinization are reliably demonstrated by Gd-DTPA enhanced T1-weighted GE images (Figs 2.1, 2.2b, 2.5b and 2.7a). Our results show that this technique is more sensitive in demonstrating irregular enhancement than the T1-weighted SE technique and might even be more sensitive than contrast enhanced computer tomography (CT) (Figs 2.7a,b). With this technique, tumor necrosis in nodes has the same characteristics as in contrast enhanced CT. One must however be careful not to misinterpret minor enhancement variations as necrosis. Furthermore, the varying flow related enhancement in vessels may mimic necrotic nodes. Gd-DTPA enhancement was seen in all reactively enlarged as well as in all metastatic lymph nodes. Very small lymph nodes did not always exhibit Gd-DTPA uptake. To visualize small (< 3 mm) necrosis, better spatial resolution with large signal intensity differences between viable tumor and necrosis is necessary.

Signal intensity measurements did not show a specific signal intensity for metastatic or reactive nodes in enhanced or unenhanced SE or GE images (Fig 2.1). This is in agreement with previous findings regarding varying and overlapping relaxation times of nodes (19).

In conclusion, our results show that axial T1-weighted SE images combined with T2-weighted GE images demonstrate cervical lymph nodes more reliable than a combination of T1 and T2-weighted SE images. Gd-DTPA enhanced T1-weighted GE images should be used to reveal tumor necrosis in lymph nodes.

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Chapter 3

CERVICAL LYMPH NODE METASTASIS: ASSESSMENT OF RADIOLOGIC CRITERIA

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To estimate the accuracy of different radiologic criteria of cervical lymph node metastasis in patients with head and neck carcinoma, 7 different characteristics of 2719 lymph nodes in 71 neck dissection specimens from 55 patients were assessed. Three lymph node diameters, their location, their number, the presence of metastatic tumor and the amount of necrosis and fatty metaplasia were recorded.

The minimal, and not the maximal diameter in the axial plane was found to be the most accurate size criterion for predicting lymph node metastasis. A minimal axial diameter of 10 mm was determined to be the most effective size criterion. The size criterion for lymph nodes in the subdigastric region (level 2) was 1 mm larger (11 mm). Groups of three or more borderline nodes were proved to increase the sensitivity, but did not significantly decrease the specificity. Radiologically detectable necrosis (3 mm or larger) was found only in tumorous nodes and was present in 74 % of the positive neck dissection specimens. Shape was not a valuable criterion for the radiologic assessment of the cervical lymph node status.

3.1. INTRODUCTION

Assessment of the status of cervical lymph nodes in patient with primary squamous cell carcinoma in the head and neck region is difficult. The overall error rate in assessing the presence or absence of cervical lymph node metastasis by palpation varies greatly per study, and is on average estimated in the range of 20-30% (1,2). Therefore, the treatment of patients with a clinical stage "N0" neck is controversial. If these patients are at great risk of having occult cervical lymph node metastasis, most head and neck surgeons advocate elective treatment of the neck (3,4). However, 75%-77% of these elective neck dissections prove to be free of tumor on histopathologic examination (3,4). On the other hand, up to 32% (5) of patients with clinically negative necks who are not treated develop lymph node metastasis in the neck, depending on the site and size of the primary tumor.

In most studies, the use of computed tomography (CT) compares favorably to palpation in assessing the status of the lymph nodes; the overall error rate ranges from 7.5% to 19 % (6-9). To our knowledge, only one publication reports an overall error rate of 28% with use of CT (10).

Many different radiologic criteria are being used to assess the presence or absence of metastasis in cervical lymph nodes (6-13). These criteria involve the maximal axial diameter (6-13), the irregular enhancement due to tumor necrosis (6-11), the shape (8,11,13), and the grouping of nodes (7-9,11). The differences in criteria used, account in part for the difference in reported overall error rates. Most authors defined their criteria by retrospective radiologic - histopathologic correlation, or just postulated them. To our knowledge, different radiologic criteria were compared in only one study (8). These varying, and often inadequate, criteria may cause an inflated overall error rate.

Retrospective comparison of CT and magnetic resonance (MR) images with histopathologic findings of neck dissection specimens has many disadvantages. For instance, metastatic and reactively enlarged nodes found in the specimen cannot always be identified accurately on the images. Whether or not these nodes can be identified at CT or MR depends on the skill of the radiologist and the information provided by the pathologist about the exact location and size of the (benign and malignant) nodes. This information is rarely supplied. Volume averaging effects, patient compliance, and selected techniques (eg, section thickness, contrast material administration and dosage, pulse sequence) may influence the measurements obtained at CT and MR and make them not only less reproducible, but also more difficult to compare with those of other studies. Furthermore, the longitudinal diameter cannot be accurately measured on axial images.

To avoid the previously mentioned disadvantages and to prospectively evaluate all morphologic characteristics of metastatic and reactively enlarged lymph nodes, these characteristics were studied in 2719 lymph nodes from 71 neck dissection specimens. This enabled us to define the validity of different radiologic criteria, such as size, shape, and grouping of lymph nodes. Regional variations in lymph node size, and the prevalence of tumor necrosis and adipose metaplasia were also assessed.

Knowing the maximal accuracy, of radiologic techniques may help to select patients who should be treated on behalf of their neck.

3.2. MATERIALS AND METHODS

Within a period of 10 months, 71 neck dissection specimens, from 55 patients with squamous cell carcinoma of the upper aerodigestive tract, were examined by the same investigator (M.W.M.v.d.B.). Twenty-five patients had oral carcinoma, 18 had pharyngeal carcinoma, 10 had laryngeal carcinoma and 2 had cytologically proven metastasis of a squamous cell carcinoma of unknown origin. Thirty-nine patients underwent unilateral neck dissections and 16 underwent bilateral neck dissections. Overall, 55 comprehensive and 16 selective neck dissection specimens were examined. None of the patients had previously undergone a neck dissection on the affected side or received preoperative radiation therapy or chemotherapy.

The neck dissection specimen was photographed (Polaroid and slides) directly postoperatively. Next, the specimen was nailed to a board and fixed in a mixture of 4% formaldehyde for 36-48 hours. After dissection of the sternocleidomastoid muscle (a structure with a high opacity), the specimen was immersed in a solution of 96% ethanol and a radiograph was obtained to show the exact location and size of the lymph nodes and their relation to the submandibular gland, other nodes, and, if resected, the internal jugular vein. A solution of 96% ethanol has the same X-ray absorption as fat (14). A Philips mammodiagnost U-M (Philips Medical Systems) with programmed exposure control was used. The radiograph obtained with this method is especially useful for radiologic-histopathologic correlation.

After fixation, all palpable and/or visible lymph nodes were dissected from the specimen, measured, and cut into 2-4 mm-thick slices in the axial plane for microscopic examination.

The minimal and maximal axial (perpendicular to the course of the internal jugular vein) diameters and the longitudinal diameter were measured for all dissected nodes. The minimal axial diameter corresponds to the widest diameter of the node in the axial plane that is perpendicular to the maximal axial diameter (Fig 3.1). The longitudinal diameter parallels the internal jugular vein. If all three diameters of a node were less than 5 mm, the size was not further specified. The shape was defined as the maximal axial diameter divided by the minimal axial diameter.

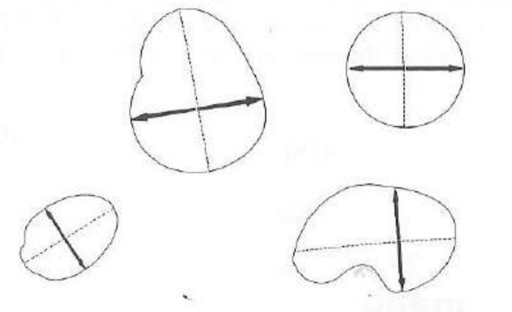


Figure 3.1. Axial sections through lymph nodes. The dotted line indicates the maximal axial diameter, the thick arrow indicates the minimal axial diameter.

To measure the possible shrinkage of benign and malignant lymph nodes due to the fixation procedure, three metastatic and three benign lymph nodes were dissected from random specimens and were measured before and after fixation. Shrinkage was also assessed by obtaining a radiograph of three specimens before and after fixation, with use of exactly the same technique, and measuring one axial diameter and the longitudinal diameter of 15 nodes on both radiographs. To assess volume averaging at CT, the on-screen measurements of axial diameters were compared to the diameters in the specimen.

The location of all nodes was indicated on the radiograph and the polaroid of the specimen. All macroscopically negative nodes were entirely removed and sectioned for microscopy. Two or more representative sections were made of each macroscopically positive node for microscopic study. The presence or absence of gross necrosis was recorded. Of all sections one microscopic slide was made, that was examined microscopically by at least 2 investigators. The number of nodes removed from the specimen for microscopic examination, the number of metastatic nodes, the size of necrotic foci and areas of adipose metaplasia inside nodes were recorded.

In this study, sensitivity and specificity of different criteria were calculated and charted as Receiver Operator Characteristic (ROC) curves (e.g. Figs 3.2 and 3.3). These curves represent the relation between the specificity (1 - specificity in the x-axis) and the sensitivity (y-axis) of different criteria tested. The perfect test is represented by a point in the uppewr righ corner. However, as no criterion is perfect, all curves follow path from the lower left to the upper right. Lines that follow the highest course represent the best criteria.

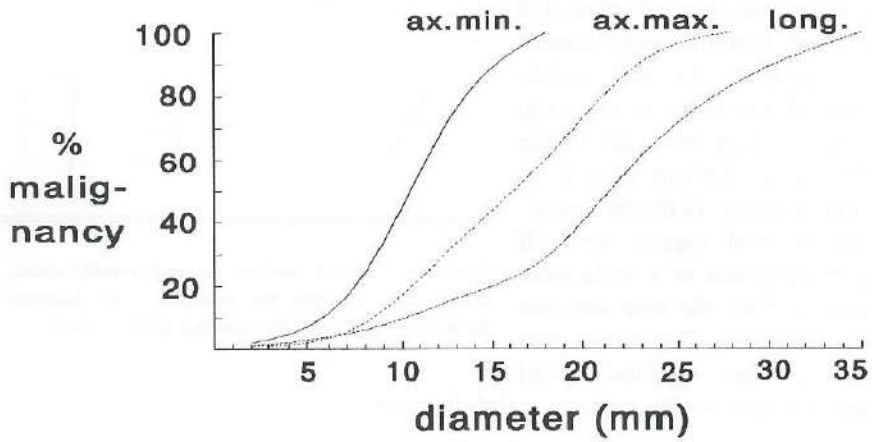


Figure 3.2. Percentage of nodes malignant versus lymph node diameter. With all three measurements, all nodes are malignant beyond a certain diameter (see also table 1).
In this and subsequent figures: ax.min. = minimal axial diameter, ax.max. = maximal axial diameter, long. = longitudinal diameter.

3.4. RESULTS

3.4.1. Number of Positive Lymph Nodes.

The mean number of lymph nodes examined from the 55 comprehensive neck dissections was 45 (range, 20-74), while an average 15 nodes were found in the 16 selective neck dissections (range, 7-41). Out of the 2719 lymph nodes examined, 144 nodes in 38 specimens of 34 patients contained metastatic squamous cell carcinoma. The number of metastatic nodes in the positive comprehensive neck

dissections ranged from 1 to 23 (mean, 3.8). Only one of the 16 supraomohyoid neck dissections contained metastatic nodes (two nodes were positive).

3.4.2. Lymph Node Size.

Table 3.1 and figure 3.2 show the number and percentage of negative and positive lymph nodes in relation to the longitudinal and maximal and minimal axial diameters. The smooth curves in figure 3.2 were obtained by applying the logistic regression model to the data (15).
The longitudinal diameter varied between 3 and 60 mm. Figure 3.2 shows that only nodes with longitudinal diameters measuring 35 mm or larger (found in only 10 of the 144 malignant nodes) correspond to 100% malignancy. There is a large range of overlap in size between positive and negative nodes.

In this respect, the use of the maximal axial diameter (ranged, 3-43 mm), was not significantly more accurate (Fig 3.3). At a maximal axial diameter of 14-15 mm, which is often used in as a size criterion, only 45 % of the nodes contained tumor (Fig 3.2). One reactive lymph node had a maximal axial diameter of 22 mm.

The minimal axial diameter (range, 2-30 mm) proved to be the most accurate diameter to use in predicting tumor-positive lymph nodes (Fig 3.3). All 34 nodes with an minimal axial diameter larger than 12 mm were metastatic. Although metastatic lymph nodes with an minimal axial diameter smaller than 10 mm made up 58 % of all malignant nodes (Table 3.1), and were found in 30 specimens, only four specimens contained exclusively metastatic nodes of this size.

Table 3.2 and Figure 3.3 show the sensitivity and the specificity for several cut off points of these size criteria per lymph node. Note that the specificity remains high (greater than 85%) for all criteria because of the large number of (true) negative nodes (low incidence of metastases).

Because clinicians are concerned about whether a side contains metastasis or not, the sensitivity and specificity of these criteria were calculated per neck dissection as well. As illustrated in Table 3.2 and 3.3 and Figure 3.4, the minimal axial diameter proved to be the most valid size criterion in predicting a tumor-positive side.

Lymph node shrinkage by fixation could not be measured with use of the previously described tests. Comparing lymph node size at CT and in the specimen, we found that in 20 nodes, axial lymph node diameters were 11% smaller to 22% larger (mean, 6.1% larger) in the specimen than at CT.

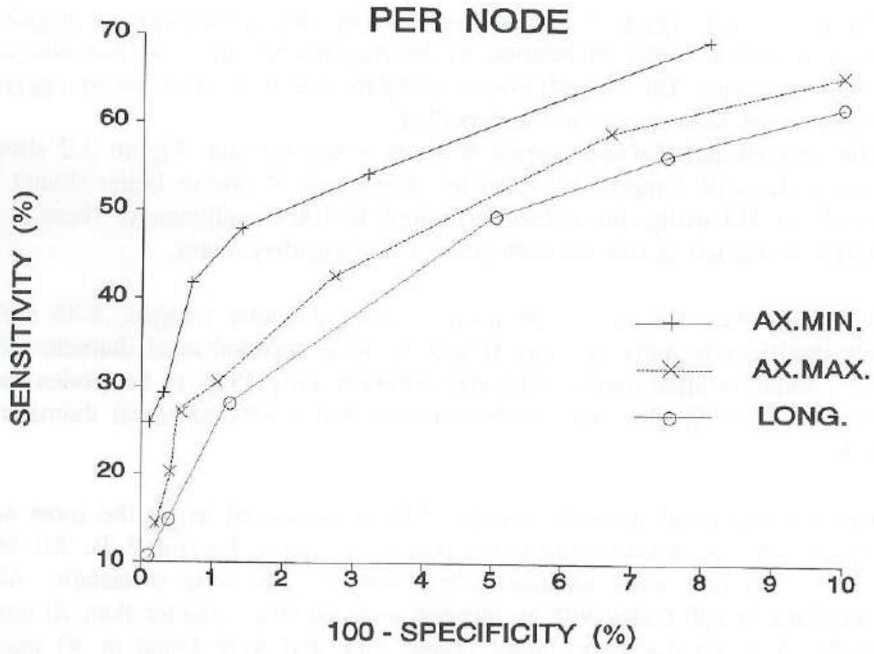


Figure 3.3. Receiver Operator Characteristic curves of the different size criteria per node as also shown in table 3.2. The x-axis represents 1 - specificity (x 100%), the y-axis represents the sensitivity (x 100%). Because the curve of the ax.min. criterion follows the highest course, the ax.min. is the best criterion. Note that the specificity remains high (> 90%) for all values of sensitivity shown. This is caused by the large number negative nodes (2575 of 2719) of wich most were smaller than 5 mm and contained no metastases. All criteria thus had relatively many correct negatives.

3.4.3. Lymph Node Shape.

The shape criterion itself (maximal axial diameter divided by minimal axial diameter), or the minimal axial diameter or maximal axial diameter combined with a roundish shape were all less valid than the minimal axial diameter criterion alone (Table 3.3, some results not shown). The ROC curves of combinations of the minimal axial diameter or maximal axial diameter criterion together with a roundish shape criterion for borderline lymph nodes (1 or 2 mm smaller) were below the curve of the minimal axial diameter (not shown). Thus any combination of shape with either the minimal axial diameter or maximal axial diameter was not as valid a criterion as minimal axial diameter alone.

3.4.4. Lymph Node Size Variations per Level.

Negative and positive nodes in level 1 and 2 had axial diameters that were an average of 1-2 mm larger than nodes in other levels. The mean minimal axial diameter of metastatic nodes in level 1 and 2 was 2-3 mm, and the mean maximal axial diameter was 4-5 mm larger than metastatic nodes in other levels.

	Lymph node size (mm)					
	≤5	6-10	11-15	16-20	21-25	≥26
Longit.	1%	6%	16%	29%	47%	78%
n+/ntot	20/1895	28/440	38/240	26/91	14/30	18/23
Ax.max.	1%	8%	33%	60%	82%	100%
n+/ntot	23/1935	49/615	43/130	12/20	9/11	8/8
Ax.min.	2%	23%	75%	100%	100%	100%
n+/ntot	44/2411	58/257	27/36	8/8	4/4	3/3

Table 3.1 Diameter versus Percentage Malignant Lymph Nodes.

The longitudinal diameter of both malignant and reactive lymph nodes was 3-6 mm larger for nodes in the jugular chain (levels 2,3 and 4) than for nodes in other levels (Table 3.4).
The use of a larger minimal axial diameter criterion (minimal axial diameter + 1 mm) for lymph nodes in levels 1 and 2 did not change the course of the ROC curve. When only the minimal axial diameter criterion for level 2 nodes was increased a somewhat higher course of the ROC curve was obtained (Table 3.3). When even larger diameters were used for these levels (minimal axial diameter + 2 mm), an unacceptable loss of sensitivity resulted.

Diameter (mm)	per Node sens	per Node spec	per Specimen sens	per Specimen spec
Minimal axial diameter				
≥ 6	69.4	91.9	100	12
≥ 8	54.2	96.8	97	21
≥ 9	47.9	98.6	89	58
≥ 10	41.7	99.3	89	73
≥ 11	29.2	99.7	79	85
≥ 12	25.7	99.9	66	94
Maximal axial diameter				
≥ 8	72.9	85.9	100	0
≥ 10	59.0	93.3	97	9
≥ 12	43.4	97.3	89	24
≥ 14	30.6	98.9	82	48
≥ 15	27.1	99.5	71	73
≥ 16	20.1	99.6	58	79
≥ 20	13.9	99.8	47	88
Longitudinal diameter				
≥ 10	72.9	85.0	100	3
≥ 13	56.3	93.5	97	18
≥ 15	49.3	95.0	97	24
≥ 20	27.8	98.8	74	55
≥ 25	15.3	99.6	53	88
≥ 30	10.4	99.9	32	94

(sens. = sensitivity, spec. = specificit, Ax.max. = maximal axial diameter, Ax.min. = minimal axial diameter, Long. = longitudinal diameter).

Table 3.2. Percentage Sensitivity and Specificity of Size Criteria. Per Node: 144 +, 2575 -; Per Specimen: 38 +, 33 -

size mm	ax.min. sens	ax.min. spec	ax.min.[1] sens	ax.min.[1] spec	ax.min.[2] sens	ax.min.[2] spec	ax.min.[3] sens	ax.min.[3] spec
≥8	97	21	92	36	92	48	97	21
≥9	89	58	89	70	89	73	92	52
≥10	89	73	82	82	82	85	89	67
≥11	79	85	71	94	66	94	79	85
≥12	66	94	61	100	61	100	74	94
	ax.min.[5]		**ax.min. + necrosis**		**ax.min.[3] + necrosis**		**ax.min.[4] + necrosis**	
≥8	100	21	97	21	97	21	95	30
≥9	95	33	92	58	95	52	95	58
≥10	92	39	92	73	92	67	87	76
≥11	87	61	87	85	87	85	87	94
≥12	84	73	84	94	84	94	82	100

ax.min.[1]: subdigastric nodes 1 mm larger; *ax.min.[2]*: subdigastric and submandibular nodes 1 mm larger; *ax.min.[3]*: ax.min. + ≥ 3 borderline nodes grouped in first two echelons (borderline means 1 or 2 mm smaller); *ax.min.[4]*: subdigastric nodes 1 mm larger, and ≥ 3 borderline nodes grouped; *ax.min.[5]*: ax.min + borderline nodes with a round shape (≥ 0.8).

Table 3.3. Percentage sensitivity and specificity of some modified ax.min. criteria per side.

SITE	NUMBER all	NUMBER posit	AX.MAX. all	AX.MAX. posit	AX.MIN. all	AX.MIN. posit	LONG. all	LONG. posit
level 1	201	13	9.3	14.0	6.0	11.2	8.3	12.0
level 2	305	65	9.7	15.0	6.7	11.1	13.4	19.4
level 3	144	26	7.8	10.5	5.3	8.5	13.2	17.5
level 4	70	4	7.2	9.8	4.8	8.0	11.3	16.8
level 5	174	12	7.3	13.3	4.7	9.0	9.5	15.0
level 6	8	5.0	8.5	9.2	6.1	6.2	10.5	7.6

Table 3.4. Number and size (cm) of lymph nodes larger than 5 mm per level of the neck. "All" indicates all lymph nodes larger than 5 mm, "posit" indicates all tumor positive lymph nodes larger than 5 mm.

3.4.5. Groups of Borderline Nodes.

The presence of groups of two or more borderline lymph nodes (minimal axial diameter of 1-2 mm smaller than the criterion used) in the first or second lymph node drainage region of the primary (as described by Lindberg [16]) combined with the minimal axial diameter criterion resulted in a ROC curve similar to the curve obtained with the minimal axial diameter criterion alone (not shown). Groups of three or more borderline nodes combined with the minimal axial diameter criterion slightly increased the sensitivity at a high specificity (Table 3.3 and Fig 3.4).

3.4.6. Lymph Node Tumor Necrosis.

Areas of tumor necrosis, cystic tumor growth or extensive tumor keratinization larger than 3 mm (minimal diameter) were visualized with both contrast enhanced CT and MR imaging (Fig 3.5) (17). These areas were present in 46 (32%) of the 144 metastatic lymph nodes in 28 neck dissection specimens. Necrotic foci of 1-3 mm, that can not be reliably visualized using current imaging techniques, were present in another 27 lymph nodes in six additional neck dissection specimens. These necrotic areas were not only found in large nodes, but were often seen in nodes with a minimal axial diameter smaller

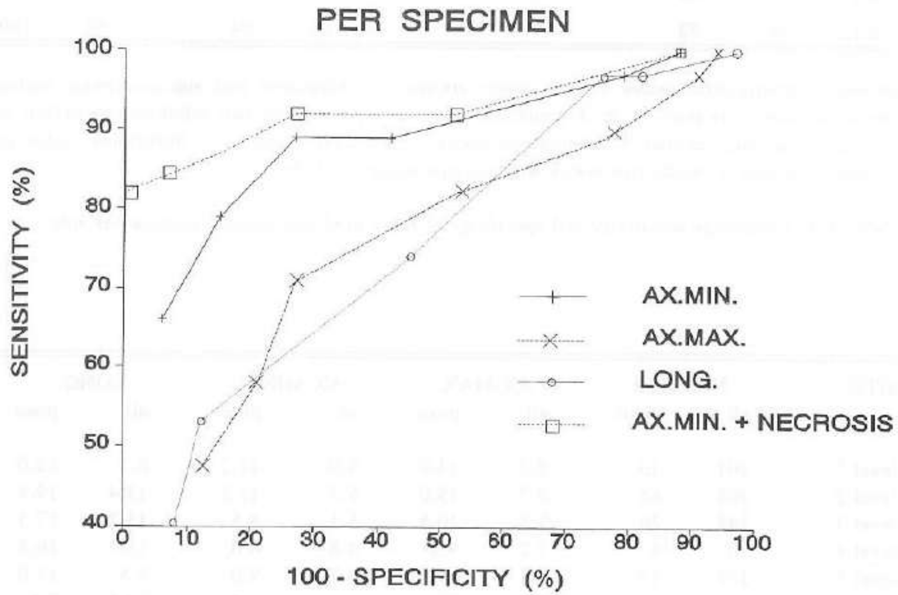
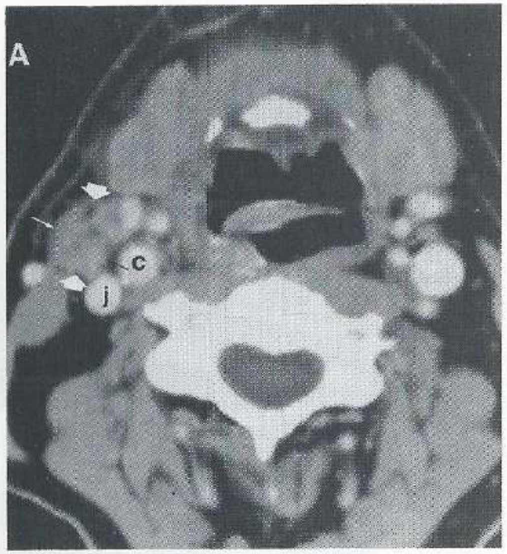
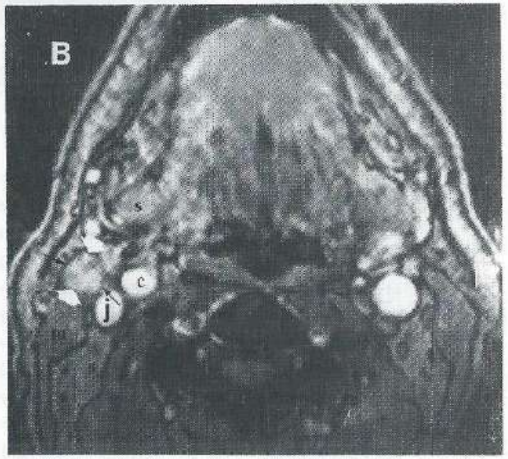


Figure 3.4. Receiver Operator Characteristic curves show the relation between the sensitivity and specificity of the size criteria per neck dissection specimen. The minimal axial diameter (+ necrosis) is again the most valid criterion, as its curve follows the highest course. Note that the ax.min. criterion plus necrosis is a much better criterion than ax.min. alone.





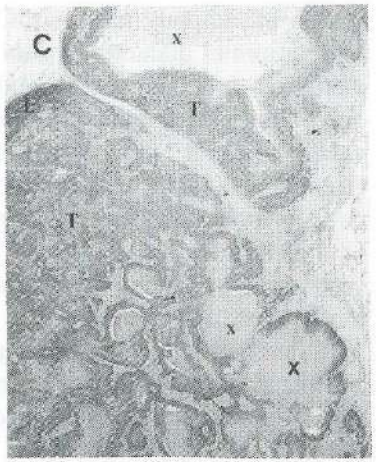


Figure 3.5. A. Contrast-enhanced CT scan (Philips 350 tomoscan), with 6-mm section thickness was obtained at the subdigastric level in a 58-year-old man with a T2N0 supraglottic carcinoma. Two metastatic subdigastric nodes lying against each other on the right side (thin arrows indicate minimal axial diameter, thick arrows indicate maximal axial diameter) show several areas of irregular enhancement caused by small (3 mm) necrotic tumor foci. j = internal jugular vein, c = common carotid artery. B. Gadolinium-DTPA enhanced T1-weighted gradient recalled echo MR image (0.6 T, Technicare, General Electric) obtained with a 3-mm section thickness at the same level shows small necrotic areas (low signal intensity) inside the nodes. Thin arrows indicate minimal axial diameter, thick arrows indicate maximal axial diameter. s = submandibular gland, m = sternocleidomastoid muscle. C. Histopathologic section through the metastatic nodes show the small areas of necrosis (x) that were also seen at CT and MR imaging. L = preexistent lymphatic tissue, T = squamous cell carcinoma.

than 1 cm as well. The sensitivity of the criterion of tumor necrosis, cystic tumor growth or tumor keratinization in areas larger than 3 mm was 32% per node, with a specificity of 100%.
Per side, the prevalence of necrotic areas larger than 3 mm was 39%, while the sensitivity and specificity of this criterion were 74% and 100% respectively. Table 3.3 shows the effect of a combination of this criterion with several modified minimal axial diameter criteria. It is clear that necrosis increases the sensitivity of all modified minimal axial diameter criteria.

3.4.7. Lymph Node Adipose Metaplasia.

Areas of adipose metaplasia larger than 1 mm (minimal diameter) within lymph nodes were found in 123 lymph nodes, most often occuring in the submandibular region. However, this fat was part of the hilar structures in 103 of these lymph nodes, giving the node a horseshoe shape on section (depending on the section plane). In 15 nodes from 13 specimens this hilar fat measured 3 mm or more, and was visualized at CT (Fig 3.6). The fat was situated centrally in 20 nodes, and these central foci were 3 mm or larger in only four nodes from four specimens. Two of these 4 specimens contained no metastatic nodes. Central foci of 3 mm or larger may simulate necrosis (Fig 3.7) by causing central hypoattenuated areas in lymph nodes at CT.

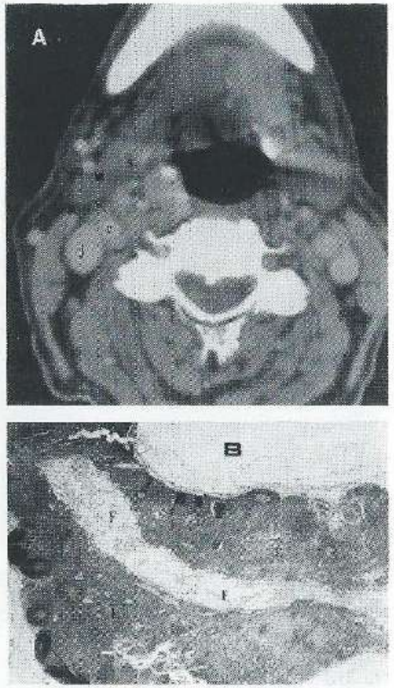


Figure 3.6. A. Contrast-enhanced CT scan (6-mm section thickness) obtained at the submandibular level in a 69-year-old man with a T3N0 oropharyngeal carcinoma on the right side. The node behind the submandibular gland (s) on the right side (thin arrows indicate minimal axial diameter, thick arrows indicate maximal axial diameter) shows irregular enhancement by adipose metaplasia inside the node. j = internal jugular vein, c = common carotid artery. B. Histopathologic section of the reactively enlarged submandibular node shows the central fat tissue (F). No tumor was found in the neck dissection specimen of this patient. L = lymphatic tissue.

3.5. DISCUSSION

In the literature, the size criterion for cervical lymph node metastasis varies between 8 and 30 mm (6-13). The shape (8,11,13), number (7,8,9,11) and site (11,12) of the node(s) may influence the size criteria. To our knowledge, all authors recommend using the maximal axial diameter to assess metastasis. However, in our study, the maximal axial diameter was not found to be as valid as the minimal axial diameter in predicting tumor-positive nodes (Table 3.2, Figs

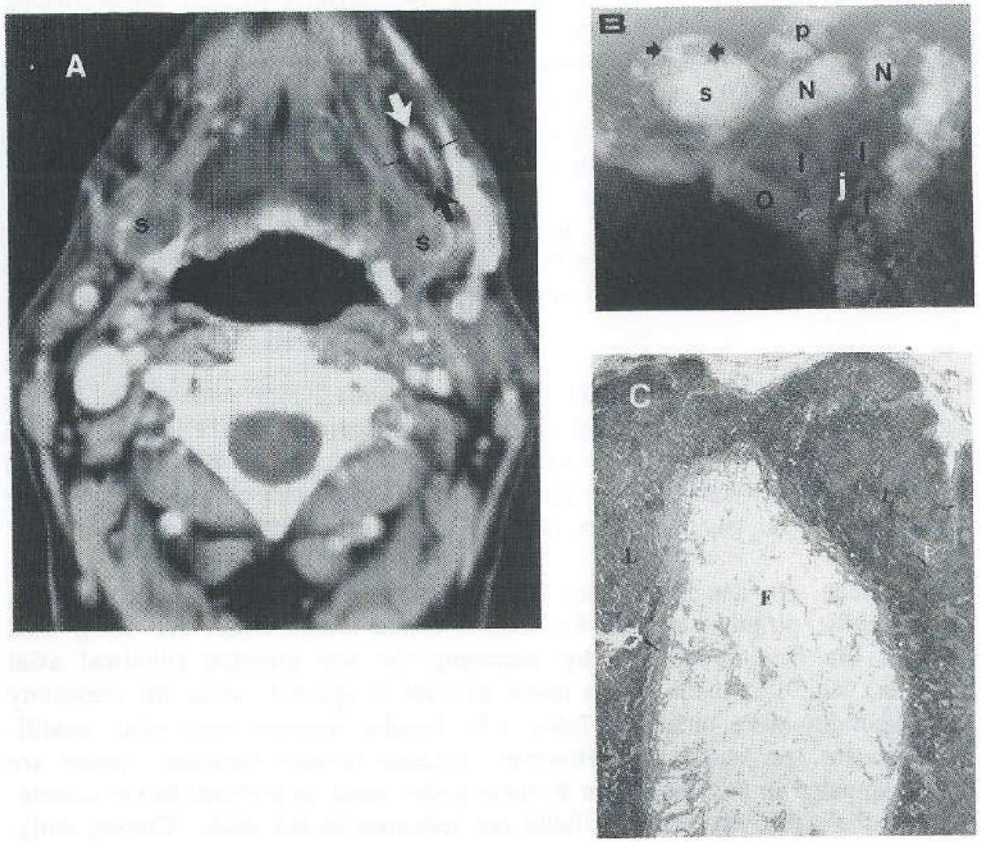


Figure 3.7. A. Contrast enhanced CT scan (6 mm section thickness) obtained at the submandibular level in a 75-year-old patient with a T3N1 supraglottic carcinoma on the left side. Note the horseshoe-shaped submandibular node (thin arrows indicate minimal axial diameter, thick arrows indicate maximal axial diameter) with the hilar structure clearly visible. s = submandibular gland. B. Radiograph of the left neck dissection specimen. The submandibular node with adipose metaplasia is indicated with two arrows (maximal axial diameter). The internal jugular vein is radiolucent (j), as it contained no blood. The positive subdigastric nodes are shown in front, and behind the internal jugular vein (N). o = omohyoid muscle, s = submandibular gland, l = reactively enlarged nodes, p = parotid gland underpole. C. Histopathologic section of the reactively enlarged submandibular node shows the widened hilar structure filled with fat (F). L = lymphatic tissue.

3.3 and 3.4). The most useful criterion for the minimal axial diameter is between 10 and 12 mm. Because the longitudinal diameter was found to be a less valid size criterion as well (Table 3.2, Figs 3.3 and 3.4), coronal and sagittal MR scans will not add significant information for cervical lymph node staging. Friedman et al. (18) found that lymph node size can be up to 24 % (mean 15 %) larger in the specimen, than the measurements obtained at CT. We found that lymph node diameters in the specimen are 11% smaller to 22% larger (mean, 6.1% larger) larger than those measured at CT. This effect is probably caused by volume averaging effects or oblique scanning planes. We have determined that the fixation procedure does not shrink lymph nodes. Our size criteria thus have to be diminished by an average of 6.1% (we suggest using 10% to minimize sensitivity loss), depending on the section thickness used.

It is important to realize that, in some neck dissection specimens, reactively enlarged nodes were larger than the actual metastatic node(s). These reactively enlarged nodes may have caused these specimens to be classified as true-positive.

In contrast to some authors (8,11,13), we found that lymph node shape, combined with any diameter did not increase the accuracy of the minimal axial diameter criterion. This may be caused by the fact that maximal axial diameter combined with a roundish shape (greater than 80%) in fact corresponds to minimal axial diameter (shape = maximal axial diameter/minimal axial diameter).

Lymph node size and shape vary among the different levels in the neck, and, consequently, different criteria for level 1 and 2 lymph nodes are being used (11,12). We have found that by increasing the size criterion (minimal axial diameter) with 1 mm for lymph nodes in level 2, optimal values for sensitivity and specificity were obtained (Table 3.3). Results obtained from other modifications were less acceptable. However, because isolated metastatic nodes are seldom situated in the levels 5 or 6, these nodes never contributed to the calculations of the sensitivity and specificity per specimen in our study. Consequently, the size criteria for these nodes may differ from the ones in our study.

Groups of borderline nodes in an area of lymphatic drainage of the primary tumor (16) are suggestive of metastasis, and many authors use grouping as an additional criterion (7-9,11). Recently however, its value has been questioned (13). Our data show that groups of three or more borderline (minimal axial diameter minus 1-2 mm) lymph nodes are suggestive of lymph node metastasis. Adding this criterion increased the sensitivity of the size criterion but did not significantly influence the specificity (Table 3.3, Fig 3.4). However, the number

of patients meeting this criterion is too small to make definite conclusions. Groups of 2 borderline lymph nodes, proved to be a rather aspecific criterion.

Irregular contrast enhancement in the nodes, which can be caused by tumor necrosis, cystic tumor growth or (avascular) keratinization is used as a 100% specific criterion (6-11). As expected, this criterion was the most specific criterion in our study as well. To our knowledge, the sensitivity of necrosis has never been defined. For necrosis measuring 3 mm or larger, we found a sensitivity of 74%. These small foci can be detected reliably with use of conventional well performed contrast-enhanced CT or MR imaging with a section thickness of 3-6 mm (Fig 3.7) (17).
Because smaller necrotic foci are more common, the sensitivity of this criterion may be increased by making thinner sections or by increasing the contrast.

However, spontaneous lymph node necrosis, other malignancies, cysts, abscesses or adipose metaplasia may also simulate necrosis radiologically. In our series only centrally located adipose metaplasia imitated necrosis at contrast enhanced CT (Fig 3.6). Central adipose metaplasia of 3 mm or larger was present in four nodes of four specimens. This feature decreases the specificity of the tumor necrosis criterion at CT (hypoattenuated area) from 100% to 94%; thus it is still a reliable criterion. In MR imaging, fat tissue has a characteristic signal intensity, which decreases the probability of false-positive findings.

To interpret of the criteria used in this study, it is important to realize that all percentages were calculated for neck dissections with a certain prevalence of metastasis (54%), and the specimens were obtained from both palpatory positive and negative sides. The results shown might thus not apply to patients with a lower prevalence of lymph node metastasis, or for palpatory negative sides.

To select the most appropriate criteria for cervical lymph node imaging, one must decide whether a specific or a sensitive test is to be used. To reliably select patients who do not need elective neck treatment, criteria with a high negative predictive value should be chosen. To obtain this high negative predictive value, the number of false-negative results should be as low as possible.
In conclusion, we propose using the following radiologic criteria for assessing cervical metastasis in patients with a primary squamous cell carcinoma in the head and neck (Table 3.3):

1. Nodes with a minimal axial diameter of 11 mm or more in the subdigastric region and 10 mm or more in other lymph node-bearing regions should be considered metastatic.

2. Groups of three or more lymph nodes of 9 or 10 mm in the subdigastric region, and of 8 or 9 mm in other lymph node drainage regions of the tumor should be considered metastatic.

3. All nodes that show irregular enhancement at CT or MR and that are surrounded by a rim of enhancing viable tumor or lymph node tissue should be considered metastatic. At CT one must beware of hypoattenuated areas that are continuous with the lymph node border (hilus).

Together, these criteria had a sensitivity of 87% and a specificity of 94% per neck dissection specimen in our patient group (Table 3.3). With a prevalence of 54%, the negative predictive value was 86%, while the positive predictive value was 94%. The overall error, when using these criteria, was 9.9% (7 of 71).

Acknowledgement: We want to thank Mr. Willem W. de Jong for his technical support.

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Chapter 4

MAGNETIC RESONANCE IMAGING VS PALPATION OF CERVICAL LYMPH NODE METASTASIS

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In a series of 100 patients with head and neck carcinoma the preoperative findings of palpation and magnetic resonance (MR) were compared to the histopathologic findings in the neck dissection specimen. Results were compared with regard to both laterality and lymph node level (1 through 6). The accuracy for palpation in detecting affected sides was 68%. Gadolinium-enhanced MR images reliably upstaged 60% of the palpatory negative necks, the accuracy of MR imaging being 84%. However, for both modalities the sensitivity per level was too low to allow for selective neck dissections in case of only one positive level.
These findings show that apart from primary tumor staging, MR can improve the preoperative staging of cervical lymph nodes. In selected cases this may change the treatment plan to a "wait-and-see" policy or a more conservative type of neck dissection.

4.1. INTRODUCTION

The assessment of the status of the neck in patients with squamous cell carcinoma of the head and neck remains a problem. The false positive rate of palpation is in the range of 4% to 42% (1-12). The false negative rate by palpation alone depends mostly on the site and on the size of the primary tumor, and is in the range of 0 to 77 % (Table 4.1) (1,2,6,7,11-21).

In most institutions, a frequency of occult lymph node metastasis exceeding 15% to 20% is considered acceptable to justify elective treatment of the neck nodes. The neck is also treated electively if the neck must be entered for excision of the primary tumor, or if it is unlikely that the patient will turn up regularly for follow-up visits.

An accurate staging method could decrease the need for elective neck treatment only for the group of patients in whom this is considered exclusively on the basis of a high likelihood of occult nodal metastasis. This group consist mainly of patients with T1-2 floor of mouth and mobile tongue carcinomas, T1-3 supraglottic carcinomas, and patients undergoing bilateral neck dissections in carcinomas approaching or over the midline. Furthermore, patients that are currently not treated prophylactically, can benefit from accurate staging modalities as occult metastasis are detected earlier.

It is evident that there is a great need for overall improvement of the assessment of the neck, and particularly for palpatory negative necks. In this respect, many authors have emphasized the value of computed tomography (CT) as an imaging modality for assessing the neck (3-5,22,23). However, the overall error remains in the range of 7.5% (4) to 31% (8,22), depending on the imaging techniques, the criteria for malignancy used and the patient population studied.

To date, no large prospective study has been carried out on the value of magnetic resonance (MR) imaging for cervical lymph node staging (5,9,10,24-26). Based on a small study population, several authors have stated that conventional nonenhanced T1- and T2-weighted spin-echo (SE) images do not have diagnostic benefit over CT (5,10), or even over physical examination (9). In the previous chapter we established optimal MR examination techniques, using recent techniques such as gradient-recalled-echo (GE) and gadolinium (Gd)-DTPA as a contrast agent to enhance depiction of necrotic tumor tissue, avascular keratinized tumor areas or cystic tumor growth inside cervical lymph nodes (Fig 4.1) (24).

Author	Cases	Site and T-Stage	Incidence
Sako[2]	21	Oral Tongue (Tx)	38 %
Spiro[21]	95	Oral Tongue (T1)	29 %
Byers[19]	29	Oral Tongue (T1-2)	19 %
Spiro[21]	77	Oral Tongue (T2)	43 %
Fakih[17]	35	Oral Tongue (T1-2)	60 %
Cunningham[18]	25	Oral Tongue (T1-2)	44 %
Mendelson[6]	295	Oral Tongue (T1-3)	20 %
Spiro[21]	13	Oral Tongue (T3)	77 %
Byers[19]	19	Oral Tongue (T3-4)	32 %
Ali[1]	35	Oral Cavity (All, Tx)	23 %
Cunningham[18]	29	Floor of Mouth (T1-2)	41 %
Mohit-Tabat.[20]	114	Floor of Mouth (T1-2)	16 %
Byers[19]	43	Floor of Mouth (T1-2)	19 %
Patterson[16]	42	Floor of Mouth (T1-3)	17 %
Byers[19]	19	Floor of Mouth (T3-4)	26 %
Byers[19]	10	Lower Lip (T1-2)	40 %
Byers[19]	14	Oropharynx (T1-2)	14 %
Ali[1]	9	Oropharynx (All, Tx)	44 %
Byers[19]	20	Oropharynx (All, T3-4)	50 %
Sako[2]	11	Oropharynx (Tonsil, Tx)	36 %
Sako[2]	11	Oropharynx (Tongue, Tx)	55 %
Candela[7]	27	Oropharynx (Tongue, Tx)	33 %
Candela[7]	21	Oropharynx (Lat Wall, Tx)	29 %
Candela[7]	13	Hypopharynx (Pir Sin, Tx)	15 %
Candela[7]	11	Hypopharynx (Wall, Tx)	18 %
Byers[19]	33	Hypopharynx (Tx)	55 %
Ali[1]	5	Hypopharynx (Tx)	20 %
Galioto[12]	42	Larynx (All, Tx)	29 %
Byers[19]	14	Glottic Larynx (T1-2)	21 %
Mendenhall[15]	75	Glottic Larynx (T2)	3 %
McGavran[11]	4	Glottic Larynx (T2-3)	0 %
O'Keefe[13]	18	Glottic Larynx (T2-4)	11 %
Byers[19]	57	Glottic Larynx (T3-4)	14 %
Ali[1]	20	Supraglottic Larynx (Tx)	5 %
McGavran[11]	25	Supraglottic Larynx (Tx)	4 %
Byers[19]	13	Supraglottic Larynx (T1-2)	30 %
Levendag[14]	79	Supraglottic Larynx (T1-2)	35 %
O'Keefe[13]	28	Supraglottic Larynx (T2-4)	32 %
Byers[19]	80	Supraglottic Larynx (T3-4)	25 %
McGavran[11]	23	Subglottic Larynx (Tx)	22 %
O'Keefe[13]	22	Subglottic Larynx (T2-4)	23 %
McGavran[11]	16	Transglottic Larynx (Tx)	31 %

Tx = all T stages

Table 4.1. Incidence of occult nodal metastasis per site and T-stage.

Basis on a pathoanatomic study, we defined more accurate radiologic criteria for cervical lymph node malignancy (chapter 3, ref 27). Nodes are interpreted as malignant on MR images if: 1. central necrosis is depicted; 2. their minimal axial diameter exceeds 11 mm in the subdigastric region (level 2), or 10 mm in other lymph node regions (levels 1,3,4,5 and 6); and 3. groups of 3 or more borderline nodes (minimal axial diameter 1 or 2 mm smaller, i.e. 9 or 10 mm for subdigastric nodes, 8 or 9 mm for all other nodes) are seen in the first or second echelons of the primary tumor.

In this study, 100 patients with head and neck cancer, undergoing a neck dissection as part of the treatment, were evaluated preoperatively with MR to establish the sensitivity and specificity of MR for all patients, and especially for the patients undergoing elective neck dissections. All findings were correlated with the histopathologic findings in the neck dissection specimens. The possible consequences for neck treatment policy are discussed.

4.2. PATIENTS AND METHODS

Within 1.5 years, 100 patients scheduled for a therapeutic or elective neck dissection for squamous cell carcinomas of the upper air and food passages (Table 4.2), were examined preoperatively with MR. A total of 136 comprehensive (all levels) and/or selective (not all levels) neck dissections were performed. Sixty-four patients underwent unilateral and 36 patients underwent bilateral neck dissections, usually in continuity with excision of the primary tumor. Histopathologic examination showed that 82 out of 136 neck dissections contained metastasis (prevalence of metastasis 60%), whereas 54 proved to be free of lymph node metastasis. Sixty sides were electively operated on, of which 14 sides were in patients with T1-2 anterior floor of mouth or mobile tongue carcinoma and 20 were contralateral sides in patients with (other) tumors approaching or crossing the midline.

Imaging and histopathologic examination protocols were as described in the previous chapters. Images were made within 4 weeks before surgery on a 0.6-Tesla MR system (Teslacon II, Technicare), using a partial volume (half saddle-shaped) coil. Axial slices were made from skull base to the clavicle. Axial T1-weighted SE images (TR/TE: 595 ms/20 ms, 4 excitations) and T2 weighted GE images (TR/TE/flip angle: 285 ms/32 ms/8°-12°, 6 excitations) with a slice thickness of 5 mm (interslice gap 50 %) were made in all patients. If MR images showed enlarged or borderline nodes, Gd-DTPA (Magnevist, Schering, Germany) was injected intravenously while obtaining T1-weighted GE images

(TR/TE/flip angle: 95-126 ms/16-20 ms/45°, 8 excitations) with a slice thickness of 3-5 mm of the levels in which suspect nodes were visualized.

	T-Stage				
Primary Site	T1	T2	T3	T4	All
Oral cavity	5	17	15	6	43
Oropharynx	2	6	13	5	26
Hypopharynx	1	3	6	1	11
Larynx	0	7	5	5	17
Other	0	1	0	2	3
All	8	34	39	19	100

Table 4.2. Patient population.

All patients were clinically staged by one head and neck surgeon (GAC) and all MR images were interpreted by two experts (JAC and MWM vdB) who had to reach a consensus. All investigators were "blind" about each others' findings. Findings were recorded per lymph node region, as well as per side.

To compare reliably the histopathologic examination with the MR images, a radiograph of all neck dissection specimens was obtained having immersed these in 96% ethanol (Figs 4.1.c and 4.3.c). This technique enables exact localization of lymph nodes in the specimen, as density variations by thickness variations of the specimen are not visualized. All lymph nodes were excised from the specimen and examined microscopically, at 3-4 mm intervals, by at least two investigators (MWMvdB, HVS or IvdW). The clinical and MR findings per side (left or right neck) and per lymph node level were compared with the histopathologic outcome of the neck dissection specimen. Because lymph node metastases are relatively rare in levels 5 and 6, these levels are taken together.

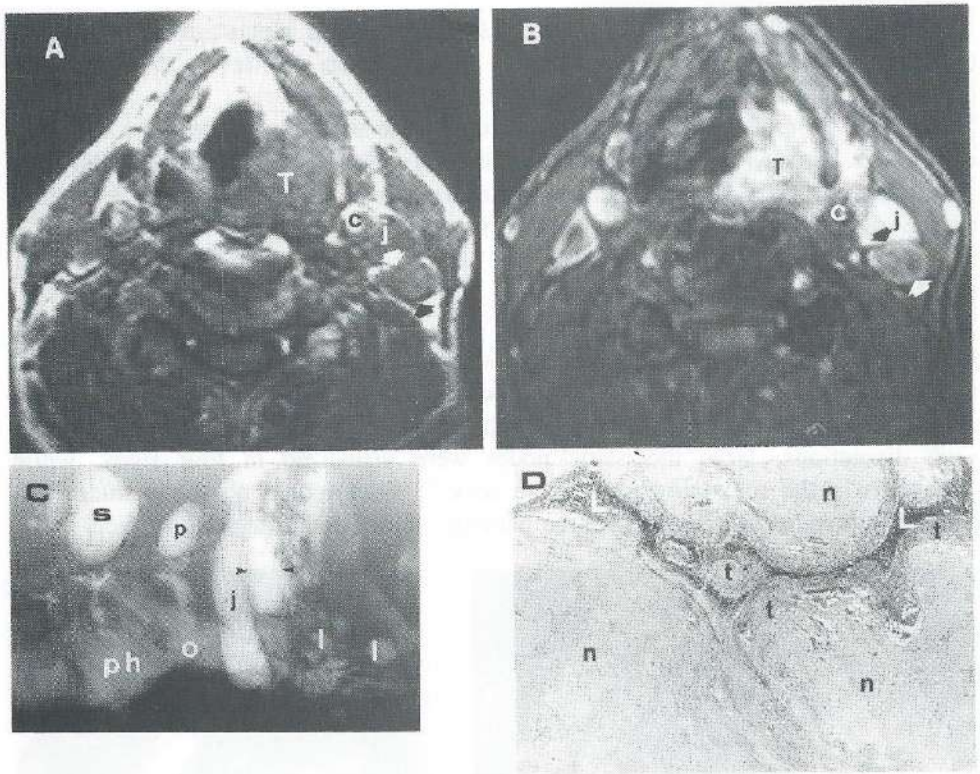

Figure 4.1. A. T1-weighted spin echo MR image at the midjugular level in a 76 years old man with a T4N2b oro-hypopharyngeal carcinoma on the left side. Note the homogeneous lymph node (arrows indicate the minimal axial diameter) dorsal to the internal jugular vein (j). T = primary tumor, c = carotid artery. 1B. Gadolinium enhanced T1-weighted gradient echo MR image at the same level. The lymph node (arrows) is clearly depicted with inhomogenous signal intensities. The enhancing primary tumor surrounds the thyroid cartilage. 1C. Specimen radiograph of the left neck dissection with the peripharyngeal-laryngeal tissue (ph), made after removal of the larynx, pharynx and sternocleidomastoid muscle. The arrowheads indicate the positive midjugular node. l = some reactive lymph nodes, S = submandibular gland, p = peripharyngeal reactive node, o = omohyoid muscle, j = jugular vein. 1D. Microscopic detail of the midjugular metastatic node, showing viable tumor cells (t), necrotic tumor tissue (n) and preexistent lymphatic tissue (L).

4.3. RESULTS

4.3.1. Histopathology.

A total number of 5376 nodes from 609 levels in 136 neck dissection specimens were examined histopathologically. Three-hundred-nineteen of these nodes, in

146 levels, in 82 specimens from 67 patients contained metastases of squamous cell carcinoma. On the other hand, 5057 lymph nodes, 463 levels, 54 specimens and 33 patients were free from metastatic tumor.
Because of volume averaging effects, and oblique scanning planes, the differences in size between nodes depicted on the images (on screen measurements), and the nodes measured in the specimen varied between 12% larger, to 25% smaller on the images (mean, 7% smaller on the images).

4.3.2. Excluded patients.

MR examinations were diagnostic in most of the cases. In two patients, who underwent three neck dissections, the quality of the images obtained was too poor to allow reliable interpretation. In another five patients, who underwent seven neck dissections, large metastatic nodes were visualized in four sides, while metastasis in the remaining part of the neck (3 sides) could not be excluded because of movement artifacts. In three patients major dental material artifacts

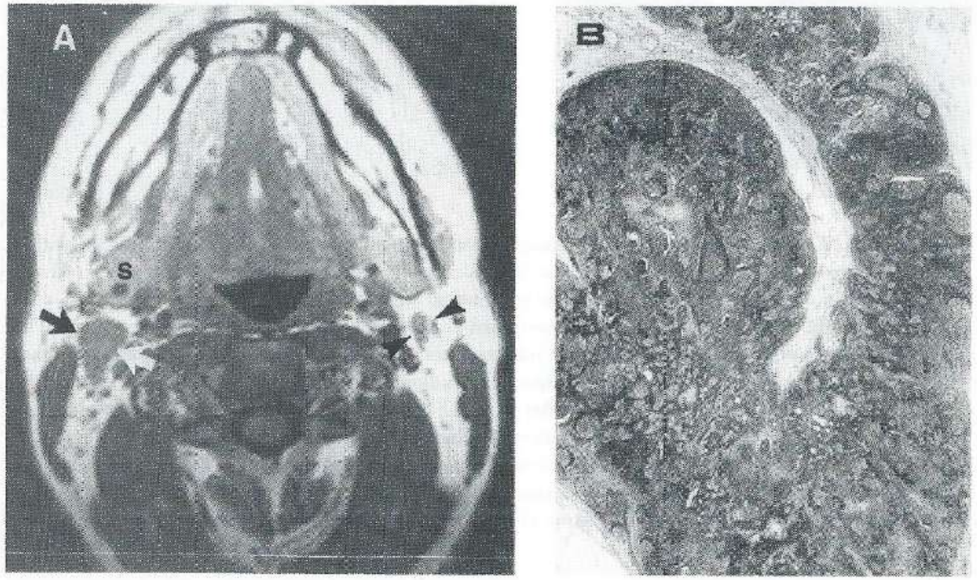

Figure 4.2. A. T1-weighted spin echo MR image at the subdigastric level in a 47 years old man with a T4N1 carcinoma of the retromolar trigone on the right side. The image clearly shows the large palpated lymph node (minimal axial diameter indicated with arrows: 13 mm). On histopathological examination this node, and all other nodes in the specimen, were free from tumor. A small node on the left side is indicated with arrowheads. S = submandibular gland. 2B. Microscopic slide of the reactively enlarged subdigastric lymph node on the right side. In none of the sections through this lymph node metastatic tumor tissue was found.

obscured the first level. Two patients, who were left out of this study refused MR examination because of claustrophobia. One hundred and thirty sides (78 positive, 52 negative), containing 557 lymph node levels (129 positive, 428 negative) from 98 patients were available for clinicoradiologic comparison.

4.3.3. Findings per side.

Findings at physical examination are given in table 4.3. Palpation was correct in 88 of 130 sides (accuracy 68%). Seventeen sides were falsely interpreted as positive. In 25 clinically negative sides occult metastases were found. Consequently, sensitivity of palpation was 68%, and specificity was 67%.
Interpretation of MR images (Table 4.3) was correct in 109 of 130 sides (accuracy: 84%). MR findings were false positive in six sides (Fig 4.2). Fifteen sides were falsely scored negative (Fig 4.3). Consequently, MR sensitivity was 81% and specificity was 88%. Regarding the 60 sides that were electively dissected (clinically N0), MR sensitivity, specificity and accuracy were 60%, 89% and 77% respectively (Table 4.4).

4.3.4. Findings per level.

The palpatory findings in the 557 lymph node levels compared with histopathological outcome revealed an accuracy of 84% for palpation (Table 4.5). Sensitivity and specificity were 51% and 94% respectively. Sensitivity of palpation for level 1, 2, 3, 4 and 5 or 6 was 43%, 62%, 41%, 50% and 33%, respectively.

	PATHOLOGY		TOTAL
	posit.	negat.	
Palp. +	53	17	70
Palp. -	25	35	60
MR +	63	6	69
MR -	15	46	61
TOTAL	78	52	130

Palpation: Sensitivity: 68%, Specificity: 67%, Accuracy: 68%.
MR: Sensitivity: 81%, Specificity: 88%, Accuracy: 84%.

Table 4.3. Findings in 130 sides.

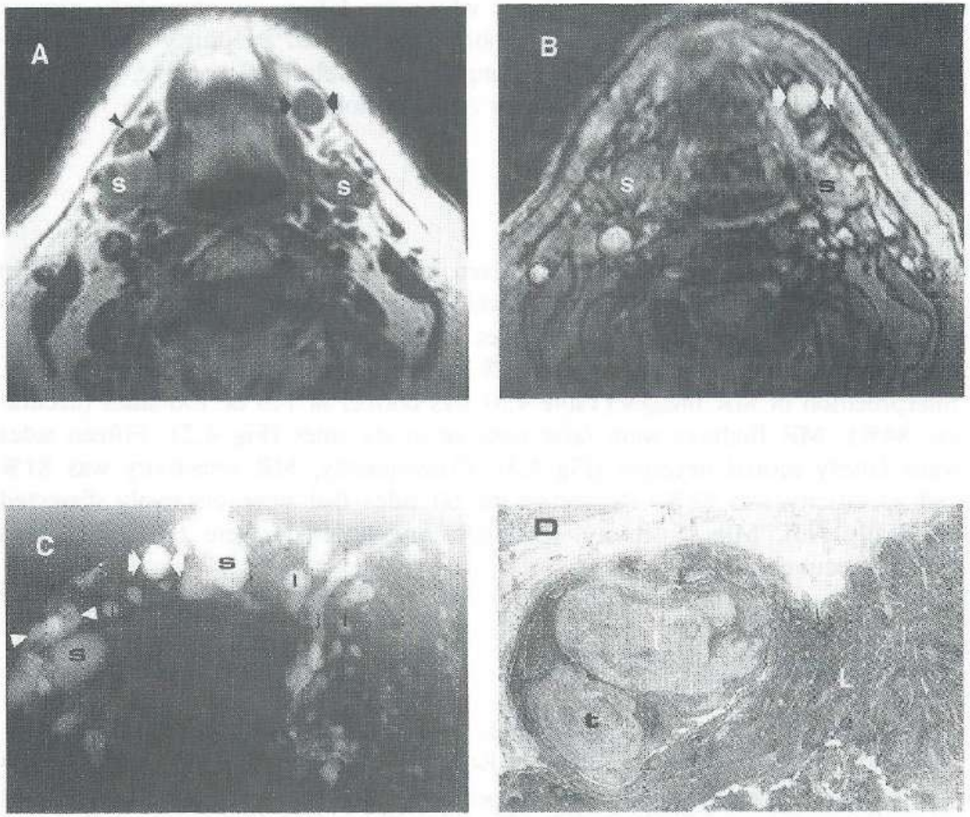

Figure 4.3. A. T1-weighted spin echo MR image at the submandibular level in a 68 years old man with a T1N0 midline floor of mouth carcinoma. On the left side a lymph node in front of the submandibular gland (s) is clearly shown (arrows indicate the minimal axial diameter of 1 cm). A small node (4 x 5 mm) on the right side enclosed by a horseshoe shaped node (14 x 9 mm) is depicted as well (arrow-heads). 3B. Gadolinium enhanced T1-weighted gradient echo image at the same level. The enlarged lymph node on the left side (arrows) shows irregular enhancement, indicating metastasis. The small lymph node on the right side is not clearly depicted anymore, but proved to be metastatic on histopathological examination. 3C. Specimen radiography of the comprehensive neck dissection specimen on the left side and the anterolateral specimen on the right side (the primary tumor and the sternocleidomastoid muscle are dissected off). The metastatic submandibular node on the left side is indicated with arrows, whereas the metastatic node on the right side is indicated with arrow-heads. (j = internal jugular vein, l = some reactive lymph nodes). 3D. Microscopic detail showing the missed metastatic submandibular node on the right side (t = viable tumor cells) surrounded by the horseshoe shaped lymph node (L).

Specificity of palpation for level 1, 2, 3, 4 and 5 or 6 was 90%, 82%, 98%, 100% and 98% respectively.

Comparison of the MR findings in the 557 lymph node levels with histopathological outcome revealed an accuracy of 90% (Table 4.5). MR sensitivity and specificity were 67% and 97% respectively. Sensitivity of MR for level 1, 2, 3, 4 and 5 or 6 was 57%, 83%, 59%, 25% and 50%, respectively. Specificity of MR for level 1, 2, 3, 4 and 5 or 6 was 97%, 88%, 98%, 100% and 100% respectively.

	PATHOLOGY		TOTAL
	posit.	negat.	
MR +	15	4	19
MR -	10	31	41
TOTAL	25	35	60

Sensitivity: 60%, Specificity: 89%, Accuracy: 77%.

Table 4.4. MR findings in 60 clinical N0 sides.

	PATHOLOGY		TOTAL
	posit.	negat.	
Palp. +	66	25	91
Palp. -	63	403	466
MR +	87	13	100
MR -	42	415	457
TOTAL	129	428	557

Palpation: Sensitivity: 51%, Specificity: 94%, Accuracy: 84%.
MR: Sensitivity: 67%, Specificity: 97%, Accuracy: 90%.

Table 4.5. Findings in all 557 levels from 130 neck dissection specimens.

4.4. COMMENT

To our knowledge, the value of contrast (gadolinium)-enhanced, gradient recalled echo MR imaging to assess the status of the neck in a large number of head and neck cancer patients has not been studied before. Furthermore, recently established radiologic criteria for lymph node metastasis in the neck (27) might contribute to greater accuracy for all imaging modalities. As the indications for MR examinations in patients with head and neck cancer are rapidly increasing (26,28-33), the need to determine the accuracy of MR for cervical lymph node staging is growing. Our results show that Gd-DTPA enhanced MR imaging is a valuable tool for cervical lymph node staging, the overall error being twice as low as that of palpation. In contrast to findings by Feinmesser et al. (9) we found that necrosis as small as 3 mm can be depicted in a well conducted MR examination (Figs 4.2 and 4.4). It can however be missed in case of minor movement artifacts.

The sensitivity to detect metastasis in the neck in this study (81%) (Table 4.3) is slightly lower than the 87% predicted in our previous pathoanatomic study (27). This may have several reasons. Firstly, borderline lymph nodes and small necrotic foci can be overlooked on the images. Secondly, lymph node size on the images can be underestimated because of volume averaging effects. Furthermore, small necrotic areas (3 - 5 mm) may not be depicted in MR examinations with minor movement or pulsation artifacts. Fast-imaging techniques might resolve this problem in future.

The findings in 557 lymph node levels (Table 4.5) as compared to the findings in 130 sides, show an increase of specificity, whereas sensitivity decreases for both palpation (to 51%) and MR (to 67%). The loss of sensitivity is caused by small undetected metastatic nodes at lower levels in the neck, that often accompany detectable metastatic nodes in the first lymph node drainage region of the primary tumor. Furthermore, in some patients the radiologically suspect node proved to be reactively enlarged, whereas a small metastatic node at another level remained hidden. The low incidence of lymph node metastasis per level (129/557 = 23%) as compared to the incidence per side (60%) contributes to the higher specificity. The differences in sensitivity in the different levels for palpation can be explained by the size of the metastasis (more often micrometastasis as the only metastasis in level 3 - 6) and by the location of the submandibular gland and the sternocleidomastoid muscle. The differences per level for MR detectability are more diffcult to explain. Apart from the first above mentioned reason, the use of a partial volume coil encircling the anterior neck, might explain the low sensitivity

for the posterior neck (level 5). Images at low jugular region (level 4) are often disturbed by breath movements and the shoulders being projected in the small field of view. The mobile mandible and the abundant fat often obscure nodes in the submandibular region (level 1) by motion artifacts and volume-averaging effects.

These figures clearly show, that neither MR nor palpation is accurate in evaluating the number and level of lymph node metastasis, as the sensitivity of both modalities in detecting small metastasis is insufficient. Consequently, even if only one metastasis is detected, it is our policy to perform a comprehensive neck dissection.

In this study, no comparison between MR and CT was made. The sensitivity and specificity of CT in some studies is reported to be better than our MR results (4,5,23), whereas other studies have reported figures not as good as ours (3,8,10,22). The sensitivity of 60% that we found for the electively treated sides, compares favorably to the 38% Stern et al. (22) found for CT. However, reliable comparison of the sensitivity and specificity between different studies is impossible owing to nonequivalent patient populations (different primary tumors and stages; Table 4.1). Furthermore, different studies are not comparable owing to the varying radiologic criteria used and the different imaging techniques.

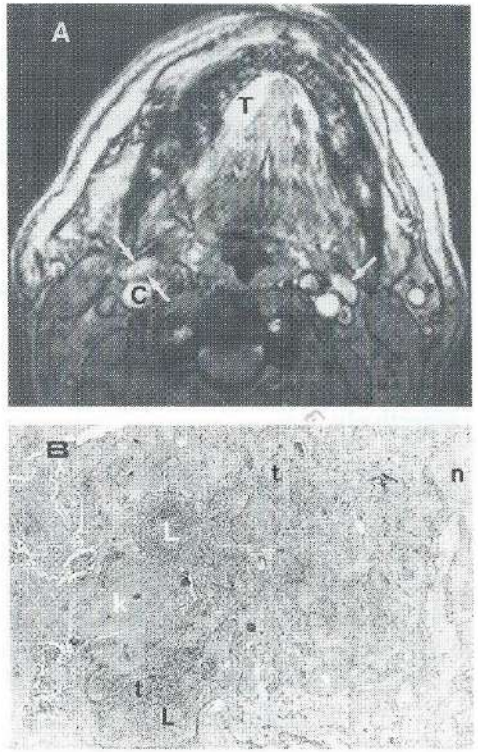

Figure 4.4. A. Gadolinium enhanced T1 weighted gradient echo image at the subdigastric level in a 54 years old man with a T2N0 squamous cell carcinoma of the floor of mouth on the right side (T), approaching the midline. In front of the right internal carotid artery (C) an irregularly enhancing node is visualized (arrows indicate a minimal axial diameter of 7 mm). This pattern of enhancement corresponded to the pattern of necrotic tumor foci in this node. The small bilobular node located at the same place on the left side (arrow) with a minimal axial diameter of 8 mm, though depicted with a low signal intensity central area, and thus interpreted as malignant, contained only a small micrometastasis on histopathologic examination. 4B. Microscopic detail of the depicted metastatic subdigastric node on the right side showing small foci of tumor necrosis (n), fields of non-vascularized tumor keratinization (k), viable tumor cells (t) and preexistent lymphatic tissue (L).

As discussed in the introduction, improved staging of the neck may decrease the need for elective neck treatment in relatively small primary carcimas like T1-2 mobile tongue and anterior floor-of-mouth carcinomas, and for the contralateral side in tumors crossing or approaching the midline. In the 98 patients studied, 14 elective neck dissections were performed for T1-2 mobile tongue or anterior floor-of-mouth carcinomas, whereas another 20 dissections were elective contralateral dissections for primary tumors crossing or approaching the midline. In 11 (32 %) of these 34 elective neck dissection specimens, occult metastatic lymph nodes were found. MR was capable of reliably upstaging seven (64%) of these 11 falsely negative staged sides, whereas in only four sides were occult metastasis not detected. Two sides were falsely interpreted as positive at MR. MR sensitivity and specificity in this important group are thus 64% and 91% respectively.

Because only 60% to 64% of the palpatory occult metastases can be detected with MR (Table 4.4), it seems irresponsible to rely exclusively on MR findings in selecting the patients for prophylactic neck treatment. However, the risk of occult lymph node metastasis is greatly influenced by the site (Table 4.1) and other factors (11,12,20,34) concerning the primary tumor. Therefore, a multifactorial analysis, including the above-mentioned factors as well as the general condition of the patient in addition to the MR (or other radiologic) findings of the neck may provide the optimal means to select patients for prophylactic neck treatment. MR imaging can also be helpful to select the most appropriate prophylactic neck treatment modality or technique. In this respect a negative MR examination can direct the treatment to a more selective type of neck dissection, or an unilateral in stead of bilateral neck dissection in case of tumors approaching or crossing the midline. Consequently, all patients with risk for occult metastasis should be subjected to additional radiologic investigations for lymph node staging.

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Chapter 5

OCCULT METASTATIC NECK DISEASE: DETECTION WITH ULTRASOUND AND ULTRASOUND-GUIDED FINE NEEDLE ASPIRATION CYTOLOGY

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A prospective study on the value of ultrasound (US) and US-guided fine needle aspiration cytology (FNAC) for the assessment of the "N0" neck was performed. Preoperative US was performed in 107 patients with squamous cell carcinoma of the head and neck, who underwent 132 elective neck dissections. During the US examination of the last 54 patients, who underwent 70 elective neck dissections, US-guided FNAC was used. US alone was found to be an unreliable method for detecting occult lymph node metastasis; the accuracy never exceeded 70% (93/132), with a sensitivity of 60% (32/53) and a specificity of 77% (61/79). In contrast, US-guided FNAC had an accuracy of 89% (62/70), a sensitivity of 76% (25/33) and a specificity of 100% (37/37).
Because of the high sensitivity and specificity of US-guided FNAC for the assessment of the "N0" neck, this modality can play an important role in directing treatment of the palpably negative neck in future.

5.1. INTRODUCTION

Cervical lymph node staging in patients with head and neck carcinomas remains a major concern of all head and neck cancer surgeons. Staging of neck lesions with palpation is reported to yield false-negative results in 0% to 77% of cases (1,2), depending on the site (3), size (4) and other parameters (5) of the primary tumor.
To date, computer tomography (CT) and magnetic resonance (MR) imaging have enabled detection of 38% to 67% of these occult lymph node metastases (6-8). These figures however, have not led to a more conservative approach towards the palpably negative neck in most institutions. Consequently the need for a more sensitive technique remains.
Most studies involving ultrasound (US) of the neck claim that US is superior to palpation for the detection and quantification of cervical lymph node metastasis (9-20). Although some authors defined criteria for diagnosis of malignant or benign nodes at US (14-17), US alone does not enable differentiation between enlarged reactive nodes and enlarged metastatic nodes (9-13). This can be explained by the fact that US does not reliably depict tumor cells, necrotic tumor tissue or tumor keratinization in lymph nodes. Therefore, the only criteria remaining for differentiating between reactive and metastatic lymph nodes are size (minimal axial diameter) and grouping of three or more borderline lymph nodes (21).
US-guided fine needle aspiration cytology (FNAC) may give cytologic evidence of tumor in a large percentage of metastatic nodes. Although some authors studied US-guided FNAC in patients with head and neck cancer (11,18,20), to our knowledge none has studied this technique in a homogeneous group of previously untreated patients who underwent elective neck dissections for their palpably negative neck sides.
In this study the usefulness of US and US-guided FNAC for detecting occult cervical lymph node metastasis is assessed.

5.2. PATIENTS AND METHODS

One hundred seven patients with head and neck squamous cell carcinoma that was previously untreated (Table 5.1) were examined with US over a period of 1½ year. These 107 patients underwent a total of 132 elective neck dissections that were either comprehensive or selective. At palpation by an experienced head and neck surgeon, these 132 necks were found to contain no metastatic lymph nodes (N0). Decisions regarding elective neck treatment were based mainly on the site and stage of the primary tumor.

In principle, US and US-guided FNAC findings had no influence on the treatment policy of the neck; whereas negative US or US-guided FNAC findings never influenced the policy, in four cases positive aspirates necessitated performance of an unanticipated neck dissection.

Site	T-Stage				All
	T1	T2	T3	T4	
Oral cavity	4	24	15	5	48
Oropharynx	0	6	9	4	19
Hypopharynx	0	4	5	0	9
Larynx	0	6	11	10	27
Other	0	0	0	4	4
All	4	40	40	23	107

Table 5.1. Patient population per primary tumor site and stage.

In the second part of this study in which 54 of the 107 patients, who underwent 70 elective neck dissections, were examined with US, US-guided FNAC was available. US-guided FNAC of 57 of these 70 sides was performed.

All specimens obtained at neck dissection were thoroughly examined histopathologically; all nodes that were visible on the specimen radiograph of the specimen or were palpable in the specimen itself were excised and documented by one physician (MWMvdB). Depending on the size of the lymph node, sections were made every 3 to 4 mm, and all sections were examined histopathologically, as described in the previous chapters. Exact documentation of the site and size of all lymph nodes that were examined in the specimen enabled us to retrospectively correlate the lymph node that was punctured at US-guided FNAC with the lymph node found in the specimen in the great majority of sides. All histopathologic slides were revised by an experienced pathologist (HVS or IvdW). Correlation between histopathologic and US findings was determined for each specimen (side) and for each level in the neck. Histopathologic and US-guided FNAC findings were correlated for each specimen (side) only.

Real-time, B-scan US examinations (Aloka SSD 650, Tokyo) were performed using a 7.5 MHz linear array transducer. Levels 1 through 5 of both sides of the

neck were fully examined for the presence of enlarged lymph nodes. All nodes that were visible at US were measured on screen. Levels 2-5 were examined craniocaudally in the axial plane. Only nodes in level 1 were examined in the coronal and sagittal planes. Radiographic prints were made of all enlarged lymph nodes, indicating the size and the region and side of the neck being imaged. Since in chapter 3 it was shown that the minimal axial diameter is the most accurate criterion for size, we again used this criterion for evaluation of nodes depicted at US. For subdigastric nodes the minimal axial diameter criterion was considered to be 1 mm larger than that of other nodes. In addition, a grouping of three or more borderline nodes (each of which was 1 or 2 mm smaller than the size criterion chosen) in the tumor drainage regions was also considered to contain metastasis. In this study, several size criteria for nodes seen at US were compared to assess which was most accurate for evaluation of clinically negative necks (Table 5.2).

During the last 8 months of the study, US-guided FNAC was performed (MWMvdB). Lymph nodes varying from 3 to 12 mm in minimal axial diameter in 57 sides were aspirated. The most suspicious (largest) lymph node(s), in the tumor drainage regions in one or both sides of the neck was punctured. One to three lymph nodes per side were aspirated. Most lymph nodes were punctured twice to ensure that sufficient material was obtained.

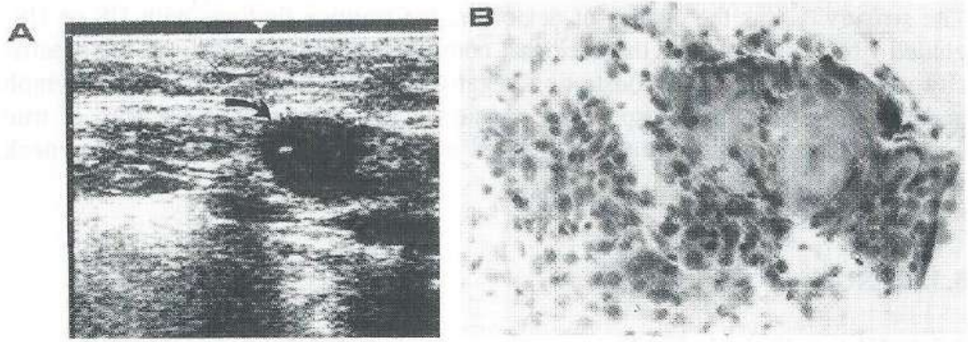

Figure 5.1.A. US image obtained with a 7.5 MHz linear array transducer during aspiration of a subdigastric lymph node (curved arrow) that was fully replaced by a metastasis. Note the hyper-echogenic spot inside the node, representing the needle tip. B. Detail of the obtained cytologic smear stained with May-Grünwald-Giemsa. Note the keratinizing cells, as often seen in smears from squamous cell carcinomas.

After antiseptic preparation, US-guided aspirations were performed without use of a biopsy guide attached to the transducer, by using a syringe holder (Cameco, Taeby, Sweden) and a 0.6 mm x 25 mm needle. The needle was introduced into the skin 0.5 to 1 cm from the transducer, at the middle of the long axis of the transducer. After visualization of the needle point inside the lymph node (Fig 5.1), aspiration was started and continued by moving the needle gently up and down. The smears were fixed using 70% ethanol and stained with Papanicolaou and air-dried and stained with May-Grünwald-Giemsa solution. The needle and syringe were washed with carbowax (Union Carbide, Danbury, Conn) to obtain additional smears. All smears were examined and revised by one observer (HVS).

To obtain a high sensitivity at US-guided FNAC, necks were considered to be positive if one or more aspirates proved to be positive or suspicious for malignancy at cytologic examination. Neck sides were considered negative at US-guided FNAC examination if no suspicious nodes were visualized in the drainage regions of the primary tumor (and thus no aspirate was obtained), or if all smears were found negative at cytologic examination. Smears that contained insufficient material for a cytologic diagnosis were considered to be negative as well, although calculations excluding these aspirates are given as well.

Sensitivity, specificity and accuracy of US and US-guided FNAC were estimated by using the histopathologic findings in the neck dissection specimens as a standard of reference. Findings at US and histopathology were compared for each side and each level of the neck, and not for each node or for each patient. The sensitivity was the chance of demonstrating positive findings with US or US-guided FNAC in a side of the neck that contained metastasis, whereas the specificity was the chance of demonstrating negative findings when no metastatic lymph nodes were present in the specimen. Accuracy was estimated as the sum of true positive and true negative results, divided by the total number of examined neck sides.

5.3. RESULTS

5.3.1. Histopathologic Findings.

Of the 132 neck dissection specimens obtained, 53 (40%) contained metastatic lymph nodes, whereas 79 (60%) were tumor negative on histopathologic examination. Consequently, the sensitivity, specificity and accuracy of palpation were 0%, 100% and 60% respectively. At histopathologic examination of the sides

examined with US-guided FNAC, 33 of the 70 specimens obtained were found to contain metastatic lymph nodes, whereas 37 were found to be free of tumor.
Twenty-four to 87 (mean: 46) lymph nodes were found in specimens obtained from comprehensive neck dissections. In specimens obtained from selective (supraomohyoid, lateral or anterolateral) neck dissections, six to 48 lymph nodes were found (mean: 16).
The number positive nodes in the tumor positive specimens varied from one to five metastatic nodes (mean 1.8).

5.3.2. US Findings.

US findings were compared with the histopathologic findings in the neck dissection specimens of all 107 patients. All US examinations were diagnostic. Because metastatic lymph nodes often contain necrotic or keratinizing tissue, as well as preexisting lymphatic tissue, we looked for specific US features to serve as criteria for malignancy. US pattern and homogeneity were compared between metastatic and reactively enlarged nodes.

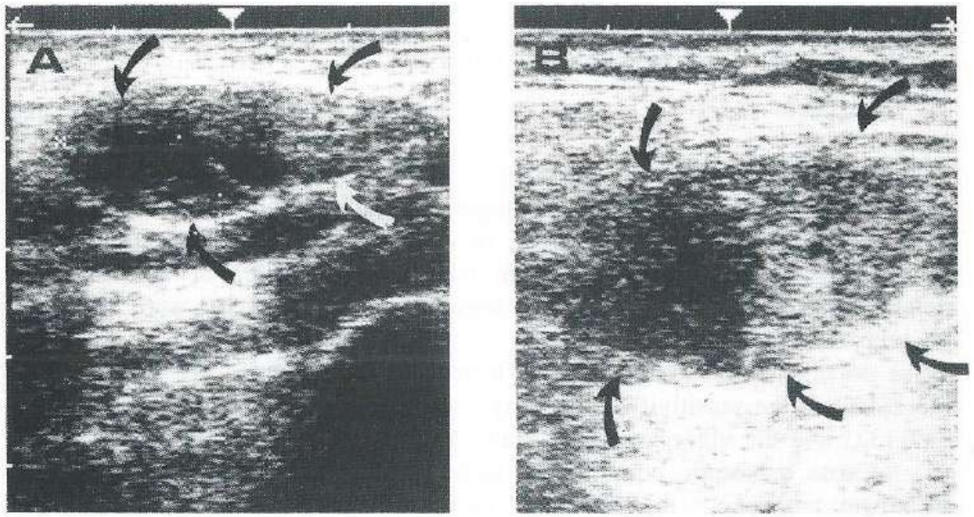

Figure 5.2. US images of two large lymph nodes (curved arrows) in different patients with inhomogenous US reflection patterns. Although these inhomogenities are certain arguments for metastasis and are caused by a mixture of keratinizing tumor, cystic tumor, viable tumor cells or reactive lymph node tisue and fat, such patterns are almost never encountered in small non-palpable lymph nodes.

Although large metastatic nodes often exhibit inhomogeneous patterns at US (Fig 5.2) - reflecting cystic or necrotic tumor, lymphatic tissue, solid tumor, fat or keratinizing tumor - these inhomogeneous US patterns were less frequently encountered in small nonpalpable lymph nodes, as evaluated in this study. With use of a 7.5 MHz transducer, reactively enlarged nodes, as well as small metastatic nodes were often found to be well circumscribed and homogeneously hypoechogenic. Furthermore, areas of hyperechogenicity could represent fatty tissue as well as keratinizing tumor (Fig 5.3). Thus, we used only the criterion of nodal size and grouping at US to predict malignancy. In table 5.2 the sensitivity, specificity and accuracy of several minimal axial diameters are shown.

Size*	Sensit %	Specif %	Accur %
≥ 4 mm	89	33	55
≥ 5 mm	85	44	61
≥ 6 mm#	81	59	68
≥ 7 mm#	60	77	70
≥ 8 mm#	42	85	67
≥ 9 mm#	26	95	67
≥ 10 mm#	15	97	64

* : Minimal axial diameter, and 1 mm larger for subdigastric nodes
# : Three or more nodes grouped that are 1 or 2 mm smaller.

Table 5.2. Sensitivity, specificity and accuracy of different US criteria for malignancy in 132 N0 sides.

Accuracy was optimal (70%) when a single node had a minimal axial diameter of 7 mm (8 mm in the subdigastric area), or when each node in a group of at least three borderline nodes was not more than 2 mm smaller in minimal axial diameter. The corresponding optimal sensitivity and specificity were 60% and 77% respectively.

Precise documentation of the US and histopathologic findings per level enabled us to calculate the sensitivity, specificity and accuracy for level 1 (n=108), level 2 (n=132) and the other levels (3, 4 and 5 together) (n=126) separately (Table 5.3). Because metastatic lymph nodes in level 6 are rare, and did not occur in this patient population, this level was excluded from this study. Accuracy per level proved to be much more dependant on the specificity, because the majority of levels were free from tumor at histopathological examination. The optimal size criterion (acceptable sensitivity) for level 1, 3, 4 and 5 nodes was smaller than 7 mm, as the sensitivity for this criterion was only 43% for level 1 nodes and

40% for level 3, 4 and 5 nodes. The best criterion for level 1 nodes was 5 mm or 6 mm, whereas the best criterion for level 3, 4 and 5 nodes was 4 mm or 5 mm. The nodal size criterion found for level 2 corresponded best to the optimal criteria we found per side. This can be explained by the fact that most early metastases are found at this level.

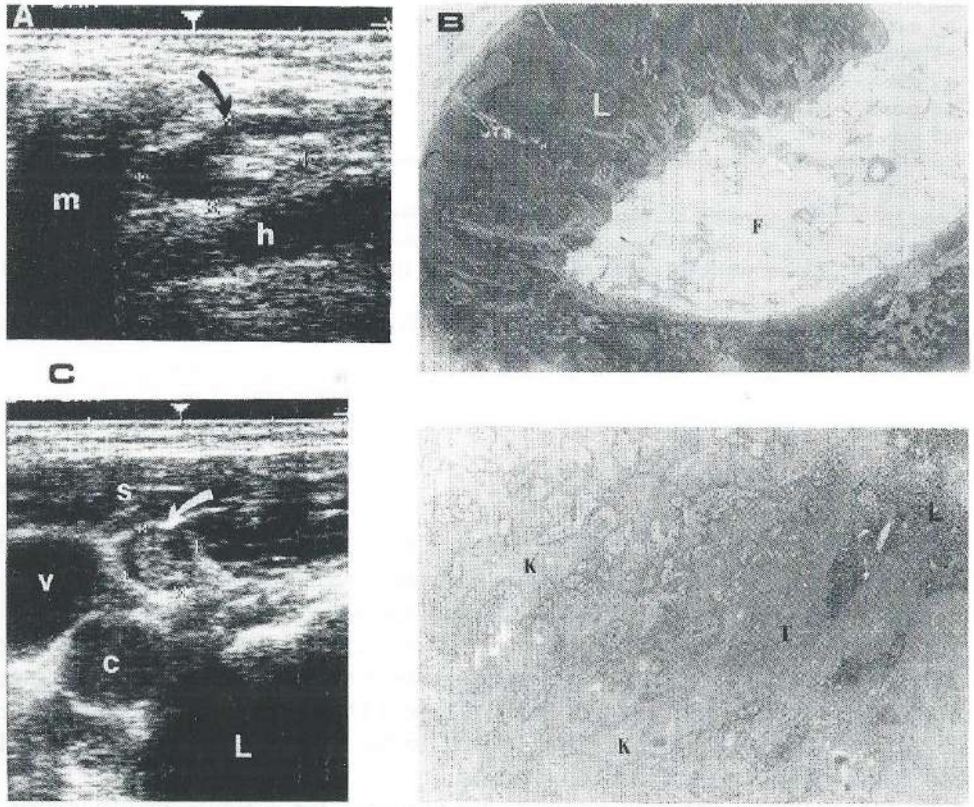

Figure 5.3 A. Fifty-seven-year-old male patient with a T4N1 mobile tongue carcinoma. US image of a submandibular node (curved arrow) with a hyperechogenic area inside. m = mandible, h = mylohyoid muscle. B. Histopathologic section of the same submandibular node, showing that the hyper-echogenic area was caused by fat tissue (F) in the hilar structure. L = preëxistent lymphatic tissue. C. Axial US image of a midjugular node (curved arrow) in a patient with a T2N0 floor of mouth carcinoma. Note the very similar hyper-echogenic area inside the node. v = internal jugular vein, c = carotid artery, L = pharyngeal lumen. D. Histopathologic detail of the same midjugular node, showing that this hyper-echogenic area was caused by a metastatic highly keratinizing squamous cell carcinoma (K). L = preëxistent lymphatic tissue, T = viable tumor cells.

Size	Sensitivity			Specificity			Accuracy		
	Level			Level			Level		
	1	2	3-5	1	2	3-5	1	2	3-5
≥4 mm	86	85	70	69	44	68	71	54	68
≥5 mm	79	85	65	73	53	75	74	61	74
≥6 mm	64	79	55	82	65	91	80	69	85
≥7 mm	43	76	40	93	79	96	86	78	87
≥8 mm	21	58	30	97	86	97	87	79	87
≥9 mm	14	39	10	99	92	100	88	79	86

Level 1: 108, of which 14 contained metastases, and 94 were free from tumor.
Level 2: 132, of which 33 contained metastases, and 99 were free from tumor.
Level 3-5: 126, of which 20 contained metastases, and 106 were free from tumor.

Table 5.3. Percentage sensitivity, specificity and accuracy of different US criteria for malignancy, separately calculated for levels 1, 2 and 3-5.

5.3.3. Findings at US-guided FNAC.

Results of US-guided FNAC were available for 54 patients who underwent 70 elective neck dissections (Table 5.4). Aspirated were obtained from 57 sides. Lymph nodes were aspirated only if the minimal axial diameter was at least 3-4 mm, depending on the level of the node. If no lymph nodes exceeding this size were found at US examination, no aspirate was obtained. Consequently aspirates were not obtained from 13 neck sides. These 13 necks were considered to be negative at US-guided FNAC, and proved to be negative on histopathological examination of the neck dissection specimen.
From six necks, insufficient material was aspirated for a cytological diagnosis. These necks were considered negative; however, three proved to be positive at histopathologic examination.

There was a clear relationship between the size of the lymph node and the ability to obtain sufficient material for a diagnostic smear. Four of the six insufficient aspirates were obtained from lymph nodes that measured 5 mm or less in minimal axial diameter. As a total of 12 aspirates were obtained from lymph nodes measuring 5 mm or smaller, the chance for a diagnostic smear for lymph nodes this size was 67%. Smears from nodes larger than 5 mm were diagnostic in 96% in this study.

	PATHOLOGY		TOTAL
	posit.	negat.	
USgFNAC +	25	0	25
USgFNAC -	8 (5)	37 (34)	45 (39)
TOTAL	33 (30)	37 (34)	70 (64)

Sensitivity: 76% (83%), Specificity: 100%, Accuracy: 89% (92%).

Table 5.4. Results of the US-guided FNAC examinations. Between bracklets are the values obtained if the non-diagnostic aspirations are omitted from the study.

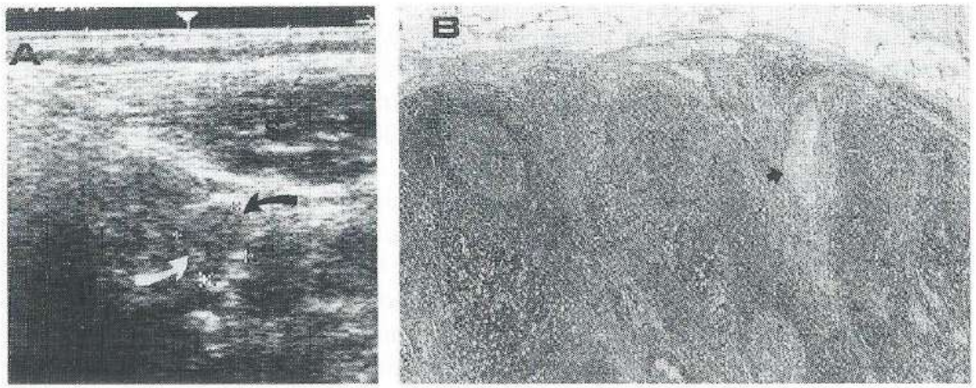

Figure 5.4 A. Axial US image of a subdigastric node (6 mm x 9 mm) (curved arrows), with a normal lymph node appearance in a 63 years old male patient with a clinical T2N0 floor of mouth carcinoma. B. Detail of a histopathologic section through the same subdigastric node, showing a micrometastasis (arrow), which was not detected by US-guided FNAC. (L = preëxistent lymphatic tissue).

Table 5.4 shows that 25 aspirates were considered to be tumor positive at US-guided FNAC; 19 were definitely malignant whereas 6 were suspicious for malignancy.
Results of cytology were negative in 32 necks, and 13 necks were not aspirated, making a total of 45 neck sides considered to be negative. Eight of these 45 neck sides were found to have false negative results. In five of these eight necks with false negative results, no malignant cells were aspirated, even though correlation between the US and histopathologic reports regarding the size and the site of the

punctured node indicated that the correct node had been punctured (Fig 5.4). In two of these five punctures insufficient material was obtained for a diagnosis, whereas in the other three punctures the aspirates can assumed to be obtained from the wrong part of the node as only lymphatic cells were found. In the other three aspirations with false negative results, the wrong nodes were aspirated; at histopathologic examination it was found that a reactively enlarged node that was larger than the actual metastatic node was not in the same region as the metastatic node. The sensitivity, specificity and accuracy of US-guided FNAC were 76%, 100% and 89% respectively.
If the 6 non-diagnostic (insufficient) smears are left out of the study the sensitivity, specificity and accuracy of US-guided FNAC were 83%, 100% and 92% respectively.

5.4. COMMENTS

Palpation is known to be an inaccurate technique for assessment of the neck of patients with head and neck cancer (1-6). Consequently most head and neck surgeons advocate performance of elective treatment of the neck if the risk of occult lymph node metastasis exceeds 15% to 20%. In selected cases, prophylactic neck treatment could be avoided if an accurate staging method were available that reduces the risk of occult metastasis to values below 15% to 10%. However, the need for prophylactic neck dissection can be ruled out only for patients in whom the neck does not have to be entered for excision of the primary tumor, as is the case in limited oral and laryngeal carcinomas. Prophylactic dissection can also be ruled out in the contralateral neck of patients with tumors approaching or extending over the midline that have to be excised through the neck. However, all these patient must agree to return for regular follow-up visits. A group of patients that might benefit from a reliable staging technique as well, are patients that are usually not treated prophylactically on the neck, and in whom subsequent metastasis develop in only a small percentage of patients, like patients with nasal cavity/sinus or vestibular, lip, skin and glottic carcinoma.

CT and MR imaging have been used to re-stage a lesion upward in a large percentage (38%-67%) of neck sides with false negative results at palpation (6,7,8). Consequently 33%-62% of these occult lymph node metastases remain undetected. Furthermore, both CT and MR have the disadvantages of being expensive and not readily accessable for repeated use in follow-up of patients.

The results of this study show that the accuracy of US alone never exceeds 70%, as any rise in sensitivity is always accompanied by a decrease in specificity (Tables 5.2 and 5.3). For neck sides that are negative on palpation, the optimal minimal axial diameter to distinguish between positive and negative lesions proved to be 8 mm for subdigastric lymph nodes and 7 mm for all other lymph nodes. As shown in chapter 3, groupings of 3 or more lymph nodes that are each a maximum of 2 mm smaller should also be considered malignant. However, analysis of our findings per level shows that lymph node metastases found in level 1, 3, 4 and 5 are often smaller than 7 mm, as with this criterion only 40-43% of the "malignant levels" are detected. Consequently, lymph nodes larger than 4-5mm in these levels should be considered suspect and thus aspirated.
These criteria differ markedly from those we reported previously in a random study group of patients with various head and neck cancers with use of CT and MR (i.e. 11 mm and 10 mm, respectively) (21). This difference has two major causes. First, at palpation, all neck sides in this study were "N0", whereas patients in the previous study were not selected according to any one stage; therefore, the mean size of the metastatic nodes in this study was smaller and the incidence of metastasis was lower. Second, as tumor necrosis cannot be a criterion at US, loss of sensitivity has to be compensated for by a decrease in the size criterion. This illustrates that size criteria depend very much on the group of patients studied and the radiologic modality employed.

Cytologic examination of the lymph nodes detected with US enables a more reliable diagnosis of malignancy and increases the accuracy of the US examination. In this study, US-guided FNAC proved to be a quick (10-20 minutes) and safe (no complications) technique that caused only moderate discomfort to the patient.

Although seeding of tumor cells along the needle tract has been reported after use of Tru-Cut needles (Baxter Healthcare, Pharmaseal, Valencia, Calif) (22), to our knowledge such seeding has never occurred with use of thin aspiration needles (23). Although the carotid artery was punctured in one patient, neither hematoma nor bleeding occured. As shown in the result section herein, the chance of obtaining a diagnostic smear from small nodes decreases as the size of the lymph node decreases, ranging from 96% for lymph nodes larger than 5 mm in minimal axial diameter, to 67% in lymph nodes that are 5 mm or less in diameter. However, use of US-guided FNAC enabled detection of metastatic tumor cells in 2 nodes that measured 5 mm or less in minimal axial diameter. In two aspirated metastatic nodes that were less than 5 mm in diameter, the cytologic report was diagnostic but gave false negative results; a micrometastasis was present in these nodes.

Selection of the correct node to aspirate is crucial. For this, a thorough knowledge of the lymph drainage pathways of different primary tumors to the neck is necessary. In case multiple enlarged nodes are visualized at US, the most suspicious, and preferrably more than one node should be aspirated. As a simple guide, lymph nodes in levels 1, 3, 4 and 5 larger than 4 mm are suspicious for metastasis and should be aspirated. At level 2, lymph nodes 5 mm or larger should be aspirated. Reactively enlarged nodes occur more frequently in levels 1 and 2. However, early metastasis of oral, pharyngeal, nasal and lip carcinoma are most frequently located in level 1 and 2 as well. Tumors that approach the midline or extend over it may give rise to bilateral (or contralateral) metastasis.

In this study, false negative results at US-guided FNAC were the result of aspirating the wrong node (three cases), obtaining insufficient aspirate (two cases), or aspirating from the wrong part of the node (three cases). In six cases, obtaining these false negative results appeared to be inevitable because either the metastases inside the lymph nodes or the lymph nodes themselves were too small to allow sufficient aspiration of tumor cells (Fig 5.4). Thus, the sensitivity of US-guided FNAC could only be slightly increased by aspirating more nodes more often. However, as micrometastases cannot be reliably detected with either US-guided FNAC or any other currently available technique, the sensitivity of US-guided FNAC will probably not rise much over 82% (27/33). Insufficient material for a cytologic diagnosis was accepted as a negative US-guided FNAC result in this study. In practice however, it seems wise to repeat these aspirations in order to obtain sufficient material if possible.
The specificity of US-guided FNAC will not fall much under the 100% reported herein, as false positive results at cytologic examination of squamous cell carcinoma in cervical lymph nodes are rare. However, study of aspirates obtained from salivary glands might result in inaccurate false positive or suspicious results at FNAC, as can study of aspirates from previously irradiated lymph nodes (24).

To our knowledge, the sensitivity (76%-83%) and specificity (100%) of US-guided FNAC in this study are higher than those reported for CT or MR in the literature (6-8); therefore, the technique described herein deserves an important role for the detection of occult metastatic neck disease. However, as one-fifth to one-fourth of the occult metastases are not detected at US-guided FNAC, it is questionable whether this technique fully solves the problem of when to recommend elective neck treatment. We believe, however, that the need for elective (sometimes contralateral) neck treatment can be diminished by performance of US-guided FNAC. This is especially the case for the patient groups defined above for whom elective neck treatment would mean the risk of increased

morbidity. This concerns mainly patients in whom the neck does not have to be entered for primairy tumor excision or patients in whom a therapeutic neck dissection is indicated on the other side. General condition and age might play a role as well. A wait and see policy implies that careful (US-guided FNAC) follow-up can be provided to ensure early detection of recurrence in the neck.

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Chapter 6

COMPUTED TOMOGRAPHY, MAGNETIC RESONANCE, ULTRASOUND AND ULTRASOUND GUIDED ASPIRATION CYTOLOGY FOR THE ASSESSMENT OF THE NECK; A COMPARATIVE STUDY

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The indications for and the value of radiologic staging methods for the neck in patients with a primary squamous cell carcinoma of the head and neck remain controversial. In the light of the known inaccuracy of palpation, this study compares palpation with four currently available radiologic techniques for staging of the neck: computer tomography (CT), magnetic resonance (MR) and ultrasound (US) with or without guided fine needle aspiration cytology (FNAC). The possible indications for these techniques and the therapeutic consequences are discussed.

One-hundred and thirty-two patients with squamous cell carcinoma of the head and neck, were examined radiologically before undergoing a total of 180 neck dissections as part of their treatment.
CT and MR proved to be more accurate than palpation for cervical lymph node staging. US-guided FNAC proved to be the method of choice to stage the neck in head and neck cancer patients. The sensitivity, the specificity and the accuracy of this technique were significantly better than of any other technique used in this study. Positive US-guided FNAC results should always lead to appropriate neck treatment. On the basis of a well performed negative US-guided FNAC examination, it is justified to withold from neck treatment in many head and neck cancer patients, or to be as selective as possible, when performing an elective neck dissection.

6.1. INTRODUCTION

Staging of the neck in patients with a known squamous cell carcinoma in the head and neck region by palpation is known to be inaccurate (table 6.1) (1-15). The high false positive rate (low specificity) of palpation causes overtreatment in many patients. On the other hand, the high false negative rate (low sensitivity) of palpation is the source of continuing discussion if elective (prophylactic) neck treatment is to be preferred over a wait and see policy with subsequent therapeutic neck dissection when a metastasis becomes evident (16-18). Whereas most head and neck oncologists are proponents of elective neck treatment (5,9,15,19), others advocate a wait and see policy for the palpatory negative neck (20-23). This discussion is further complicated by the fact that there is no consensus on the effects on survival of a wait and see policy followed by delayed therapeutic neck treatment if metastasis become evident. Some authors found no difference in survival between these two policies (24,25), whereas others found a better survival when the neck was treated electively (7,26,27). Most head and neck oncologists nowadays tend to treat the neck electively if the risk of occult metastases, that is greatly related to the size and site of the primary tumor, exceeds or is in the range of 15% to 20% (17,28).

Author	Tumor	Number	FPos	FNeg
Sako[1]	All	235	28%	35%
Ali[2]	All	266	20%	21%
Shah[3]	All	1081	18%	33%
O'Brien[4]	All	86	13%	37%
Southwick[5]	Oral Cavity	158	30%	40%
Noone[6]	Oral Cavity	104	46%	12%
Martis[7]	Oral Cavity	222	38%	21%
Ferri[8]	Oral Cavity	47	57%	18%
Lyall[9]	Oral Tongue	35	45%	60%
Okamoto[10]	Oral Tongue	98	47%	35%
Galioto[11]	Larynx	130	41%	29%
McGavran[12]	Larynx	91	29%	16%
O'Keefe[13]	Larynx	153	39%	24%
Bocca[14]	Supraglottic	407	12%	35%
Murakami[15]	Hypopharynx	69	17%	38%
This Study	All	132	21%	41%

Table 6.1 False positive (FPos) and false negative (FNeg) palpatory findings by different authors for various primary tumors.

The number of patients that are overtreated and undertreated with regard to the neck can be diminished by an accurate staging method, that is able to detect or exclude reliably cervical lymph node metastasis. In previous chapters we established the optimal magnetic resonance (MR) imaging techniques and malignancy criteria for computed tomography (CT) and MR imaging (29,30). In a study group of 100 patients, we found that MR is more accurate than palpation for cervical lymph node staging (31), and that ultrasound (US)-guided fine needle aspiration cytology (FNAC) is the most reliable technique to upstage palpatory negative necks (32).

To our knowledge no large study has been published that compares palpation, CT, MR, US and US-guided FNAC for cervical lymph node staging for the same group of patients. This study was designed firstly to establish the accuracy and to evaluate the limitations of these four radiologic techniques, secondly to define possible indications for additional staging and thirdly to assess the therapeutic consequences of it.

6.2. MATERIALS AND METHODS

In a period of 20 months, 132 not previously treated patients with squamous cell carcinoma of the upper aerodigestive tract (table 6.2) who underwent a neck dissection as part of their treatment, were examined with preoperative MR, CT and US imaging. As US-guided FNAC became available later in this study, 67 patients were examined with this technique as well. The outcome of the imaging had no influence on the planned treatment. Within 1 to 4 weeks after imaging, all patients underwent a uni- or bilateral neck dissection as part of their treatment. A total of 142 comprehensive (levels 1 through 5) and 38 selective (supraomohyoidal, anterolateral or lateral) neck dissections were performed.

Preoperative palpation was performed, as much as possible, by the same, experienced head and neck surgeon. The number and level of all suspect lymph nodes were recorded.

All CT studies were made on a third generation Philips Tomoscan 350 after intravenous administration of contrast medium (Omnipaque 350 mg I/ml, Nycomed AS, Oslo, Norway). Contiguous axial 5 to 6 mm scanning planes were used.

Site	T-Stage				All
	T1	T2	T3	T4	
Oral cavity	5	16	19	7	47
Oropharynx	4	9	18	8	39
Hypopharynx	1	3	8	1	13
Larynx	0	8	12	9	29
Other	1	0	0	3	4
All	11	36	57	28	132

Table 6.2. Patient population according to site and stage of primary tumor.

MR examinations were done on a 0.6 Tesla imaging system (Teslacon, Technicare - General Electric, Milwauki) using a partial volume coil. Axial T1-weighted spin echo, T2-weighted gradient echo and Gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA) (Magnevist, Schering AG, Germany) enhanced T1-weighted gradient recalled echo images were made in all patients. Slice thickness varied from 3 to 5 mm, with an interslice gap of 50% as described in earlier studies (29,31).

US examinations were performed on an Aloka SSD 650 system (Aloka Co. LTD, Tokyo, Japan) with use of a 7.5 MHz linear array transducer. Radiographs were obtained of all visualized nodes, while measuring these nodes on screen. US-guided FNAC were obtained in 67 patients using a Cameco syringe holder and a 0.6 mm x 25 mm needle. Nodes in palpatory negative sides of the neck were aspirated if they were larger than 3 to 4 mm and considered suspect. Lymph nodes in palpatory positive sides of the neck were aspirated, if exclusively nodes smaller than 14 mm in the subdigastric region, or smaller than 13 mm elsewhere in the neck were detected with US. The most suspicious nodes (i.e. the largest in the drainage region of the primary tumor) on one or both sides of the neck were aspirated. While some smears were fixed with ethanol 70% and stained with Papanicolaou, others were air-dried and stained with May-Grünwald-Giemsa. The needle and syringe were washed with carbowax to obtain additional smears. The smears were all reviewed for this study by one pathologist (HVS).

Malignancy criteria defined in a previous chapter were used (30). At CT or MR, neck sides were considered malignant if nodes with necrosis were depicted, or if the minimal diameter in the axial plane of a node was 11 mm or more for nodes located in level 2 (subdigastric) and 10 mm or more for all other nodes, or if groups of 3 or more borderline lymph nodes (1 or 2 mm smaller) were seen. As tumor necrosis is not reliably depicted at US, criteria for malignancy of lymph nodes visualized at US were only related to the size of the nodes, and a grouping of borderline nodes. Sides of the neck examined with US-guided FNAC were considered positive for tumor metastasis if the cytology of one or more nodes was positive or suspect, or if in a palpatory positive neck, a node with a minimal axial diameter of 13 mm or larger (subdigastric: 14 mm or larger) was seen, that was not aspirated. We used this last criterion because in a previous study, all nodes with a minimal axial diameter 13 mm or more proved to be infiltrated by tumor (30). If no enlarged nodes were detected (and thus no node was aspirated) or if all cytologic smears were negative, the neck side was considered negative.

All CT and MR examinations were independently scored by two experienced examiners, who were blinded to the results of the other examinations and the pathologic outcome. The site and stage of the primary tumor were known to these examiners. In case of disagreement, they had to reach a consensus. The investigator that performed the US examination, did not know of the outcome of the MR and CT scans. The McNemar's test was used to calculate significancy of differences in accuracy between the different modalities.

All neck dissection specimens were meticulously examined histopathologically as described in our previous chapters (30,31). After obtaining a photograph and a radiograph of the specimen, the specimen was fixed for 36-48 hours in 4% formaldehyde. All nodes visible on the radiograph and/or palpable in the specimen were excised for microscopic examination. All macroscopically negative nodes were sectioned at every 3 to 4 mm. Of all macroscopically positive nodes 2 or more representative sections were made. Of all sections at least one histopathologic slide was made for microscopic examination. The size and location of all nodes were recorded and the location was indicated on the photograph and the radiograph of the specimen. All microscopic slides were revised by an experienced pathologist.

6.3. RESULTS

6.3.1. Histopathology.

Of the 180 neck dissections obtained, 109 contained tumor metastases, whereas 71 were free from tumor on histopathologic examination. On average 45.7 nodes were found in the 142 comprehensive type of neck dissection specimens (104 tumor positive, 38 tumor negative), whereas on average 15 nodes were found in the 38 selective type of neck dissection specimens (5 tumor positive, 33 tumor negative). For the tumor positive neck dissection specimens the number of metastatic nodes varied from 1 to 30 nodes for the comprehensive specimens (mean 4.5 positive nodes; median 3 positive nodes) and from 1 to 4 nodes for the selective specimens (mean 1.8 positive nodes; median 1 positive node).

6.3.2. Palpation.

There were 36 false negative sides and 19 false positive sides of the neck by palpation. Table 6.4 shows the sensitivity (chance of detecting metastasis in a tumor positive side of the neck), specificity (chance of correctly excluding metastasis) and accuracy (chance for a correct diagnosis) of palpation in this study. The accuracy of palpation was significantly worse than of all other modalities ($p \leq 0.086$ for all modalities). The false positive rate (chance that positive palpatory findings are false) and the false negative rate (chance that negative palpatory findings are false) are shown in table 6.1. The relative preponderance of advanced oral and pharyngeal carcinomas (table 6.2) may account for the relatively high false negative rate in this stdy. However, these figures are comparable to others quoted in table 6.1. Tables 6.5 and 6.6 show the sensitivity, specificity and accuracy for patients who were judged to have positive findings or negative findings at palpation respectively.

6.3.3. Ultrasound.

Ultrasound examinations were diagnostic in all patients. Several size criteria (minimal axial diameter), combined with the criterion of lymph node grouping were compared. The size criterion used for subdigastric nodes was 1 mm larger.

SIZE	SENSITIVITY			SPECIFICITY			ACCURACY		
CRITERION#	All	N+	N0	All	N+	N0	All	N+	N0
≥ 5 mm	94	97	86	38	21	44	72	82	61
≥ 6 mm*	90	96	78	48	21	58	75	80	66
≥ 7 mm*	83	96	58	66	42	75	77	85	68
≥ 8 mm*	75	92	42	75	58	81	75	85	65
≥ 9 mm*	70	90	28	86	68	92	76	86	66
≥ 10 mm*	63	86	17	90	74	96	74	84	64
≥ 11 mm*	57	81	8	97	95	98	73	84	61

: Size criterion concerns minimal axial diameter, the size criterion for subdigastric nodes is 1 mm larger.
All : 180 sides, 109 positive, 71 negative.
N+ : 92 sides, 73 positive, 19 negative.
N0 : 88 sides, 36 positive, 52 negative.
* : or groups of 3 or more nodes that are 1-2 mm smaller.

Table 6.3. Percentage sensitivity, specificity and accuracy of different US criteria in different populations.

In table 6.3 the sensitivity, the specificity and the accuracy of different criteria are shown. The sensitivity falls, and the specificity rises, while the accuracy has a biphasic curve as the size criterion becomes larger. The optimal size criterion for US varies according to the patient population studied. In our opinion the most acceptable size criterion for the whole (random) patient group was 9 mm for subdigastric nodes and 8 mm for all other nodes. The sensitivity, specificity and accuracy with this criterion is 75%. As shown in table 6.3, this criterion is not optimal for palpatory negative or palpatory positive sides of the neck, as the incidence and the size of metastatic lymph nodes in these separate groups differs significantly. For the palpatory negative neck US alone never reaches a high accuracy, but is optimal (68%) at 8 mm for subdigastric nodes and 7 mm elsewhere in the neck. For palpatory positive sides of the neck, that have a higher incidence of metastasis, the criterion is optimal at 9 to 10 mm (accuracy 86%).

5.3.4. Ultrasound-guided FNAC.

Of the 93 neck sides (in 67 patients) examined, in 69 one or more aspirations were performed, of which 37 showed cytologic evidence (n=26) or suspicion (n=11) of metastatic tumor. These 37 sides of the neck proved to contain metastatic lymph nodes at histopathological examination. In 30 sides only reactive lymph nodes tissue was found in the aspirate, whereas in 2 sides, insufficient material was aspirated for a reliable cytologic diagnosis. These 2 sides of the neck (that contained metastasis on histopathological examination) were excluded from the study group. As shown in tables 6.4, 6.5 and 6.6, US-guided FNAC had the best sensitivity, specificity and accuracy compared to the other modalities. The accuracy of this technique was significantly better than of all other techniques (for US: $p = 0.0076$, for MR: $p = 0.0006$, for CT: $p = 0.0018$, for palpation: $p < 0.0001$). As there were no false positive findings at US-guided FNAC, the specificity was 100% for all patient groups. Table 6.5 shows that in 48 sides of the neck positive at palpation, US-guided FNAC was able reliably to detect all 8 neck sides that were false positive at palpation, as aspirations in these sides showed no evidence of metastasis. As only 6 sides proved to be false negative at cytology, US-guided FNAC enabled detection of 73% of the false negative palpatory findings (Table 6.6). Meticulous comparison of the lymph node region and size between the US-guided FNAC examination and the histopathological examination yielded that these false negative aspirations were caused by aspirating the wrong lymph node, or aspirating from the wrong part of a lymph node with only a small metastatic area.

TECHNIQUE	SIDES	SENSIT	SPECIF	ACCUR
PALPATION	180	67%	73%	69%
US (8-9mm)	180	75%	75%	75%
USgFNAC	91	90%	100%	93%
CT	178	83%	70%	78%
MR	174	82%	81%	82%

All: 180 sides, 109 positive, 71 negative.
USgFNAC: 91 sides, 62 positive, 29 negative.

Table 6.4. Results for all 180 sides (USgFNAC: 93 - 2).

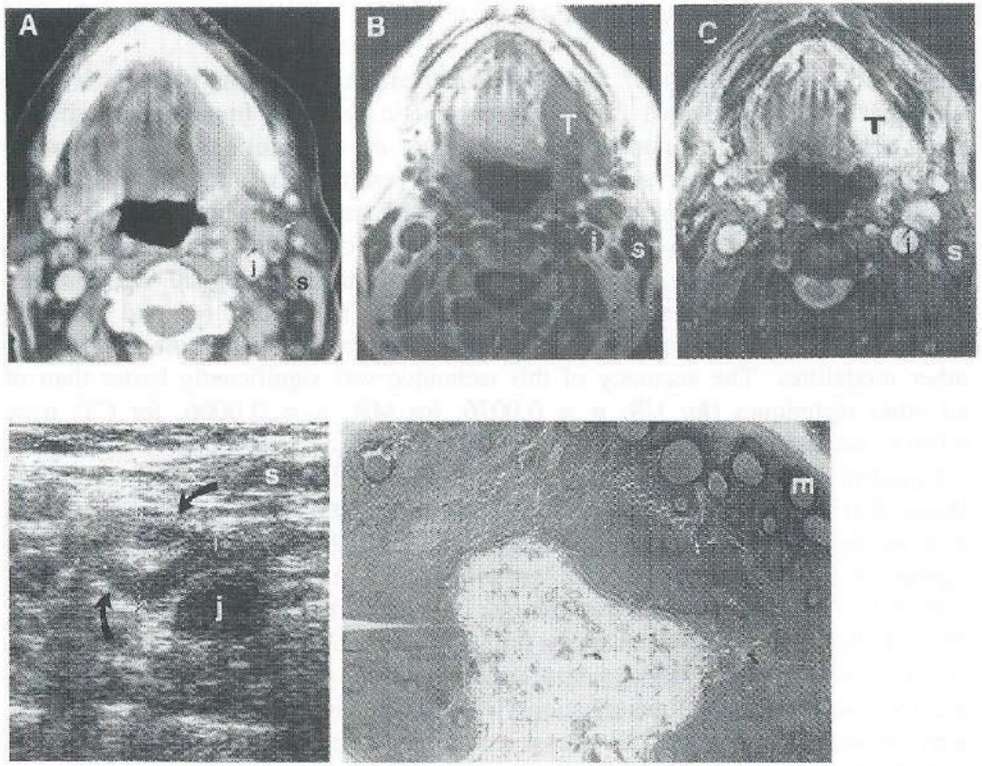

Figure 6.1 A. CT scan at the subdigastric level in a 75 year old female patient with a T3N1 floor of mouth carcinoma on the left side, showing a large (minimal axial diameter 12 mm, see arrows) lymph node with a central hypodense area. The differential diagnosis is between fatty metaplasia and tumor necrosis. On the basis of its size and the enhancement pattern this node was classified as malignant. T = floor of mouth carcinoma, j = internal jugular vein, s = sternocleidomastoid muscle. B. T1-weighted spin echo MR image showing the same node (arrows), with fatty hilar structure (high signal intensity), but a minimal axial diameter of 12 mm; the node was thus classified as malignant. C. Gd-DTPA enhanced T1-weighted gradient echo MR image at the same level, showing regular enhancement of the nodal tissue around the hilar structure. The primary tumor shows clear gadolinim uptake. The internal jugular vein is depicted with high signal intensity. D. US image of the same large subdigastric node (curved arrows), with use of a 7.5 MHz linear aray transducer. The node is depicted in front of the internal jugular vein with a hyper-echogenic center, that is an unsure argument for fat or keratinizing tumor[37]. Aspiration cytology showed only reactive lymph node tissue.
E. Histopathologic overview after H&E staining. The fatty center (f) is encircled by reactive lymph node tissue (L). No metastasis was found.

6.3.5. Computed Tomography.

CT examinations were diagnostic in the great majority of patients. Only 2 neck sides could not at all be interpreted because in two patients no I.V. contrast was administered (because of previous allergic reactions), and there were no enlarged

TECHNIQUE	SIDES	SENSIT	SPECIF	ACCUR
PALPATION	92	100%	0%	79%
US (9-10mm)	92	90%	68%	86%
USgFNAC	48	100%	100%	100%
CT	92	100%	47%	89%
MR	91	94%	63%	88%

PALP N+: 92 sides, 73 positive, 19 negative.
USgFNAC: 48 sides, 40 positive, 8 negative.

Table 6.5 Results for 92 palpably N+ sides (USgFNAC: 48).

TECHNIQUE	SIDES	SENSIT	SPECIF	ACCUR
PALPATION	88	0%	100%	59%
US (7-8mm)	88	58%	75%	68%
USgFNAC	43	73%	100%	86%
CT	86	49%	78%	66%
MR	83	55%	88%	75%

N0: 88 sides, 36 positive, 52 negative.
USgFNAC: 43 sides, 22 positive, 21 negative.

Table 6.6 Results for 88 palpably N0 sides (USgFNAC: 45 - 2).

nodes depicted. Of the remaining 178 sides of the neck, 108 were tumor containing, whereas 70 were free from tumor on histopathological examination. Because of the short exposure time, movement artifacts were not a problem at CT examinations. Dental material artifacts obscured submandibular or subdigastric lymph nodes in some patients. Supraclavicular and low jugular nodes were sometimes obscured by artifacts from the shoulders.
Results of the CT findings are shown in tables 6.4 through 6.6. The sensitivity we found for the CT examination (83%) was higher than for palpation (67%), and comparable to the sensitivity of MR (82%). However, the specificity of CT

was rather low in all patient groups: 70% for all sides, 47% for the palpatory positive sides and 78% for the palpatory negative sides. As 21 of the 178 sides of the neck were false positive at CT (Fig 6.1), the specificity of CT (70%) was slightly less than the specificity of palpation (73%) (Table 6.4). As a result of the high sensitivity however, the accuracy of CT (78%) was significantly higher than of palpation (69%) ($p = 0.0137$). As CT was able to detect 17 of the 35 sides that were false negative at palpation, the sensitivity in this group was 49% (Table 6.6).

6.3.6. Magnetic Resonance.

Because of the long acquisition time, MR is more susceptible to movement artifacts than CT. As a consequence, and because sometimes no Gd-DTPA was administered, 6 sides of the neck could not be interpreted reliably. For the remaining sides (105 containing tumor; 69 free of metastasis), MR had a significanly better accuracy (82%) than palpation (Table 6.4) ($p = 0.0016$). The accuracy of CT and MR ($p = 0.35$) and US and MR ($p = 0.06$) did not differ significantly. As the specificity of MR remained relatively high for all patient groups (tables 6.4, 6.5 and 6.6), we think that our criteria can be recommended for all patient groups, although further differentiation of the criteria for palpatory negative and positive sides of the neck separately can be defended. As the specificity of MR is only 63% for the sides positive at palpation (seven false positives at MR) (Fig 6.1 and Table 6.5), neither MR nor any other imaging modality apart from US-guided FNAC seems able to select reliably overstaged patients. As MR was able to detect 18 of 33 sides of the neck that were false negative at palpation (Fig 6.2), the sensitivity of MR for this important "N0" group was 55% (Table 6.6).

6.4. DISCUSSION

While most studies agree on the efficacy of additional staging modalities like CT (33-36), MR (31,37), US or US-guided FNAC (32,38-40) for cervical lymph node staging, in some other studies no advantages of CT or MR over palpation was found (41-43). Only a few small studies were performed to compare the efficacy of different radiologic modalities (44-47). In none of these comparative studies were all investigated imaging modalities used for all patients, neither were all these 4 modalities compared. Hillsamer et al. (44) compared palpation CT and MR in 27 patients. Although MR (in 20 patients) had the best sensitivity and specificity, and palpation did worst, their findings did not reach statistical

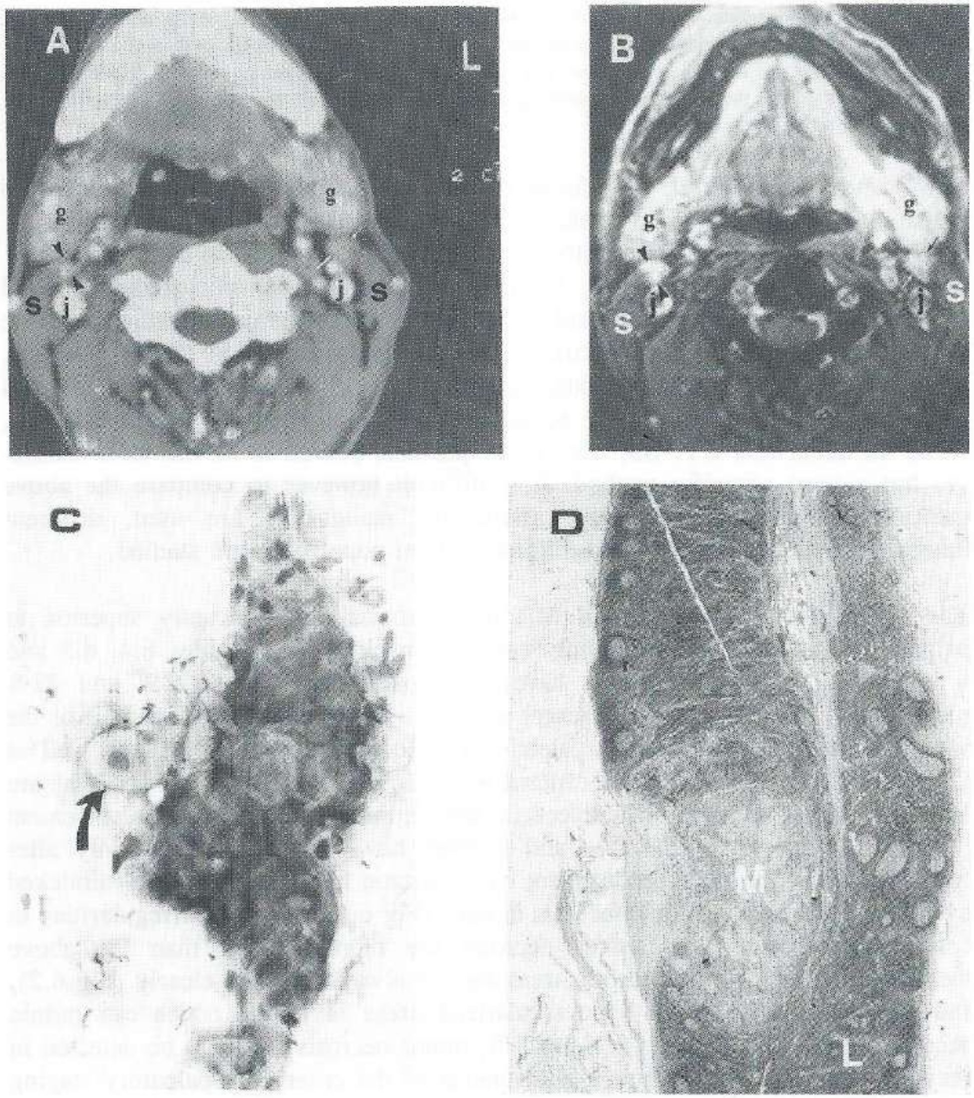

Figure 6.2 A. Contrast enhanced CT scan in a 52 years old man with a T2N0 floor of mouth carcinoma, treated with a commando resection and a comprehensive neck dissection of the left side. At the right subdigastric level a 5 mm node (arrowheads), and at the left side a 7 mm node (arrows) are depicted. Both nodes are located in front of the internal jugular vein (j), just medial and anterior to the sternocleidomastoid muscle (s), behind the submandibular gland (g). Although the node on the left was depicted with very small non-enhancing spots, it was erroneously classified as non-metastatic. B. Gd-DTPA enhanced gradient echo MR image at the same level. The node is now much more clearly depicted with irregular enhancement, and was classified as metastatic. The node on the right is

depicted with homogenous signal intensity (arrow heads). C. Cytologic smear of the node on the left (Papanicolaou staining, original amplification 40 X), showing atypical epithelial cells and a keratinized cell (curved arrow) as seen in a squamous cell carcinoma. D. Histopathologic section (H&E staining, amplification 5 X) of the same node, showing a small squamous cell metastatis (M) surrounded by normal lymph node tissue (L).

significance. Heppt et al. (45) found that US and CT were superior to MR and palpation. However, only 15 of the 72 patients studied underwent MR. On the other hand, at CT examinations 10 mm slices were made, and no clear criteria for malignancy were formulated. Leichner-Düber et al. (46) who studied US and CT, found a higher sensitivity and specificity for US, whereas palpation was the most specific method. The specificity they found for palpation (94%) however, was very high as compared to other studies. Quetz et al. (47) compared CT, US and MR with palpation. Of the 62 patients examined, only 14 underwent MR, while 48 underwent CT. US, used in all patients, proved to be the most sensitive, but a very aspecific method. It is difficult however to compare the above mentioned studies, as different criteria for malignancy are used, different imaging techniques are used and different patient populations are studied.

This study shows that CT and MR are statistically significantly superior to palpation in detecting or excluding metastatic neck disease (Tables 6.4, 6.5 and 6.6; Fig 6.2). Both techniques have a comparable accuracy (78% and 82% respectively, no significant difference) and are able to reliably upstage half of the sides that are false negative at palpation (Table 6.6). However, MR as well as CT and US use morphological criteria for malignancy of lymph nodes, that are based on tumor induced differences in size, number and contrast enhancement (31,32). Changes in nodal size and number however, are induced only after considerable lymph node replacement by metastatic tumor, and can be mimicked by reactive enlargement or infectious disease (Fig 6.1). Although irregularities in contrast enhancement by tumor necrosis are more specific than the above mentioned criteria, small necrotic areas are not always depicted clearly (Fig 6.2), and adipose metaplasia or hypovascularized areas in lymph nodes can mimic necrosis at CT (30) (Fig 6.1). Using US, tumor necrosis can only be detected in very large nodes (32). Although adjustments of the criteria by palpatory staging can be defended, it seems very unpractical and is based solely on different size and incidence of metastasis, that are not known on beforehand. Furthermore, by modifying criteria, a rise of the sensitivity is always accompanied by a fall of the specificity (Table 6.3). The limitations of these morphologic criteria can only be overcome by obtaining cytologic (US-guided) or histopathologic (staging neck dissection) evidence of metastasis, or in future maybe by immunoimaging techniques using specific monoclonal antibodies (48).

Most head and neck oncologists will treat the neck if an enlarged lymph node is palpated. In this study however, 19 sides of the neck were falsely staged "N+" by palpation. Although superior to palpation, neither CT, MR nor US were able to exclude metastasis reliably in this patient group, as the specificity of these three techniques was not satisfactory high (Table 6.5). Table 6.5 shows that only US-guided FNAC has an accuracy high enough (100% in 48 sides of the neck) to exclude reliably metastasis in a palpatory positive side, enabling a selection of patients who do not benefit from neck treatment (Fig 6.1). However, as false negatives can occur with this technique as well (micrometastasis can be missed and aspirations can be obtained from the wrong nodes), it remains a difficult decision not to treat a patient with palpatory suspicion of metastasis.

The paramount problem however remains the palpatory negative (ipsi- or contralateral) neck. Most head and neck oncologists tend to treat these necks electively if the risk for occult metastases is more than 15%-20% (17,28). This means that in many small carcinomas of the upper aerodigestive tract, the neck will not be treated electively, and occult metastasis will become evident during follow up. On the other hand, in patients with larger primary carcinomas, most of the electively operated neck sides are tumor negative at histopathologic examination. There is a tendency to perform selective neck dissections, that are difficult to standardize, in these patients (3,21). As the efficacy of selective types of neck dissections in curing metastasis is disputable and not yet proven, an unanticipated single metastasis found in the specimen obtained often leads to postoperative radiotherapy, that could have been avoided by preoperative detection of this metastasis. However, as the morbidity of elective modified neck dissections is limited, this type of overtreatment for some patients can be defended as long as there is a reasonable chance that occult metastasis is found, necessitating postoperative radiotherapy.

This study shows that although CT, MR and US are able to reliably upstage more than half of the false negative necks, US-guided FNAC is the most sensitive, specific and accurate technique to detect or exclude the presence of metastasis preoperatively (significantly better). This reliability was obtained by performing multiple aspirations of one or more suspicious nodes on each side of the neck. The accuracy of this technique depends exclusively on the skill and motivation of the examiner and the cytopathologist. As 73% of the false negative palpatory sides can be detected with this technique, the risk for occult metastasis will fall to under 15% for most primary tumors. If for example the risk of occult metastasis at palpation is around 35%, as estimated for T2-3 floor of mouth carcinoma, with US-guided FNAC this risk can be deminished to 9%. This low risk of occult metastasis can obviate the need for elective neck treatment in many patients. However, as the risk of occult metastasis remains, regular follow-up, preferably with US-guided FNAC, should be guarantied. An alternative remains to perform a selective type of staging neck dissection in case of a negative US-guided FNAC, that carries only moderate morbidity for most patients. An other important consequence of US-guided FNAC is, that elective treatment with a selective type of neck dissection can be replaced by a therapeutic comprehensive neck dissection for patients in whom metastasis are detected, thus obviating the need for postoperative radiotherapy when only limited metastatic disease is found at histopathology. Furthermore, for patients who previously would not have been treated electively, as their primary tumor predispose to only moderate risk of occult metastasis, postponed therapeutic neck treatment could be accelerated by positive US-guided FNAC findings.

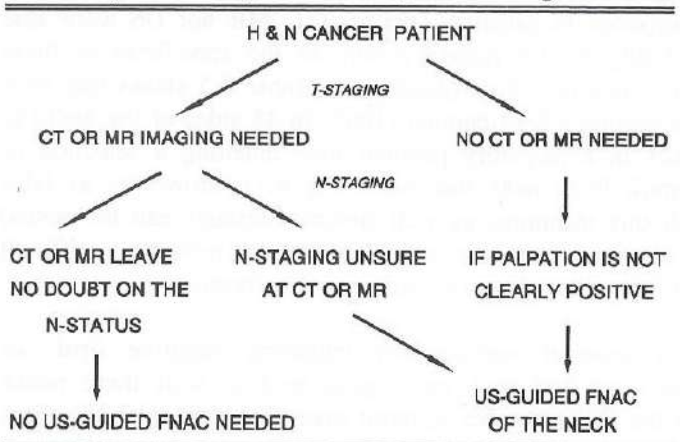

Figure 6.3. Flow chart on indications for CT, MR or US-guided FNAC.

The question concerning which imaging modality to chose for neck node staging can now be answered. The preferable radiologic technique should be accurate enough to allow for a reliable treatment planning, minimizing the number of under- and overtreated sides. To obtain reproducible results, enough experience should be gained with one technique.

The most accurate technique, that can fulfill these requirements, is US-guided FNAC. However, as with US no standardized permanent document is obtained, the accuracy fully depends on the examiner. Furthermore, US can not depict nor stage most primary tumors, often necesitating the use of CT or MR anyway. As MR is the superior technique for depiction of most primary tumors, and also is more accurate than CT for neck node staging, this technique will in future play a greater role for both primary tumor and neck staging.

To our opinion not all head and neck cancer patients should be evaluated with US-guided FNAC preoperatively (Table 6.7). Patients with undoubtly palpatory evidence of unilateral mobile metastasis on the side of the primary tumor that is well confined to one side, or with bilateral palpatory mobile metastases do not need further neck staging. Another group that does not always need US-guided FNAC are patients who need radiologic staging (CT or MR) for their primary tumor anyway. US-guided FNAC is indicated for these patients only if there remains any doubt about the neck at this CT or MR scan. Other indications for US-guided FNAC exist if no CT or MR is made and there is a risk of occult metastasis or if positive palpatory findings are uncertain. In the hands of an experienced examiner, this technique can reduce the number of undertreated as well as overtreated patients.

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Chapter 7

MICROMETASTASES FROM SQUAMOUS CELL CARCINOMA IN NECK DISSECTION SPECIMENS

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Submitted for publication

The size, number, level, and side of lymph node metastases in the neck are important prognostic factors for patients with primary squamous cell carcinoma of the head and neck region. In this study the incidence of micrometastases in cervical lymph nodes detected with routine histopathological examination is studied. Micrometastases were found in 66 lymph nodes in 41 of the 92 tumour positive neck dissection specimens. In nine neck dissection specimens micrometastases were the only metastases present. The detection of these micrometastases has influenced our postoperative treatment in three of the 77 patients with neck node metastases.

The value of additional sectioning for detecting micrometastases was assessed. Additional sectioning of 600 originally histopathologically negative lymph nodes from 64 patiens at a deeper level revealed seven additional micrometastases in five patients. In only one of these patients, the earlier detection would have influenced postoperative treatment.

Antikeratin staining with use of a mixture of two monoclonal antibodies (AE1 and AE3), revealed four additional micrometastases in 739 originally histopathologically negative lymph nodes in three out of the 13 patients studied. In two of these patients, earlier detection would have changed postoperative therapy.

In conclusion, meticulous routine histopathological examinations enables the detection of the great majority of micrometastases. In fact, almost 20% of all metastases detected were 3 mm or smaller. With use of either additional sectioning or immunostaining, only a relatively small number of additional micrometastases were detected. Because of the unknown prognostic significance of micrometastases and the consequent arbitrary consequences for postoperative treatment, and the extra workload of immunostaining and deeper sectioning, the routine use of either of these latter two procedures does not seem warranted.

7.1. INTRODUCTION

The presence or absence of cervical lymph node metastases is the most important prognostic factor for patients with squamous cell carcinoma of the head and neck. Apart from the presence of metastases, the number, level and side relative to the primary tumour of lymph node metastases as well as the presence of extranodal tumour spread (ENS) are important prognostic indicators (1-5). In our institution several features of the lymph node metastases in the neck lead to postoperative radiotherapy. Apart from the presence of ENS and one metastasis measuring more than 3 cm, the presence of three or more lymph node metastases in the neck are considered indications for postoperative radiotherapy. On the basis of a recent study this policy has been changed (2). Patients with two or more metastases are now being irradiated postoperatively as well.

As preoperative investigations like palpation or radiological techniques are unreliable in assessing the exact number and level or extranodal spread of lymph node metastases (6), the only possibility to obtain this prognostic information is by performing a neck dissection to allow histopathological examination (staging neck dissection).

The reliability of routine histopathological examination of neck dissection specimens for establishing the number and level of lymph node metastases is seldom questioned. However, the number of lymph nodes dissected from the neck dissection specimen (7,8), and the numer of sections investigated microscopically (9-12) influence the reliability of the histopathological staging of the neck. In this respect, only one study has been performed on neck node metastases, that found no additional value of step sectioning for detecting micrometastases (13).

Because of the recent development and availability of monoclonal antibodies against epithelial keratins (14,15), or even more specific, against squamous cell carcinoma (16,17), immunohistochemistry might help to detect micrometastases in the neck. Some recent reports on detection of micrometastases of breast carcinoma in axillary lymph nodes with monoclonal antibodies (18,19) have given support for this theory. However, studies on colorectal and vulvar carcinoma are much less optimistic on the additional value of immunostaining (20,21).

This study aims to investigate the incidence and therapeutic importance of micrometastases in lymph nodes of head and neck cancer patients detected using meticulous routine histopathological examination. Furthermore, the value of additional sectioning and immunostaining for detecting micrometastases is assessed.

7.2. MATERIALS AND METHODS

Within two years, 154 neck dissection specimens from 115 patients with a variety primary squamous cell carcinomas in the head and neck region were examined by the first author as described in previous chapters. Different stages of primary tumours originating from various sites within the mucous linings of the upper aerodigastive tract were included in this study. None of these patients had previously been treated on the neck.

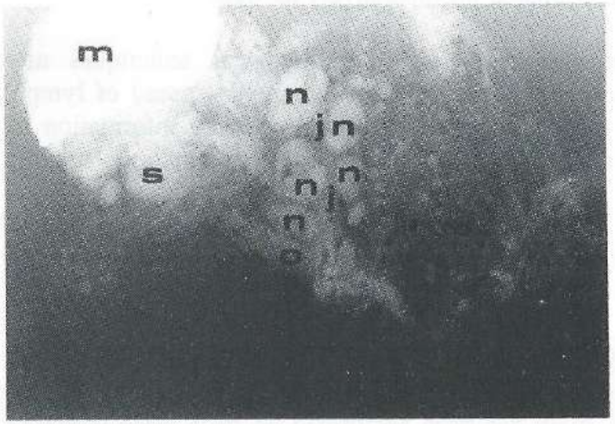

Figure 7.1 Specimen radiography of a specimen obtained at a commando resection with a segmental mandibula resection (m) and a comprehensive neck dissection on the left side. Many enlarged lymph nodes (n) are depicted around the tract of the internal jugular vein (j). The vein itself is not depicted, as it contained no blood. s = submandibular gland, o = omohyoid muscle. At histopathologic examination, none of the lymph nodes contained metastasis.

The specimens were either obtained from comprehensive neck dissections (n=119) or from selective neck dissections (n=35). After reaching the pathology laboratory, pictures (Polaroid and slides) of the marked unfixed specimens were taken, whereafter the sternocleidomastoid muscle was dissected if possible. Subsequently, the specimen was pinned to a board and fixed in 4% formaldehyde for at least 36 hours. After fixation, a radiograph of the specimen was obtained, while immersing it in a solution of 96% ethanol to correct for differences in thickness of the neck dissection specimen (22). This radiograph, that depicts nodes as small as 1-2 mm was used as a dissection guide, and as a permanent document for topographical orientation (Fig 7.1). All depicted nodes, and all lymph nodes palpated and visualized during serial sectioning of the specimen were examined microscopically. All nodes smaller than 5 mm were as a whole embedded in paraffin for microscopic examination. All macroscopically tumour negative nodes that were 5 mm or larger were sectioned every 3-4 mm and totally embedded. Of all nodes that

showed macroscopic tumour, three or more representative sections were made for microscopic examination. Of all paraffin blocks one 5 μm thick section was obtained and stained with hematoxylin-eosin (H&E). All microscopic slides were examined by at least two examiners (MWMvdB, HVS or IvdW). Not only the presence of metastases, but also the size of small metastases was recorded. Furthermore the presence of tumour cell emboli in lymphatic vessels was recorded.

Six-hundred lymph nodes from 76 neck dissection specimens (64 patients) were selected for additional sectioning (Table 7.1). All these lymph nodes were selected from the first or second echelon lymph node level of the primary tumour. To assess the value of additional sectioning for detecting micrometastases in tumour free specimens, 495 selected lymph nodes from all 62 tumour negative neck dissection specimens were selected for deeper sectioning. To assess the value of deeper sectioning to detect additional metastases in previously tumour positive specimens, 105 lymph nodes from 14 selected specimens specimens that contained 1-4 lymph node metastases (mean, 2.1 metastases) were sectioned at a deeper level. These specimens were selected because additional lymph node metastases can only influence treatment if they occur in specimens with a limited number of metastases. One extra 5 μm section at one deeper level of the paraffin block was made and stained with H&E.

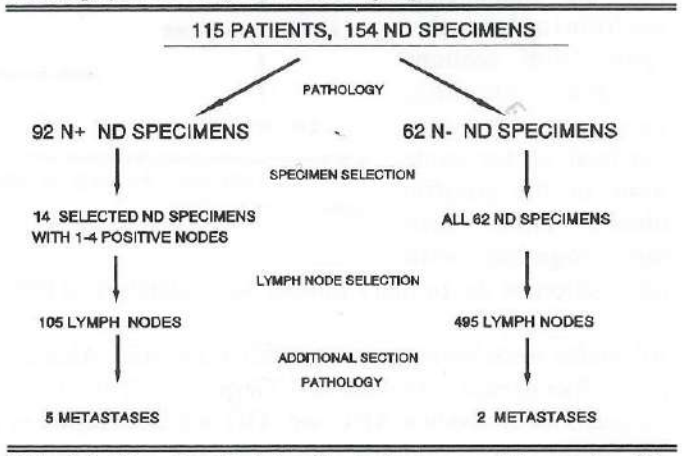

Table 7.1. Flow chart depicting the study group and the results of the aditional sectioning study.

Immunostaining was performed on all 739 tumour negative formalin fixed, paraffin embedded lymph nodes from 13 patients who underwent 21 neck dissection (Table 7.2). The neck dissection specimens were randomly selected from the dissections that contained no more than 3 positive nodes. This selection criterion was used because only in patients with less than three metastases the detection of an additional micrometastasis can be therapeutically relevant.

At previous H&E staining, 11 of these 21 neck dissection specimens contained metastases (range, 1 to 3 positive nodes per specimen; mean, 1.6 positive nodes). For the immunohistochemical study, apart from sections for H&E staining, extra sections were obtained at the same level in the paraffin blocks. These sections, together with one section of the primary tumour were attached to Poly-L-Lysine coated glasses.

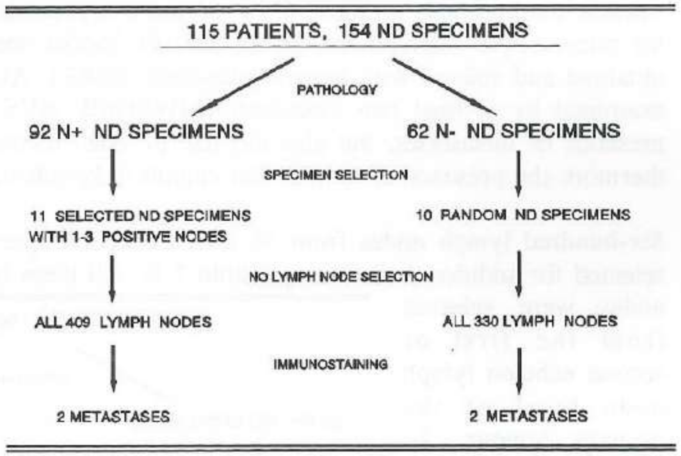

Table 7.2. Flow chart depicting the study population and results of the immunostaining study.

All nodes were immunostained with a 1% AE1:AE3 solution (Boehringer Mannheim Biochemica, Mannheim, Germany). This is a 1:20 mixture of mouse monoclonal antibodies AE1 and AE3 which recognizes almost all human epithelial keratins, with minimal cross-reactivity to formalin fixed lymph node reticular cells (24-26). The Avidin Biotin Complex immunostaining technique was used (Vectastain, Vector laboratories Inc., Burlingame, California). Peroxidase activity was visualized using DAB solution. All immunostained sections were independantly scored by two experienced pathologists (HVS and PvdV).

7.3. RESULTS

7.3.1. Routine Histopathology.

A total of 5941 lymph nodes were dissected from the 154 neck dissection specimens. On average 45.5 lymph nodes were found in neck dissection specimens obtained from comprehensive neck dissections (all levels), whereas on average 15.9 lymph nodes were found in specimens obtained from selective neck dissections (most supraomohyoidal). In total 338 nodes (5.7%) in 92 (60%) neck dissection specimens from 77 (67%) patients proved to contain metastases at routine histopathological examination. ENS was found in 148 nodes in 52

specimens (57%). In 62 neck dissection specimens (40%) no metastases were found.

Size of metastases	Lymph nodes with micrometastases	Neck dissection specimens with micrometastases	
		Total number	With only micrometastases
emboli	6	5	0
0-1 mm*	34	28	7
0-2 mm*	56	37	8
0-3 mm*	66	41	9

*: together with emboli detected next to reactive lymph nodes.

Table 7.3. Number of lymph nodes and neck dissection specimens with micrometastases of different sizes and tumour cell emboli adjacent to tumour negative lymph nodes. The last column gives the number of neck dissection specimens in which exclusively micrometastases were found. All these micrometastases were detected using routine H&E staining in 92 positive neck dissection specimens (in 338 positive nodes).

Because no definition of micrometastases exists, in table 7.3 the incidence of small metastases, both in small and enlarged lymph nodes, according to their size (≤1 mm to ≤3 mm) is shown. In this study, metastases measuring 3 mm or smaller were defined as micrometastases. In table 7.3 the incidence of tumour emboli in lymphatic vessels adjacent to tumour-free lymph nodes is shown as well. In total, 66 metastases in 41 neck dissection specimens were 3 mm or smaller, whereas in 9 specimens (10%) only metastases of this size were detected. It is important to realize that micrometastases can occur both in enlarged and small lymph nodes. The great majority are situated in the subcapsular sinus of the lymph nodes (Fig 7.2). In a previous study we have shown that although only 1-2% of all lymph nodes smaller than 5 mm contain metastases, these small metastases make up 14-16% of all metastases present (22).
In only three patients in this study a micrometastasis was the third metastasis detected and thus influenced postoperative treatment. In these three patients, no ENS or large metastases were present. However, if postoperative radiotherapy would have been indicated in the presence of two or more metastases, as is our current policy (2), the detection of these micrometastases would have influenced postoperative treatment in six patients.

7.3.2. Additional Sectioning.

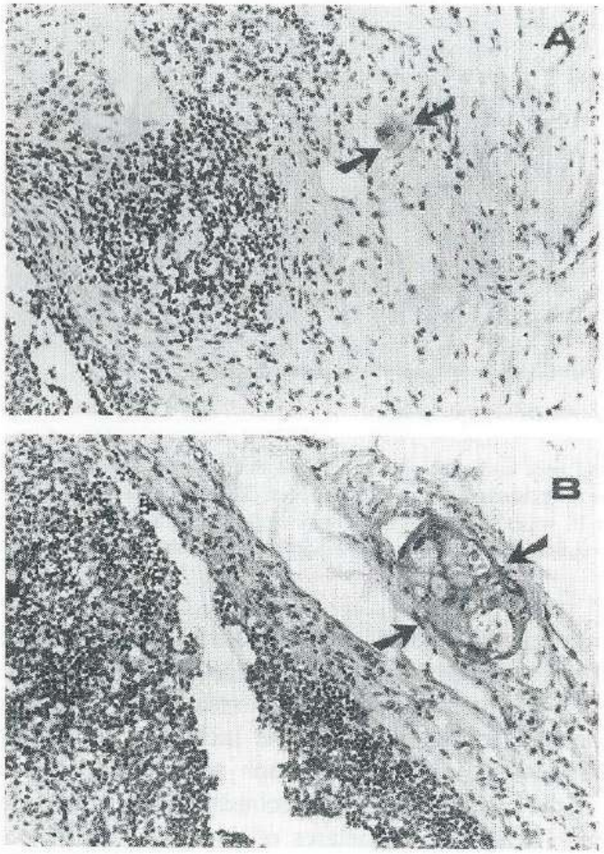

Figure 7.2. A. H&E section (original amplification 40 x) of a lymph node with an extremely small micrometastasis (arrows) in the subcapsular region that was detected during routine histopathological examination. It is clear that such micrometastases can easily be overlooked. B. The same node, sectioned at a deeper level, now clearly showing the same micrometastasis (arrows) (H&E, original amplification 40 x).

Of the 600 first or second echelon - tumour negative - lymph nodes that were sectioned at one deeper level, seven originally negative lymph nodes in five neck dissection specimens from five patients proved to contain micrometastases in the deeper cut section (Table 7.1). Two of these seven micrometastases were found in neck dissection specimens that were negative at routine histopathological examination; In one patient this was the only metastasis detected, whereas the other had two small contralateral metastases without ENS. Of the remaining five additional micrometastases, one was found in a neck dissection specimen that previously contained two positive nodes (with ENS), whereas all others were found in specimens that already contained three or four metastases at routine histopathological examination. On revision of the original slides, three of these seven micrometastases had been present but overlooked. In only one of the five patients the detection of these micrometastases would have influenced postoperative treatment, as it would have been the third metastatic node detected. Using our current criteria for postoperative radiotherapy, these additional micrometastases would not have influenced our policy in any patient.

7.3.3. Immunostaining using Antikeratin Antibodies.

All primary tumours and metastatic lymph nodes that were stained as controls with AE1:AE3 showed immunoreactivity. Of 739 previously tumour negative lymph nodes that were stained with AE1:AE3, micrometastases were detected in four lymph nodes in three neck dissection specimens from three patients (Table 7.2. and Fig 7.3). Two of these four nodes were found in a single neck dissection specimen that previously had been negative at routine histopathological examination, whereas the contralateral side of that patient contained two small metastases without ENS. The other two micrometastases detected with immunostaining were found in neck dissection specimens with two (other) positive lymph nodes without ENS, whereas in one of these two patients three contralateral metastases were present. On revision of the original H&E slides of the four nodes, all proved to have been present but overlooked. In two of these three patients the earlier detection of these micrometastases would have influenced postoperative treatment. Using our current criteria for postoperative radiotherapy, these additional micrometastases would not have influenced our policy in any of the three patients.

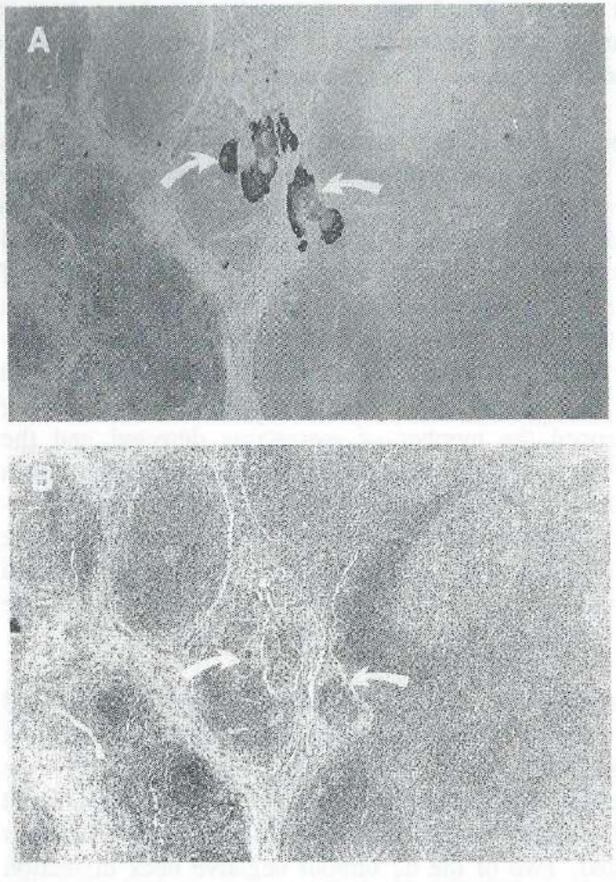

Figure 7.3 A. Section immunostained with AE1:AE3, showing a small micrometastasis (arrows) located centrally in a lymph node. B. Original H&E section in which the same metastasis (arros) had been overlooked. Although most micrometastases are located in the subcapsular sinus, this one lies centrally in the lymph node.

7.4. DISCUSSION

The prognostic significance of micrometastases in patients with head and neck cancer has never been assessed. Although extrapolation is not justified, reports on the prognostic significance of micrometastases of mammary carcinoma are contradictory. Whereas most authors found that even small metastases bear a higher risk for recurrence and distant metastases (11,18,27), others found no relation between prognosis and the presence of micrometastases (12).

This study shows that the frequency of micrometastases in cervical lymph nodes is high. In fact, almost 20% of all lymph node metastases detected in this study were 3 mm or smaller (Table 7.3). In 9 out of 92 tumour positive neck dissection specimens (10%) (with use of immunostaining and additional sectioning in 11/94 specimens) only metastases smaller than 3 mm were present. The detection of these micrometastases influenced our policy in three of the 77 patients (4%) with lymph node metastases, whereas with our new criteria for postoperative radiotherapy (2) this would have been the case in six patients (8%). Although it is an interesting question whether less accurate lymph node sampling and sectioning techniques would have influenced the number of metastases detected and the treatment of these patients, this study does not address this question. Apart from postoperative therapeutical relevance, it is important to realize that these micrometastases are not reliably detectable preoperatively with any currently available staging technique. Consequently, it can be presumed that these patients would have developed a clinically apparent lymph node metastasis at a later stage if the neck had not been treated electively.

It has been shown in other studies that examination of small lymph nodes and step sectioning of macroscopically unaffected lymph nodes enables detection of more micrometastases than does sectioning at a single level in each lymph node (7-10,23). In this study, sectioning of 600 first or second echelon lymph nodes at one deeper level of the paraffin block, revealed seven additional micrometastases in five of the 64 patients studied. Two of the 62 tumour negative neck dissection specimens (3%), in two patients, were upstaged from tumour negative to tumour positive, whereas in three of the 14 tumour positive neck dissection specimens (21%) in three patients, additional metastases were detected. In only one of the 64 patients studied, earlier detection would have influenced postoperative treatment. Because none of the additional micrometastasis was the second metastasis detected, postoperative treatment would never have been influenced if our current criteria for postoperative radiotherapy were employed. Step sectioning in a study of Saka (13), who studied only one lymph node per neck dissection specimen, showed additional metastasis in one of 46 specimens (2%).

The efficacy of immunostaining for detecting micrometastases in the neck has never been assessed. With use of a cocktail of two monoclonal antibodies against keratin (AE1:AE3), used in all 739 tumour negative lymph nodes from 13 patients, four additional micrometastases in three patients were found. Although these micrometastases were present in the original slide, they were overlooked (Fig 7.3). One of the ten tumour-negative neck dissection specimens studied (10%) was upstaged from tumour negative to tumour positive, whereas in two of the 11 tumour-positive neck dissection specimens (18%) an additional metastasis was found. In two of the 13 patients studied (15%), the earlier detection of these metastases would have changed the postoperative treatment, as these patients previously had two small metastases without ENS. The third patient already received postoperative radiotherapy. The fact that these additional micrometastases would not have changed the postoperative treatment if our current indications for postoperative radiotherapy were used, is caused by the fact that these micrometastases never were the second metastasis detected in a patient.

This study shows that meticulous routine histopathological examination, sampling on average 45.5 lymph nodes from each comprehensive neck dissection specimen and using routine sectioning at 3-4 mm intervals, enabled detection of the majority, but not all micrometastases (Fig 7.2). The percentage of additional micrometastases detected with use of immunostaining and deeper sectioning in this study varies from 3% to 10% in tumour negative neck dissection specimens, and from 18% to 21% in tumour positive neck dissection specimens. These results are comparable or slightly lower as those found in similar studies on axillary metastases from breast carcinoma patients (13-38%) (11,12,18,19).

Although a comparable number of lymph nodes were either sectioned at a deeper level (600) or immunostained (739), more additional metastases were detected using the additional sectioning technique. This can probably be explained by the fact that the nodes for additional sectioning were selected from the first and second echelon lymph nodes, causing a positive selection as all additional metastases in this study were indeed detected in these echelons. The major advantage of immunostaining however, is that this technique facilitates the detection of micrometastases by enhancing the contrast between metastatic and lymphatic tissue. It remains hard to compare these two complementary techniques, as immunostaining detected metastases that were overlooked in the original slide, whereas deeper sectioning detected metastases that were located at another level in the same lymph node.

It is clear from these data that even meticulous routine histopathological examination does not detect all micrometastases. In this respect, it would be interesting to study the difference of sampling on average 45.5 lymph nodes from each specimen and sectioning at multiple levels, as used in this study, versus sampling of a limited number of enlarged lymph nodes and single sectioning techniques. However, the most important question remains whether immunostaining or additional sectioning should be used routinely. In this respect it is important to realize that the prognostic significance of micrometastasis is not yet established for head and neck carcinomas. The therapeutical consequences attached to micrometastases are thus arbitrary. Furthermore, the workload and the costs of immunostaining and/or additional sectioning of lymph nodes must be taken into account. Until the prognostic relevance of micrometatases has been established, meticulous routine histopathological examination, which enables detection of the great majority of micrometastases, will suffice for routine practice. For studies on the prognostic significance of lymph node metastases or on the accuracy of preoperative staging techniques, it is recommendable to use these additional techniques in future.

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Chapter 8

GENERAL DISCUSSION

8.1. INTRODUCTION

Staging of the neck in head and neck cancer patients, has traditionally been based upon palpation. The current classification systems of the lymph nodes in the neck, as defined by the UICC (1987) and the AJCC (1988) still do not insist upon the need to use more sophisticated staging procedures. The advent of CT, high frequency US and more recently MR imaging and US-guided FNAC has revolutionized our possibilities to preoperatively assess the status of the lymph nodes in the neck. This thesis describes the first large *prospective* comparative radiological study on the assessment of the neck.

8.2. STAGING TECHNIQUES FOR THE NECK

By comparing different MR imaging techniques in chapter 2, optimal imaging techniques for the lymph nodes in the neck were defined. A combination of T1-weigted spin echo sequences and T2-weighted gradient refocussed echo sequences is optimal for the depiction of lymph nodes in the neck. With these techniques, lymph nodes as small as 3-4 mm can be detected, depending on their location and the patient compliance. Administration of i.v. gadolinium-DTPA in T1-weighted gradient refocussed sequences enables depiction of tumour necrosis inside lymph node metastases. Although we initially hoped that MR imaging would have enabled discrimination between reactive lymph node tissue and squamous cell carcinoma metastases, overlap in the varying signal intensities of these two tissues frustrated this idea. An important disadvantage of MR imaging is that in nervous and dyspnoeic patients, movement artifacts can affect image quality.

The radiological criteria for malignancy in neck nodes are adressed in chapter 3. Until now, there has been great controversy in the literature on the most accurate criteria for malignancy of lymph nodes in the neck. Whereas most authors agree that the depiction of central tumour necrosis can be used as a criterion, most dispute has been on the optimal size criteria and the significance of lymph node shape and grouping. The malignancy criteria outlined in chapter 3 are derived from data obtained at a pathoanatomic study of 2719 lymph nodes from 71 neck dissection specimens. It is therefore, that these criteria can be used for all radiological modalities that depict the features addressed in this study.
The radiological finding of so called "tumour necrosis" can histopathologically represent tumour necrosis, cystic tumour degeneration or tumour keratinization. In contrast enhanced CT or MR imaging these lesions can be detected if their minimal diameter is 3 mm or more. In both imaging modalities, these histopathological characteristics are depicted as unenhancing areas inside enhancing tumour and/or lymph node tissue. Depiction of "tumour necrosis" is the most specific criterion for malignancy and occurs in 74% of all tumour positive specimens. At CT scanning, the presence of fat tissue located centrally within lymph nodes can cause false positive findings of tumour necrosis. In most cases however, this fat is part of the hilar structures of the lymph nodes and can be seen in continuity with the borders of the lymph nodes. Regarding the size criterion it was a remarkable finding that not the generally used maximal diameter, but the minimal diameter in the axial plane corresponds best with the nature of the lymph nodes. When using grouping of three or more borderline - in terms of size - lymph nodes in the first or second echelons of the primary tumor as a criterion, the sensitivity increases, whereas the specificity is hardly influenced. Lymph node shape (roundish) is not a reliable criterion.

On the basis if this pathoanatomic study on the radiological criteria for lymph node metastases, optimal criteria are established:

1. All lymph nodes that show evidence of irregular contrast enhancement at CT or MR and that are surrounded by a rim of enhancing viable tumour or lymph node tissue should be considered metastatic.
2. Lymph nodes with a minimal axial diameter of 11 mm or more in the subdigastric region and of 10 mm or more in other regions of the neck should be considered metastatic.
3. Groups of three or more lymph nodes of 9 or 10 mm in the subdigastric region, and of 8 or 9 mm in other regions of the neck should be considered metastatic, as long as these regions are part of the drainage regions of the primary tumour.

The data presented in chapters 4, 5 and 6 compare the accuracy of CT, US, US-guided FNAC, MR imaging and palpation for staging of cervical lymph nodes. In these chapters, the MR imaging techniques found in chapter 2, and the criteria for malignancy defined in chapter 3 are used. The paramount importance of the initial work-up is on the choice whether or not to treat the neck. In chapters 4, 5 and 6 we therefore focussed on the accuracy of preoperative staging techniques in diagnosing the presence or absence of lymph node metastasis in the neck. Although the size, number and level of metastases as well as the presence of extranodal tumour spread are prognostically important features, these features are exclusively used to guide postoperative treatment and are much more reliably assessed by the histopathological examination of the neck dissection specimens. Consequently, these features are not studied in these chapters.

MR imaging proved to be an accurate technique to stage the neck in both a random head and neck population and for clinically negative sides of the neck. The sensitivity and specificity of this technique are significantly higher than for palpation. In this thesis, MR imaging has been shown to detect 55-60% of the metastases that are not detected with palpation. CT was slightly, but not significantly, less accurate than MR imaging. The choice to use either CT or MR should thus mainly be based on other qualities or limitations of these modalities. Although the general availability of CT is an argument in favour of this technique, the superior depiction of most primary tumours by MR imaging has convinced many head and neck oncologists to more frequently use this technique. Ultrasound enables the detection of lymph nodes as small as 3 mm. In this respect, the subdigastric nodes, that lie relatively deep, are the most difficult to assess. Whereas at CT lymph nodes are more easily depicted in fat persons, at US lymph nodes are more easily visualized in skinny patients. Soft tissue discrimination by US is insufficient to allow for reliable depiction of small areas of tumour necrosis inside lymph nodes. Consequently, only the size and grouping criteria can be used for this technique. We found that the optimal size criteria varies when different populations of patients are studied. In this respect, optimal size criteria are smaller in clinically negative sides and levels of the neck. The accuracy of US is significantly better than the accuracy of palpation. Although CT and MR are more accurate than US, the difference is not significant. The most important restriction of the US examination is that it can not be standardized or documented for revision. Consequently the reliability of US is fully dependant on the skill and motivation of the ultrasonographer. Another important disadvantage of US versus CT or MR imaging is that this technique is only very seldom capable to stage the primary tumour.

As US-guided FNAC uses cytologic criteria, it is the only modality that can overcome the disadvantages of the morphologic criteria for malignancy as used in the other modalities. Consequently, it is not surprising that US-guided FNAC is significantly more accurate to either detect or exclude lymph node metastases in the neck. Using this modality enables detection of 73-83% of the occult metastases in the neck. False positives did not occur in this study. In this study, aspirations were in general well tolerated and without complications. However, it can not be overemphasized that the accuracy of the US-guided FNAC examination is fully dependant on the skill and motivation of the ultrasonographer and the cytopathologist.

Future improvements in the detection rate of small lymph node metastases will only be possible with use of techniques like immunoimaging that selectively trace metastatic tissue inside lymph nodes. However, it remains doubtful whether the use of radiolabelled monoclonal antibodies will enable the depiction of micrometastases.

In conclusion, it can be stated that all patients presenting with a squamous cell carcinoma of the mucous membranes within the head and neck area - except those with a T1 glottic or lip carcinoma - need additional radiological staging procedures for the neck if initial findings at palpation of the neck are negative or uncertain in neck sides "at risk" to harbour lymph node metastasis. In this respect, US-guided FNAC is the method of choice if the expertise and facilities are available. The choice of the lymph nodes, depicted at the US examination, to be aspirated from should mainly depend on the size and location of these nodes. Preferrably, more than one aspiration should be performed. In this respect, lymph nodes in the first and second echelons of the primary tumor are at highest risk to harbour metastases. As ar rule of thumb, lymph nodes in level 2 should be aspirated from if their minimal diameter is 5 mm or larger. Lymph nodes in other parts of the neck should be aspirated from if their minimal diameter is 4 mm or more. In those patients in whom CT or MR imaging is indicated for the assessment of the primary tumor, the neck can be evaluated at the same time without signifant additional costs. When in such patients, the results of the CT or MR imaging are not conclusive on the status of the lymph nodes in the neck, the additional use of US-guided FNAC is indicated. Furthermore, it is recommendable to use US-guided FNAC for follow-up if the neck has not been treated electively.

8.3. THE IMPACT OF RADIOLOGICAL STAGING TECHNIQUES ON THE 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. However, if the neck is treated electively because of a high likelyhood of occult lymph node metastasis, accurate imaging techniques can certainly influence treatment policies 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 for example T2 oral carcinomas, imaging techniques that can detect 75% or more of these metastases, like US-guided FNAC, can reduce this risk to 10%. In this respect, it is generally agreed that an estimated risk of occult metastasis lower than 10-15% is acceptable to justify a watchful "wait and see" policy. However, in case accurate follow-up can not be assured, it is recommendable to perform a selective staging neck dissection in these patients, to exclude the presence of micrometastasis.

Patients with a low risk of occult metastases, are usually not treated electively. However, in a small percentage of these patients, occult metastases are present. In these patients, the treatment policy can be changed by US-guided FNAC as well, as the majority of these occult metastases can be detected at initial presentation.

The clinically positive neck, in which slightly enlarged lymph nodes are palpated poses a similar problem, as false positive findings at palpation occur in 20-40%. The results presented in chapter 6, illustrate that these false positive cases can be reliably detected with use of US-guided FNAC. Therefore, it seems reasonable to rely on the US-guided FNAC findings in these patients as well. However, it must be recognized that most head and neck surgeons will perform at least a selective staging neck dissection in case of conflicting findings at palpation and US-guided FNAC.

8.4. THE HISTOPATHOLOGICAL EXAMINATION OF NECK DISSECTION SPECIMENS

The incidence of micrometastases in lymph nodes in the neck is high (chapter 7). In fact, 10% of tumour positive neck dissections contain only metastases measuring 3 mm or less. Although it can be assumed that incidently one can be lucky to aspirate from these micrometastases, in general these metastases will be missed by the US-guided FNAC as well as by all other imaging techniques. This implicates that even in case of a well performed negative US-guided FNAC examination, at least 10% of the tumour positive sides of the neck will be missed in a random patient population. For patients with negative findings at palpation, this percentage will even be higher.

Although the accuracy of meticulous histopathological examination of neck dissection specimens proved to be high, it is not 100%. With use of deeper sectioning of tumour negative lymph nodes in 14 neck dissection specimens that contained metastases at routine histopathological examination, additional metastases were detected in 21% of these specimens. On the other hand, deeper sectioning of lymph nodes in 62 tumour negative specimens revealed micrometastases in only 3%. With use of immunostaining of tumour negative lymph nodes, additional metastases were detected in 18% of 11 previously tumour positive neck dissection specimens, whereas in one of the ten (10%) tumour negative specimens a micrometastasis was detected. The prognostic and therapeutical implications of these micrometastases are unknown. It therefore remains controversial whether these techniques should be used on a routine basis. In our opinion, the enormous workload and costs of these additional procedures are not warranted as long as the prognostic significance of micrometastases has not been proven. On the other hand, it seems recommendable to use additional sectioning and/or immunostaining in studies on the prognostic significance of nodal metastases, on the accuracy of preoperative staging techniques and on the efficacy of neck treatment modalities.

SUMMARY

In patients with head and neck squamous cell carcinomas, palpation is generally accepted to be inaccurate for the assessment of the neck lymph nodes. Consequently, the resulting over- and undertreatment of the neck is a major concern to all physicians treating head and neck cancer patients. With the use of an accurate staging technique it might be possible to more reliably select patient who should be treated on behalf of their neck and patients in whom a "wait and see" policy is warranted. This doctoral thesis describes the first large *prospective* study on the assessment of the neck in which palpation, CT, US, MR and US-guided FNAC are compared in previously untreated head and neck cancer patients. The outcome of the histopathological examination of the neck dissection specimens was used as "gold standard".

The *key questions in this study* were whether modern imaging techniques - like CT, US, US-guided FNAC or MR - could do better than palpation for the detection of lymph node metastases in the neck, and which imaging modality should preferrably be used for this purpose.

Chapter 1 describes the anatomy and patterns of lymphatic spread from primary head and neck carcinomas from different sites within the mucosal linings. As lymph node metastasis is the single most important prognostic factor for head and neck cancer patients, the prognostic and therapeutical relevance of the assessment of the status of the neck are described as well. Some technical and clinical aspects of different diagnostic modalities are outlined. The statistical measures used in this thesis are described.

In chapter 2 different MR imaging techniques for neck node imaging are compared. Although no specific signal intensity for malignant or benign lymph nodes is found using any of the techniques studied, a combination of T1-weighted spin echo images and T2-weighted gradient refocussed echo images proves to be the optimal combination for the detection of cervical lymph node metastases. Gadolinium-DTPA enhanced T1-weighted gradient refocussed images enable the detection tumour necrosis inside metastatic lymph nodes.

Chapter 3 describes a pathoanatomic study on the radiological criteria of lymph node metastases in this area. In this chapter, seven characteristics of 2719 lymph

nodes derived from 71 neck dissection specimens are analysed to assess their importance as a radiological criterion. Depiction of "tumour necrosis" is the most specific criterion and occurs in 74% of tumour positive specimens. A remarkable finding in this study is that not the maximal axial or longitudinal diameter, but the minimal axial diameter is the most important size criterion for malignancy. Grouping of three or more bordeline nodes is a valid criterion, whereas shape does not contribute to a higher accuracy.

In chapters 4, 5 and 6 the data on the different comparative clinical-radiological-histopathological studies are presented. Computed tomography, MR imaging, US and US-guided FNAC are all significantly more accurate than palpation for staging of the neck. In spite of the excellent anatomical detail depicted at CT and the superior soft tissue discrimination of MR imaging, US-guided FNAC proves to be the most accurate technique for the assessment of the status of the neck. The superiority of US-guided FNAC is caused by the fact that this technique does not only rely on descriptive radiological criteria such as size, number and necrosis for the diagnosis of malignant lesions, but additionally uses cytological smears to classify lymph nodes depicted at the US examination. However, because the accuracy of this technique fully depends on the skill and motivation of the ultrasonographer and cytopathologist, it remains to be seen whether this technique will gain widespread popularity in all head and neck cancer institutions. As these modern imaging techniques - especially US-guided FNAC - are able to detect the great majority of palpably occult metastasis, the indications for elective treatment need to be re-evaluated. Furthermore, with use of US-guided FNAC for follow-up, treatment delay can be prevented for patients that are not treated electively for occult lymph node metastases.

Chapter 7 describes the incidence of micrometastases in neck dissection specimens. Some 10% of the tumour positive specimens proved to contain only micrometastases. With use of additional sectioning and immunostaining, additional metastases can be detected in both previously tumour negative, as well as previously tumour positive neck dissection specimens. These findings show that routine histopathological examination is not as accurate as generally thought. Until more is known about the prognostic significance of micrometastases, all therapeutical implications arbitrary. Therefore, we do not recommend the routine use of these techniques.

In chapter 8 the results obtained in this study are summarized and discussed.

SAMENVATTING

De onnauwkeurigheid van palpatie voor het beoordelen van de aan- of afwezigheid van lymfeklier metastasen in de nek bij patienten met een plaveiselcel carcinoom in het hoofd-hals gebied is algemeen erkend. Door het grote percentage vals positieve en vals negatieve bevindingen bij palpatie, worden veel patienten over- en onderbehandeld voor wat betreft hun nek. Met behulp van een accurate stagiërings methode is het in principe mogelijk meer betrouwbaar patienten te selecteren bij wie de nek behandeld dient te worden en bij wie een afwachtende houding verantwoord is. Dit proefschrift beschrijft het eerste *prospectieve* onderzoek bij een grote patienten populatie met een nog onbehandeld plaveiselcel carcinoom van het hoofd-hals gebied waarin palpatie is vergeleken met computer tomografie (CT), echografie, echo-geleide punctie cytologie en kernspin tomografie (KST). De resultaten van deze onderzoektechnieken konden bij alle patienten worden vergeleken met het histopathologisch onderzoek van het halsklier dissectie preparaat.

De *belangrijkste vraag* die wij met dit onderzoek wilden beantwoorden was of moderne radiologische technieken beter zijn voor het beoordelen van nek dan palpatie. Verder was het belangrijk de verschillende radiologische technieken onderling te vergelijken om te bepalen welke techniek het meest geschikt zou zijn.

In hoofdstuk 1 wordt de anatomie van het lymfatisch systeem in de nek beschreven, en in relatie hiermee, het lymfogene metastaserings patroon van de meest frequent voorkomende plaveiselcel carcinomen in het hoofd-hals gebied. Ook wordt in dit hoofdstuk het prognostisch en therapeutisch belang van lymfeklier metastasen in de nek uitgelegd. Enkele technische en practische aspecten van CT, echografie, echo-geleide punctie cytologie, KST en enkele andere stagerings methoden worden beschreven. Enkele aspecten van de statistische parameters die voor dit onderzoek zijn gebruikt worden eveneens uitgelegd.

De studie beschreven in hoofdstuk 2 werd verricht om de meest geschikte KST technieken voor het afbeelden van halsklier metastasen te bepalen. Een combinatie van axiale T1-gewogen spin echo opnamen en T2-gewogen gradient echo opnamen is optimaal om halsklieren af te beelden. T1-gewogen gradient echo

opnamen na toediening van i.v. gadolinium zijn het meest geschikt voor het afbeelden van "tumor necrose" in lymfeklieren. Met geen enkele techniek is het mogelijk om vitaal tumor weefsel te onderscheiden van lymfeklier weefsel.

Hoofdstuk 3 geeft de resultaten weer van een pathologisch-anatomische studie naar de radiologische kriteria voor maligniteit van halsklieren. Door 7 histopathologische karakteristieken in 2719 halsklieren en halsklier metastasen en hun radiologische aantoonbaarheid te analyseren, werden de optimale kriteria voor maligniteit afgeleid. De afbeelding van "tumor necrose", hetgeen mogelijk is bij necrose haardjes van 3 mm en groter, is het meest specifieke kriterium voor maligniteit en komt voor in 74% van de tumor positieve halsklier dissectie preparaten. Een opmerkelijke bevinding in deze studie is dat de minimale axiale diameter een beter grootte criterium is dan de tot nog toe gepropageerde maximale diameter. Een groepering van 3 of meer lymfeklieren met een minimale axiale diameter van 1 à 2 mm kleiner dan het gehanteerde grootte kriterium verhoogt de sensitiviteit zonder de specificiteit aan te tasten. Een ronde vorm van lymfeklieren draagt niet bij aan de betrouwbaarheid van enig ander kriterium.

In de hoofdstukken 4, 5 en 6 worden de resultaten besproken van drie vergelijkende klinische-radiologische-histopathologische onderzoeken. Palpatie bleek signifikant minder betrouwbaar dan alle onderzochte radiologische technieken. Hoewel CT het beste oplossend vermogen heeft, en KST de weke delen in de nek met het meeste contrast kan afbeelden, bleek de echo-geleide punctie cytologie de meest geschikte methode voor het aantonen, dan wel uit sluiten van halsklier metastasen. De superioriteit van echo-geleide punctie cytologie kan verklaard worden uit het feit dat deze techniek niet alleen gebruik maakt van morfologische criteria, zoals grootte en groepering van lymfeklieren, doch ook cytologisch onderzoek van afgebeelde lymfeklieren toelaat. De betrouwbaarheid van dit onderzoek echter, valt of staat met de deskundigheid en inzet van zowel de echografist als de cytopatholoog. Door het geringe aantal oncologische KNO patienten in de meeste ziekenhuizen, is het de vraag of voldoende ervaring kan worden opgedaan met deze techniek om de betrouwbaarheid op peil te houden.
Doordat de boven beschreven technieken, in het bijzonder echo-geleide punctie cytologie, in staat zijn het overgrote deel van de - met palpatie ocult gebleven - halsklier metastasen op te sporen, moeten de indikaties voor electieve behandeling van de halsklieren worden heroverwogen. Een verdere toepassing betreft het vroegtijdig opsporen van halsklier metastasen bij follow-up van patienten die niet electief werden behandeld.

In hoofdstuk 7 wordt een studie beschreven naar de incidentie van micrometastases in halsklier dissectie preparaten. Ongeveer 10% van alle tumor positieve preparaten bleek uitsluitend micrometastasen te bevatten. Met behulp van antikeratine kleuringen en het maken van extra coupes op een dieper niveau in lymfeklieren was het mogelijk metastasen op te sporen in lymfeklieren die in eerste instantie als tumor negatief waren geduid. Deze "extra" micrometastasen werden zowel in halsklier dissectie preparaten met andere metastasen als in preparaten zonder andere metastasen aangetroffen. Deze bevindingen tonen aan dat het routine histopathologisch onderzoek niet volledig betrouwbaar is. Omdat het prognostisch en therapeutisch belang van micrometastasen echter onduidelijk is, lijkt het vooralsnog niet nodig routinematig iedere klier dieper op te snijden of antikeratine kleuringen toe te passen.

In hoofdstuk 8 worden de resultaten van de voorgaande hoofdstukken samengevat. Bovendien worden in dit hoofdstuk de implicaties van dit proefschrift weergegeven.

DANKWOORD

Dit vergelijkend klinisch - radiologisch - histopathologisch onderzoek is mogelijk gemaakt door een nauwe en goede samenwerking tussen de afdelingen keel- neus- en oorheelkunde, kaakchirurgie, radiodiagnostiek en pathologie van het Academisch Ziekenhuis van de Vrije Universiteit. Financiering door het Koningin Wilhelmina Fonds maakte deze studie mogelijk, waarvoor mijn dank. Een aantal personen zou ik met name willen bedanken voor hun bijdrage aan dit proefschrift.

Mijn promotor, Prof.Dr.G.B.Snow, wil ik bedanken voor zijn waardevolle kritiek en begeleiding. Zijn suggesties met betrekking tot de klinische toepasbaarheid van dit onderzoek zijn een kontinue stimulans voor mij geweest.
Prof.Dr.J.Valk, promotor, bood mij de ruimte om de mogelijkheden en beperkingen van de meest moderne radiologische technieken zelfstandig te onderzoeken.
Van Prof.Dr.C.J.L.M.Meyer, copromotor, heb ik de waardevolle suggesties bij het manuscript bijzonder op prijs gesteld, evenals het ter beschikking stellen van de pathologische laboratoria voor deze studie.
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Onder leiding van Dr.H.V.Stel zette ik de eerste schreden op het histopathologische pad. Herbert, door de vele coupes die we samen hebben bekeken en jouw inbreng bij het schrijven van de manuscripten, is het "pathologisch niveau" van dit, in opzet radiologisch, onderzoek gestegen boven het niveau van de "gouden standaard".

Er zijn vele anderen die aan de totstandkoming van dit proefschrift hebben bijgedragen. Drs.Gerard A.Croll heeft alle patienten preoperatief gepalpeerd. Prof.Dr.I. van der Waal en Drs.Willem B.F. de Jong reviseerden vele coupes en voorzagen ze van nuttig kommentaar. Richard P.Golding FRCR heeft zorg gedragen voor een protocollair uitgevoerd CT onderzoek, en heeft op voortreffelijke wijze de scans mede-beoordeeld. Dr.Paul van der Valk scoorde vele "immunocoupes" en droeg ideeën aan voor het immunohistochemisch onderzoek. Willem W. de Jong heeft honderden extra coupes gesneden en gekleurd. Thea

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Niet in de laatste plaats ben ik mijn vrouw, Sabine, dankbaar voor haar geduld en hulp bij het uitwerken van dit proefschrift.

CURRICULUM VITAE

De auteur van dit proefschrift werd op 1 november 1961 geboren in Heerlen. Na het doorlopen van het Gymnasium ß aan het Bernardinus College in Heerlen begon hij in 1980 aan de studie geneeskunde aan de Katholieke Universiteit Leuven. In juni 1987 slaagde hij cum laude voor het arts-examen.
Na enkele maanden als arts-assistent algemene heelkunde in het De Wever ziekenhuis in Heerlen en als waarnemend huisarts te hebben gewerkt, werkte hij van januari tot december 1988 als dienstplichtig arts-assistent KNO in het militair hospitaal "Dr.A.Mathijsen" in Utrecht. Sinds december 1988 is hij werkzaam op de afdeling keel- neus- en oorheelkunde van het Academisch Ziekenhuis Vrije Universiteit, waar hij tot juli 1990 als full-time onderzoeker werkte voor een onderzoeksproject van de Nederlandse Kankerbestrijding, het Koningin Wilhelmina Fonds (IKA 88-19). Uit dat onderzoeks-project is dit proefschrift voortgekomen. Sinds 1 april 1990 is hij in opleiding tot keel- neus- en oorarts in hetzelfde ziekenhuis (opleider: prof.dr. G.B.Snow).

Stellingen behorend bij het proefschrift

ASSESSMENT OF LYMPH NODE METASTASES IN THE NECK

a radiological and histopathological study

1. Voor de diagnostiek van halsklier metastasen is echogeleide punctie cytologie significant betrouwbaarder dan palpatie, echografie, computer tomografie of kernspin tomografie.

2. De betrouwbaarheid van het echografisch onderzoek, al dan niet aangevuld met een echogeleide punctie, is sterk afhankelijk van de kunde en de inzet van de onderzoeker.

3. Bij patienten met een carcinoom uitgaande van de slijmvliezen in het hoofd-hals gebied, correleert - wat betreft de grootte van de halsklieren - de minimale axiale diameter het best met de aanwezigheid van halsklier metastasen.

4. De sensitiviteit en specificiteit van diagnostische onderzoek methoden zijn mede afhankelijk van de bestudeerde patienten populaties.

5. Het routine histopathologisch onderzoek van halsklier dissectie preparaten is geen "gouden", doch eerder een "zilveren" standaard.

6. Electieve behandeling van de halsklieren op grond van een hoog risico op occulte metastasen, bij patienten met een carcinoom uitgaande van de slijmvliezen in het hoofd-hals gebied, is na een goed uitgevoerd echo-geleid punctie onderzoek meestal niet meer nodig.

7. De inter-individuele en intra-individuele variabiliteit bij de histopathologische diagnose van zgn. kapseldoorbraak van halsklier metastasen is groot.

8. De differentiatie van geuren berust niet op centrale verwerkings mechanismen, doch is mogelijk door een enorme verscheidenheid aan receptoren in het zintuig epitheel.
   Buck L, Axel R (1991), Cell 65:175-187.

9. Bij het aanpassen van hoorapparaten geldt: de patient heeft altijd gelijk.

10. In het kader van de wederzijdse erkenning van medische specialisten in de landen binnen de Europese Gemeenschap, zijn uniforme opleidings eisen voor medische specialisten onontbeerlijk.

11. De kosten van kinderopvang voor werkende ouders zouden volledig als beroepskosten aftrekbaar van de belastingen moeten zijn.

12. Drinkwater wordt schaars.

13. Zonder er een halszaak van te willen maken, getuigt het halsstarrig vasthouden aan palpatie als meest geschikte stagerings methode voor de hals, meer van een olifantehuid dan van ruggegraat.

14. Marry an intelligent woman; in the beginning you won't see the difference but later on it's much more fun.

[redacted]