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Regional Metastasis in Head and Neck Squamous Cell Carcinoma: Revised Value of US with US-guided FNAB¹

PURPOSE: To verify the acclaimed accuracy of ultrasound (US) combined with US-guided fine-needle aspiration biopsy (FNAB) in the detection of lymph node metastasis in the neck and to evaluate the interobserver variability.

MATERIALS AND METHODS: In a prospective, multicenter study of 185 patients with head and neck squamous cell carcinoma, US ($n = 238$ neck sides) with US-guided FNAB ($n = 178$ neck sides) was used for evaluation of the lymph node status of the neck. Findings were correlated with those of histopathologic examination in 238 neck sides.

RESULTS: US with US-guided FNAB had a sensitivity of 77% and a specificity of 100%. Nineteen of 178 aspirations were nondiagnostic. There were no significant differences between the four participating hospitals or the individual sonologists ($P > .05$).

CONCLUSION: Sensitivity of US with US-guided FNAB was slightly lower compared with previous reports. Specificity was similar to previous reports. Interobserver variability appeared to be low. The validity of US with US-guided FNAB is high and warrants widespread use of the procedure for evaluation of the neck.

Index terms: Biopsies, technology, 28.1261 • Head and neck neoplasms, metastases, 997.33 • Head and neck neoplasms, staging, 997.91 • Head and neck neoplasms, therapy, 997.12986 • Ultrasound (US), guidance, 28.12985, 28.12986

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THE status of the lymph nodes in the neck is crucial to the treatment and prognosis of patients with head and neck squamous cell carcinoma (SCC). The prognosis is mainly determined on the basis of nodal disease: The presence of a single cervical lymph node metastasis in the ipsilateral side of the neck decreases the expected survival by approximately 50%. A contralateral affected node also reduces the expected survival by half (1).

In general, a patient with head and neck SCC and regional metastasis will be treated with irradiation of the neck, surgery, or both. Even when no nodes are detected, most head and neck oncologists will treat the neck electively when (clinically undetected) regional metastasis is likely. In most hospitals, elective neck treatment will be performed if the frequency of occult metastasis is more than 15%. In clinical practice, this means that patients with oral, oropharyngeal, hypopharyngeal, or supra- and subglottic laryngeal carcinomas will be treated electively for the lymph nodes of the neck (2). If the probability of regional metastasis is reduced, the number of elective treatments will be decreased (2).

Until recently, accurate assessment of the neck of patients with head and neck SCC was not possible. Palpation and lymphangiography are not reliable (3-5). Magnetic resonance (MR) imaging and computed tomography (CT) are useful (6-10); however, these are expensive and not always avail-

able. In addition, differentiation between nodes with and those without metastases on the basis of radiologic characteristics only has a relatively low specificity (4,9,11-17). Immunologic assays may prove to be useful in the future but are still under investigation (18). Ultrasound (US) of the neck combined with US-guided fine-needle aspiration biopsy (FNAB) was demonstrated to be very accurate in the evaluation of regional metastatic disease (13,19,20). This technique combines the high sensitivity of US with the excellent specificity of FNAB (21-24). A sensitivity of 98% and a specificity of 95% have been reported (20).

In view of the test characteristics of US with US-guided FNAB, this diagnostic procedure may have a substantial impact on clinical management of patients with head and neck SCC (2). Opponents have suggested, however, that the results of both US and US-guided FNAB are very much determined by the expertise of those who perform the investigation. Therefore, a prospective, multicenter study on the value of US with US-guided FNAB was undertaken.

The object of our study was to verify the acclaimed accuracy of US with US-guided FNAB in the diagnosis of metastatic neck disease in patients with head and neck SCC. A second objective was to investigate whether major differences in the accuracy of the combined procedure occur when the tests are performed by different investigators. Furthermore, we studied other factors that could possibly influence the results of US with US-guided FNAB (eg, primary tumor site and node level).

MATERIALS AND METHODS

The multicenter study was performed at four hospitals in The Netherlands by 39

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Abbreviations: FNAB = fine-needle aspiration biopsy, SCC = squamous cell carcinoma.

sonologists between March 1992 and September 1993. All patients with head and neck SCC (nonirradiated or irradiated) who underwent neck dissection(s) as part of their treatment were eligible for this study.

The neck of each patient was examined by an experienced head and neck oncologist (P.K., J.J.M., C.A.M., H.A.M.M., H.A.A.S., M.F.d.B., R.J.B.d.J.). The findings were recorded, together with other relevant clinical information. At this stage, cytologic examination was not performed. Subsequently, the neck was examined by one of the sonologists (J.A.v.O., J.S.L., R.H.K., F.B.M.J.). All clinical information was provided. The findings of the sonologist(s) were recorded on a worksheet. Subsequently, US-guided FNAB of nodes that were depicted with US was performed in 178 cases. In case of multiplicity, US-guided FNAB was performed of the largest node, nodes showing central hypoechogenicity, or the most cranial and caudal nodes in the areas at highest risk for metastasis. The US examinations and the US-guided FNABs were performed with the following scanners: a model 620/650CL (Aloka, Tokyo, Japan), with a 7.5-MHz linear-array probe; a model SSA 250A (Toshiba Europe, Zoetermeer, The Netherlands), with a 7.5-MHz mechanical sector type of probe with a built-in water path; and a model 128 XP (Acuson, Mountain View, Calif), with a 7-MHz linear-array probe. The procedure was performed as described previously (20,25) (Figure). Cytologic examination was performed by experienced cytopathologists. Nondiagnostic aspirations had to be repeated. Because the trauma associated with rigid endoscopy may cause an increase in the number and size of lymph nodes, both palpation and US were preferably performed before endoscopy.

Neck dissection had to be performed within 3 weeks. The specimen was labeled by the surgeon as level I-V, according to the Memorial Sloan-Kettering classification (26). Subsequently, histologic examination of the neck dissection specimen was performed according to a standardized protocol, and the findings of the pathologist (J.H.J.M.v.K., F.T.B., S.C.H.L., J.M.W.v.T.) were recorded per level. The results of palpation and US with US-guided FNAB were compared with the results of the histopathologic examination. We considered the results per neck side since the treatment of metastatic disease is for a neck rather than for a single node: The detection of a single metastasis results in the treatment of the whole neck side. Moreover, it is practically impossible to match an aspirated or palpable node with the same node in the neck dissection specimen.

The test result of US with US-guided FNAB in fact consisted of the combined results of two separate tests: US and US-guided FNAB (Table 1). US may be scored positive (lymph nodes depicted) or negative (no lymph nodes visualized). No morphologic criteria were used. Merely the depiction of lymph nodes, therefore, was

used for scoring the result of US. US-guided FNAB may be (a) not performed, (b) negative (reactive), (c) positive (metastatic), or (d) nondiagnostic. Therefore, five combinations of test results were distinguished. The cases with nondiagnostic aspirates (not repeated or repeatedly nondiagnostic) were excluded. Therefore, US with US-guided FNAB was considered negative if (a) no nodes could be visualized, (b) nodes were too small to aspirate (<5 mm), or (c) nodes appeared to be reactive at cytologic examination. The test was considered positive if the aspirate contained tumor cells.

The reference standard (histopathologic examination) was considered negative when no evidence of metastases was found in neck dissection specimens and positive when one or more metastases were diagnosed.

Since the main objective of this study was to establish the value of US with US-guided FNAB in the discrimination between *neck sides* with or without metastatic disease, the result of US-guided FNAB of one or more nodes was considered to be representative for the neck as a whole. In other words, when US-guided FNAB for example showed a reactive node that was confirmed with histopathologic examination but a metastasis was found in another lymph node that was not depicted at US, the test result was considered false-negative.

Differences in test characteristics such as sensitivity and specificity were evaluated by using the χ^2 test. Differences were considered statistically significant at $P < .05$.

RESULTS

A total of 185 patients (133 men, 52 women; age range, 25–85 years; mean age, 59 years) participated in this study. Of these, 132 patients underwent unilateral and 53 patients underwent bilateral neck dissection, resulting in the inclusion of 238 neck sides. The primary tumor sites and tumor stages are listed in Table 2.

Palpation and US with US-guided FNAB

The results of US with US-guided FNAB are shown in Table 1. With palpation, a sensitivity of 66% and a specificity of 92% were achieved (Table 3). For US with US-guided FNAB, a sensitivity of 77% and a specificity of 100% were found (Table 3). Some nodes detected with palpation were not detected by using US with US-guided FNAB. Therefore, the results of palpation and US with US-guided FNAB are supplementary. When, as is done in clinical practice, the results of US with US-guided FNAB and palpation were combined, the sensitivity was 80% with a specificity of 92%.

Lymph node metastasis. US image obtained during US-guided FNAB. Tip of the needle is depicted as a hyperechoic spot (arrow). For this image, a 10-MHz sector-type probe with a built-in water path was used to obtain an optimal graphical representation.

A considerable proportion of the aspirates (19 of 178 cases) were nondiagnostic, and FNAB was not repeated. In fact, in most cases of initially nondiagnostic aspirates, FNAB was not repeated. Histologic examination of the neck dissection specimens revealed that 12 of these specimens in fact contained metastases and seven had reactive nodes. This might suggest that a nondiagnostic aspirate is more likely to be from a metastatic node. However, the proportion of metastatic nodes (12 of 19 nodes) reflects the prevalence of lymph node metastases in the entire population (155 of 238 cases). For the present study, the nondiagnostic aspirates were excluded.

Sonologists and Hospitals

To evaluate the interobserver variability, we compared the results of six sonologists who examined at least 13 neck sides (varying from 13 to 53 neck sides) and the combined results of a group of 33 sonologists (78 neck sides) who performed the examination less frequently. No statistically significant differences were found between the characteristics of these (groups of) sonologists (Table 3) or between the participating hospitals (data not shown, $P = .14$).

Primary Tumor Sites and Neck Levels

The results of US with US-guided FNAB for different primary tumor sites are summarized in Table 3. Although there seem to be marked differences, note that the number of cases in some of the groups is fairly small. There were no statistically significant differences in sensitivity for the different primary sites ($P = .51$).

Table 1
Results of US with US-guided FNAB

A: Separate Procedures				
US	US-guided FNAB	Histologic Result		Total
		Negative	Positive	
Negative	Not performed	34	17	51
Positive	Not performed	6	3	9
Positive	Negative	36	13	49
Positive	Nondiagnostic	7	12	19
Positive	Positive	0	110	110
Total		83	155	238

B: Combined Procedure*			
US with US-guided FNAB	Histologic Result		Total
	Negative	Positive	
Negative	76	33	109
Positive	0	110	110
Total	76	143	219

* The 19 nondiagnostic aspirates were excluded from this analysis.

Table 2
Primary Tumor Site and Stage of Tumor according to the TNM Classification

Variable	No. of Patients
Site	
Larynx	60
Hypopharynx	15
Oropharynx	26
Floor of mouth	22
Oral tongue	36
Oral cavity (other)	15
Other sites	7
Unknown primary	4
Stage	
T1	20
T2	40
T3	42
T4	48
Unknown primary	4
Recurrence	25
Unknown	6

To evaluate differences in detecting metastases in lymph nodes of the different neck levels (I–V), we investigated whether metastases were missed more often in particular regions. The number of lymph node metastases per level was listed, and the fraction of metastases not detected by using US with US-guided FNAB was calculated. No statistically significant differences were found between the various levels ($P = .52$) (Table 4).

DISCUSSION

To assess the status of lymph nodes in the neck in patients with head and neck SCC, various (imaging) tech-

niques have been explored. CT and MR imaging allow detection of small structures, such as lymph nodes, with high sensitivity. Although several radiologic characteristics of metastatic nodes have been defined (size, shape, central necrosis, obliteration of fascial planes, contiguous nodes), several authors have criticized these criteria (4,12,15–17,27–29). In our opinion, differentiation between benign and metastatic nodes only on the basis of radiologic characteristics remains difficult and unreliable.

US is characterized by a superior sensitivity rate for detection of lymph nodes (3,30). The detection of more lymph nodes, however, inevitably leads to a lower specificity: A considerable proportion of the lymph nodes detected with US will be benign. As with CT and MR imaging, differentiation between reactive and metastatic nodes is based on morphologic criteria (13,28,31). This leads to a relatively low specificity, although some authors reported high specificity rates up to 91% with US alone (30).

With the introduction of the concept of US-guided FNAB (19,20), the high sensitivity of US is combined with the high specificity of cytologic examination (20). Sensitivity and specificity have been reported as high as 98% and 95%, respectively. In a subsequent similar study, other authors reported an even higher specificity of 100% but at the expense of a lower sensitivity of 90% (13). Critics, however, doubted that these rates could be reproduced if the technique was performed by different sonologists in "daily practice."

In our study, only patients undergoing neck dissection as part of their treatment were included because histologic examination was used as the standard of reference. Although this introduces an inevitable bias by increasing the number of cases with metastatic disease, all reports of studies of US with US-guided FNAB, CT, or MR imaging are subject to this limitation.

The accuracy and sensitivity of US with US-guided FNAB in our study were not as high as found in previous studies. The specificity, however, was comparable. Compared with other diagnostic imaging techniques, the sensitivity of US with US-guided FNAB found in our study is in the range of that reported for CT (4,6,9,12,13,15,16) and MR imaging (5,9). The high specificity of up to 100% found in the present and previous studies (13,20) compares favorably with that of CT and MR imaging. Most studies concerning CT found a specificity of no more than 70%–85% (4,9,12,13,15,16). A few studies found higher specificity rates (up to 94%) by using morphologic criteria (28).

In most studies concerning the value of CT and MR imaging for assessment of the neck, morphologic and/or size criteria are used. By choosing an optimal cutoff point, false-positive and false-negative results will be introduced. As a consequence, in these studies, a higher sensitivity results in a lower specificity and vice versa. For example, Stevens et al (12), Close et al (15), Hillsamer et al (9), and Friedman et al (11) found sensitivity rates of 97%, 86.5%, 84%, and 95% paired to a much lower specificity of 82%, 71%, 71%, and 77%, respectively. In contrast, Feinmesser et al (4) found a relatively low sensitivity of 60% with a higher specificity of 85%. Although US alone suffers from the same phenomenon, US with US-guided FNAB does not because US determines the sensitivity and US-guided FNAB the specificity.

Another factor influencing the results of these studies is the frequency of metastasis. Studies with a high number of patients having metastasis or advanced-stage disease will show higher sensitivity rates for the studied diagnostic techniques. For example, in studies with a relatively high number of cases with clinically or histologically positive nodes, higher sensitivity rates for CT were obtained, up to 91% (6,12,15), whereas in studies with more cases with negative nodes, sensitivity rates for CT were lower (eg, 60%) (4). The only study, to our knowledge, in which the results of US with US-guided FNAB, CT, and MR imaging were compared in the same study population

showed superior results of US with US-guided FNAB (13).

Another advantage of US with US-guided FNAB over CT and MR imaging is the lower cost (in the Netherlands, the costs of CT are about four times as high as those of US with US-guided FNAB). Moreover, for US with US-guided FNAB, patients do not have to lie down (for a prolonged period of time), which is more convenient in these predominantly elderly and/or dyspneic patients. Contrary to CT and especially MR imaging, US will not be problematic in patients inclined to be claustrophobic. Finally, in our opinion, FNAB is hardly a more invasive or risky procedure than the administration of intravenous contrast material in CT or MR imaging.

Unfortunately, in 19 cases of nondiagnostic aspirates, FNAB was not repeated. Repeating these aspirations, as was requested according to the protocol, would definitely have improved the test results. We cannot, however, prove this with our material because for most cases of nondiagnostic aspirates, FNAB was not repeated. The rate of nondiagnostic US-guided FNABs (19 [11%] of 178 aspirates) is in the range found in previous studies (1%–15%) (20,32,33).

Our data show that the results of US with US-guided FNAB are not as investigator dependent as often suggested. No major differences were found between experienced and less experienced sonologists.

Although the differences were not statistically significant, it appeared that the accuracy of US with US-guided FNAB was determined by the site of the primary tumor. There are two explanations for this finding. First, this may be due to a difference in frequency (Table 3). This influences, in particular, the negative and positive predictive values. Second, different primary tumors metastasize to different neck levels, and lymph node metastases in some levels are more difficult to detect by using US with US-guided FNAB than others. This phenomenon has been described in earlier studies (34,35). In our study, it seemed more difficult to detect lymph node metastases in levels I and V than in levels II, III and IV, although the differences were not statistically significant. Therefore, the favorable sensitivity rates for laryngeal and pharyngeal carcinoma when compared with floor of mouth or oropharyngeal carcinoma may be because the former metastasize less frequently to level I.

The difficulty in the detection of nodes in level I by using US with US-

Table 3
Diagnostic Indexes

Variable	No. of Neck Sides	Frequency (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
Palpation and US with US-guided FNAB							
Palpation	238	65	66	92	94	59	75
US with US-guided FNAB	219	65	77	100	100	70	85
US with US-guided FNAB plus palpation	219	65	80	92	100	73	87
Breakdown per Sonologist							
A	13	85	82	100	100	50	85
B	13	71	90	100	100	75	92
C	15	60	67	100	100	67	80
D	48	58	68	100	100	69	81
E	20	60	75	100	100	73	85
F	37	54	80	100	100	81	89
Others	73	73	79	100	100	65	85
Breakdown per Primary Tumor Site							
Larynx	71	77	84	100	100	64	86
Hypopharynx	15	70	83	100	100	60	87
Oropharynx	28	93	73	100	100	22	82
Floor of mouth	38	37	57	100	100	80	84
Oral tongue	38	39	73	100	100	85	89
Oral cavity (other)	16	63	70	100	100	67	81
Oral cavity (total)	92	42	67	100	100	80	86

guided FNAB may be caused by the mandible. However, nodes missed with US at this level may be detected with palpation: With bimanual palpation, examination of level I is relatively easy to perform. If the results of palpation are added to the results of US with US-guided FNAB in cancer of the floor of mouth, a primary tumor predominantly metastasizing to level I, sensitivity improves from 57% to 79% at the expense of a specificity declining from 100% to 83%. It seems justified, therefore, to use the combination of the results of both methods of examination in clinical practice (Table 3).

In this prospective, multicenter study, the sensitivity of US with US-guided FNAB appeared to be slightly lower compared with that of previous studies but comparable with the sensitivity of CT and MR imaging. The specificity of US with US-guided FNAB found in our study is similar to that of previous studies and superior to the specificity of CT and MR imaging. Repeating FNAB for nondiagnostic aspirates may further improve the test characteristics of US with US-guided FNAB.

Palpation remains an important tool for assessment of the lymph nodes of the neck. A combination of palpation and US with US-guided FNAB improves the sensitivity of the diagnostic procedure. In addition, in

Table 4
Metastases per Lymph Node Level Not Detected by Using US with US-guided FNAB

Lymph Node Level	No. of Metastases	Undetected Metastases
I	44	10 (23)
II	92	16 (17)
III	65	9 (14)
IV	31	3 (10)
V	12	3 (25)

Note.—Numbers in parentheses are percentages.

this study, the often suggested interobserver variability of US and US-guided FNAB could not be confirmed. The results of this study can be considered as a validation of and recommendation for the use of US with US-guided FNAB for evaluation of the neck in patients with head and neck SCC. ■

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