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Original papers

Controversies on the management of the clinically negative neck

C. René Leemans[1], Eline J.C. Nieuwenhuis[1], Jonas A. Castelijns[2], Gordon B. Snow[1]

Adequate management of the clinically negative neck is vital and should be balanced between over and undertreatment. Compared to clinical examination ultrasound-guided fine-needle aspiration cytology (USgFNAC) at initial staging can reduce the risk of occult metastases for T1-T2 squamous cell carcinoma of the oral cavity or oropharynx considerably to 20%, which justifies local excision of the tumour and a wait-and-see policy for the neck. SN identification and aspiration did not decrease the false-negative rate, and we have therefore abandoned its use in this setting. Using USgFNAC for follow-up enabled early detection of a significant percentage of neck failures and a high salvage rate with therapeutic neck dissection of 80%. Detecting subclinical neck metastases continues to challenge clinicians and debate continues.

Układ chłonny szyi klinicznie wolny od przerzutów – co robić?

Odpowiednie postępowanie w przypadku, gdy węzły chłonne szyi są klinicznie wolne od przerzutów, musi być bardzo wyważone. W przypadku raka płaskonabłonkowego jamy ustnej i gardła biopsja cienkoigłowa pod kontrolą USG pozwala na dokładną ocenę węzłów chłonnych i potwierdzenie do 80% przypadków subklinicznych przerzutowych węzłów chłonnych. W przypadku układu chłonnego szyi taki wynik usprawiedliwia decyzję o miejscowym usunięciu guza i dalszej obserwacji chorego ("wait and see policy"). Określanie węzłów wartowniczych (wraz z biopsją cienkoigłową) nie poprawiło odsetka wyników fałszywie ujemnych, odstąpiliśmy zatem od stosowania tej metody. Biopsja cienkoigłowa pod kontrolą USG pozwoliła na wczesne wykrycie znacznego odsetka wznów węzłowych i na zwiększenie skuteczności ratujących operacji usunięcia układu chłonnego szyi do 80%. Diagnostyka subklinicznych przerzutów do węzłów chłonnych szyi nadal jednak stanowi ogromny problem i rodzi wiele kontrowersji.

Key words: head and neck cancer, radical neck dissection, ultrasound-guided fine-needle aspiration cytology
Słowa kluczowe: rak głowy i szyi, usunięcie układu chłonnego szyi, biopsja cienkoigłowa pod kontrolą USG

Introduction

If the neck is to be treated electively, there is good evidence today that selective neck dissections are appropriate and yield similar results as modified radical neck dissection. As to postoperative radiotherapy after selective dissections, however, there is less agreement. Many surgeons would advise adjuvant radiation to any node positive neck when less then a modified radical neck dissection has been performed. There is general agreement that effective treatment of the neck is indicated when there is a high likelihood of occult nodal metastases and when the neck needs to be entered for surgical access and treatment of the primary tumour, the patient will be unavailable for regular follow-up and also when the status of the cervical lymph nodes cannot be adequately assessed. When there is, however, merely a certain likelihood of occult nodal metastases, there is controversy on the management of the N0-neck. The choice is then between elective treatment and watchful waiting. This question mainly arises in the early staged carcinomas of the anterior floor of mouth and anterior tongue, because these usually can be excised transorally. The rationale of elective treatment is based on the phenomenon that occult disease in the neck will inevitably develop into clinically manifest disease and that despite regular follow-up some patients will develop inoperable disease in the neck with a wait and see policy. Untreated occult disease in the neck may also give rise to distant metastases, while the lymph node is growing into clinically detectable size. Conversely there are arguments against elective treatment. First, it entails overtreatment of the majority of patients, Second, it means increased morbidity, especially when performed bilaterally. Third, it involves increased operating time and costs. It has also been argued that removing lymph node barriers and changing patterns of spread could influence prognosis in case of local recurrence or second primary tumour.

[1] Department of Otolaryngology/Head and Neck Surgery
[2] Department of Radiology
VU University Medical Center
P.O. Box 7057, 1007 MB Amsterdam
the Netherlands

The prognostic impact of a wait and see-policy in case of clinically undetectable disease in early staged oral squamous cell carcinoma has been the topic in many studies, but only three of these studies were prospective. Vandenbrouck et al. found no significant difference in outcome between patients whose neck was treated electively and those whose neck was closely observed [1]. They concluded that in squamous cell carcinoma of the oral cavity staged T1-3N0, it seems possible, without risk, to delay neck dissection until a node is detectable, although it is reasonable to perform elective neck dissection in those cases in which the patient is unavailable for regular follow-up. A similar study was performed by Fakih et al. and by Kligerman et al., but these trials also failed to show survival benefit of elective neck dissection in early stage oral cancer above a wait-and-see policy [2, 3]. All three described relatively small numbers of patient groups, and none used an imaging modality for initial selection of patients or for follow-up after wait-and-see policy was performed. A proper randomised clinical trial will never be carried out because of the very large number of patients needed to allow for meaningful conclusions.

Therefore a practical approach is adopted towards the N0 neck. Elective treatment is performed if the risk of occult metastases exceeds 20% or in case the neck is entered for technical reasons. Conversely, a wait-and-see policy is justified if the risk of occult metastases is below 20% and if strict follow-up can be ensured. Weiss et al. performed a decision analysis study based on literature data on prognosis and outcome and substantiated this "acceptable" risk of occult metastases [4]. When assessment of the status of neck nodes is carried out by means of palpation alone, most sites and stages of squamous cell carcinoma of the head and neck, including early stage oral cavity tumours, qualify for elective treatment on this basis.

Imaging

The question arises if imaging techniques can sufficiently reduce the occult metastasis rate in certain risk groups to allow for watchful waiting. Although both computed tomography (CT) and magnetic resonance imaging (MRI) of the neck have been found to be superior to palpation in detecting cervical metastases, these modalities still have a relatively low accuracy for the N0 neck [5-7]. In contrast, ultrasound-guided fine-needle aspiration cytology (USgFNAC) has a higher sensitivity and specificity and is more cost-effective than CT and MRI (Figure 1) [5]. It can also be repeated easily during follow-up. In experienced hands, sensitivity for N0 neck can reach 73% with a specificity of 100%, although others reported sensitivities in the range of 42% to 50% [5, 6, 8, 9]. In general two major points have to be taken into account in decision making towards management of the clinically negative neck: the risk of occult neck metastases and the prognostic impact of wait-and-see policy. This last issue depends on delay of treatment since prognosis is related to number, size and level of metastases, extranodal spread and to distant metastasis. USgFNAC might be able to decrease the delay treatment in case occult metastatic nodes are present and thus increase salvage rate of subsequent neck metastasis. The literature quotes salvage rates of 28-59 % by using clinical examination alone [2, 10-12]. Using a policy of strict preoperative examination by USgFNAC Kaneko et al., recently performed a decision and sensitivity analysis in patients with cancer of the oral cavity without clinical nodal metastases [13]. They calculated the probabilities of subclinical nodal metastases and 5-year survival using registry data. Parameters included complete nodal metastases resection rate and a utility rating that describes the health state induced by dissection compared with the situation in a careful observation group. Their results showed that elective neck dissection must guarantee a complete resection of subclinical nodal metastases with no disadvantage to heath state to be evaluated as equally satisfactory as careful observation. Since especially this last premise is unrealistic they concluded that observation of the neck is preferable in the light of strict pretreatment and follow-up examinations by USgFNAC.

Outcome of a wait-and-see policy using USgFNAC

We recently performed an analysis of clinical outcome of our policy in terms of neck failures and salvage rates after therapeutic neck treatment [14]. The study group

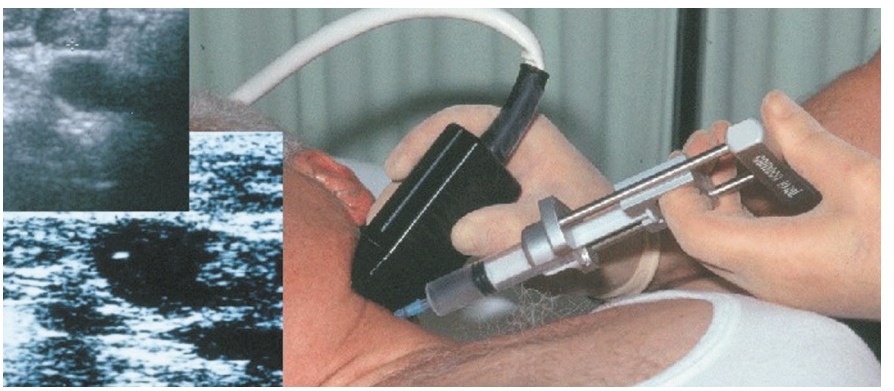

Figure 1. Ultrasound guided fine needle aspiration cytology of enlarged lymph nodes in the neck

consisted of 161 previously untreated patients (82 men, 79 women; mean age 62 years) with a T1-2N0 histologically proven SCC of the oral cavity or oropharynx from 1993-2000. All patients were treated with transoral excision of the primary tumour on the basis of negative USgFNAC findings at initial staging. USgFNAC of suspected lymph nodes was performed based on size criteria. Patients received strict follow-up of the neck, including USgFNAC every 3 months for the first 2 years. No patient in this series received postoperative radiotherapy on the basis of adverse findings in the primary tumour. Thirty-four patients (21%) developed a delayed neck metastases without local recurrence (33 ipsilateral, 1 contralateral). Thirty of these occurred in the first year following treatment and only 4 in de second year. All neck recurrences were treated by neck dissection and 31 also received postoperative radiation therapy. A total of 27 (79%) remained disease free and 7 died of their disease, including 4 regional recurrences in the treated neck (one also had distant metastasis), 2 contralateral recurrences in the non-dissected neck (one also had distant metastasis) and one patient with distant metastases.

This study shows that USgFNAC is both able to reduce the neck recurrence rate after observation from an estimated risk of 40% to 21% and to increase neck salvage rate from an average rate of 52% in the literature to 79% (Table I) [1-3, 10, 12, 14-16].

Table I. Outcome in patients with a clinically N0 neck in whom a wait-and-see policy was conducted

Author	No.	Neck Recurrences	Salvaged
Vandenbrouck et al. [1]	36	17 (47%)	14 (82%)
Cunningham et al.[15]	43	18 (42%)	9 (50%)
Fakih et al. [2]	40	23 (57%)	7 (30%)
Khafif et al. [16]	396	90-95 (24%)	53 (59%)
Ho et al. [10]	28	10 (36%)	3 (30%)
Kligerman et al. [5]	33	11 (33%)	3 (27%)
McGuirt et al. [12]	103	37 (36%)	22 (59%)
Total	679	213 (32%)	111 (52%)
Nieuwenhuis et al. [14]	161	34 (21%)	27 (79%)

Is it possible to improve the early detection rate of occult lymph node metastasis by USgFNAC even further? The possible causes of false-negative results are aspiration of the wrong node or aspiration at the wrong part of a node that contains only a small metastasis (sampling error), and false interpretation of the cytological slides. The selection of lymph nodes for aspiration is currently based on known patterns of lymphatic spread and particularly on size criteria. However, the number of nodes in the neck is large, and the patterns of spread are not always consistent. Sensitivity of USgFNAC might be improved by a more functional selection of the lymph node(s) at highest risk of harbouring occult metastases, i.e., most notably the sentinel node (SN).

Sentinel node concept

The SN concept is based on the orderly progression of tumour cells within the lymphatic system. Metastasis to lymph nodes is not a random event and can be determined by identifying the lymph flow from the tumour site to the first draining lymph node. In theory, the SN will thus be the first node to contain metastases and examination of this node should predict accurately regional lymph node status. In a pilot study we have evaluated the feasibility of the combined use of SN lymphoscintigraphy and USgFNAC [12]. Our initial experience in 12 patients showed that lymphoscintigraphic identification and subsequent aspiration of SNs was a feasible technique in patients with a squamous cell carcinoma of the oral cavity or oropharynx with a N0 neck. On the basis of these results, we decided to investigate whether the combined use of lymphoscintigraphy and SN-USgFNAC could decrease the false-negative rate in a larger group of patients compared with our former USgFNAC policy of enlarged lymph nodes only [14]. This group consisted 39 patients with a T1-2N0 oral/oropharyngeal SCC staged with additional SN aspiration (SN-USgFNAC) after USgFNAC was negative. Three to four submucosal peritumoural injections of 15-20 MBq ^{99m}Tc-labeled colloidal albumin suspended in 0.4 ml saline (Nanocoll) were administered. Within 2 minutes after injection, lateral dynamic lymphoscintigraphic images were obtained (20 × 60 sec acquisitions) with the patient in supine position under a gamma camera with a low-energy high-resolution parallel-hole collimator. Subsequently, static scintigraphy was performed during 120 sec in anterior projection to reduce superimposition caused by radioactive scatter originating from the injection site over the SNs. After visualization of the SN(s), the position was marked on the overlying skin with the use of a point-of-source ^{57}Co marker and confirmed with a 14-mm diameter handheld gamma probe. From nine patients additional static images were acquired 2 to 4 hours after injection. SNs were defined as all lymph nodes visible in 20-min dynamic scintigraphy or visualization by additional static images after 2 to 4 hours after injection. Subsequently, USgFNAC was performed of the visualized SNs and the enlarged lymph nodes. After preparation of the cytologic smears, the needle and syringe were washed in phosphate-buffered saline to obtain residues that were used for radioactivity counting in a gamma counter. In 35 of 39 (90%) patients, at least one SN was visualized by. One SN was visible in 20 patients, two SNs in 14 patients, and 1 patient showed three SNs after 20-min dynamic imaging. All SNs were located ipsilateral. In total, 51 SNs were identified scintigraphically, which were located in level I in 20 cases, in level II in 22 cases, in level III in 8 cases, and in level IV in 1 case. Confirmation of the SN position with the handheld gamma probe proved to be reliable if the SN was located in levels II through IV. In four patients with primary tumours in the anterior oral cavity, dynamic scintigraphy did not enable identification of a SN

independent of the injection site, probably because of radioactive scatter originating from the primary tumour. However, in three of these four patients, the SN could be identified afterward by measurement of radioactivity in at least one of the aspirated residues of enlarged lymph nodes. Hence, in only 1 of 39 patients we did not succeed in identifying a SN. In nine patients static images were acquired 2 to 4 hours after injection, which showed additional hot spots in four patients. In 10 of the 38 patients, 13 lymph nodes would not have been selected for aspiration on the basis of the size criteria. From this group, 11 lymph nodes of 9 patients were aspirated. The minimal diameters of these SNs varied from 1.6 mm to 3.8 mm. From 2 of these 11 SNs insufficient material was aspirated for a cytologic diagnosis, both with a minimal diameter of 1.6 mm. From the other 9 SNs with minimal diameters ranging from 1.9 mm to 3.8 mm, diagnostic smears were obtained; these were all tumour cell-negative at cytologic diagnosis.

During follow-up, 10 of these 39 patients (26%) developed a lymph node metastasis in the neck within 1.5 to 8 months after treatment of the primary tumour. All but two patients developed metastases in levels of the neck, which corresponded to those of the SNs identified at the initial staging. One of these two patients developed a lymph node metastasis on the contralateral side. These 10 patients all underwent therapeutic neck dissection, and 9 also received postoperative radiotherapy based on histopathologic findings. The sentinel node procedure is therefore not capable of improving the detection rate of occult nodal metastases by USgFNAC in head and neck cancer patients. Therefore we concluded the most likely cause of false-negative USgFNAC is aspiration of the wrong part of a node containing a very small metastasis

Micrometastasis

Conventional histopathology, serial sectioning, immunostaining and molecular analysis are increasingly sensitive in finding tumour cells (or tumour DNA) in lymph nodes. Van den Brekel et al. have used meticulous serial sectioning of 96 electively dissected neck specimen of 79 patients [18]. Nodes were sectioned every 3-4 mm and conventionally stained with Hematoxilin & Eosin. Tumour positive specimen containing only micro-metastases of 3 mm or less in dimension were found in 9 out of 36 cases (25%). This finding was later confirmed by immunohistochemistry-based techniques [19]. Current research focuses on using additional techniques, e.g., by using conjugates of monoclonal antibodies with radionuclides (particularly positron emitters).

Conclusions

USgFNAC at initial staging can reduce the risk of occult metastases for T1-T2 squamous cell carcinoma of the oral cavity or oropharynx considerably, which justifies local excision of the tumour and a wait-and-see policy for the neck. SN identification and aspiration did not decrease the false-negative rate, and we have therefore abandoned its use in this setting. Using USgFNAC for follow-up enables early detection of a significant percentage of neck failures and a high salvage rate with therapeutic neck dissection.

C. René Leemans MD
Department of Otolaryngology/Head and Neck Surgery
VU University Medical Center
P.O. Box 7057, 1007 MB Amsterdam
the Netherlands
e-mail chr.leemans@vumc.nl

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