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Mini Review

Assessment of the Neck in Head and Neck Skin Cancer

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Abstract

In this review summarizes the workup and management of the N0 neck in head and neck Merkel cell carcinomas, melanomas and aggressive squamous cell carcinomas (SCC) of the skin. Of all imaging modalities, ultrasound guided aspiration cytology (US-FNAC) has the highest accuracy. CT, MRI as well as PET-CT have a lower accuracy, mainly because of a lower specificity. The sensitivity of all modalities is in the range of 50-60%. Recently published literature suggests that in high-risk skin cancers either elective treatment or sentinel node procedures are the way to go. Sentinel node biopsies (SNB) can have a very high sensitivity, but only when performed by well trained surgeons and using modern guidance systems such as SPECT, intraoperative scintigraphy and fluorescence. The most logical routine approach in high-risk skin cancer is to select patients for SNB using US-FNAC.

INTRODUCTION

Risk and pattern of occult metastases

For all skin malignancies, lymph node metastases are a dismal prognostic feature [1]. The incidence of (occult) metastases varies enormously. Whereas basal cell carcinomas very rarely give rise to neck metastases, squamous cell carcinomas (SCC), especially when infiltrating deeply, do so in 2-20% of cases[2]. Risk factors for developing metastases in SCCs are: size > 2cm, invasion of 5 mm or more, perineural invasion, location in the pinna or near the parotid gland, poor differentiation, recurrence or tumour positive resection margins and immunosuppression[3-5].

In melanoma, the incidence of lymph node metastases in melanoma depends mainly on the depth of infiltration (Breslow) and for intermediate thickness melanoma is in the range of 15-20% [6,7]. For Merkel cell carcinoma this risk is reported to be between 16-50% [8]. In a recent study from our institute this incidence was 49%[9]. Although many studies could not find predictive characteristics for metastases, Stokes et al reported that in Merkel cell carcinoma's smaller than 1 cm the chance of regional disease is limited, whereas in the analysis of Mott et ala size over 5 mm, infiltration of the fat and an infiltrative growth pattern were predictors of regional spread [10,11].

Metastatic patterns from skin carcinomas and melanomas differ from mucosal carcinomas [12]. Metastases to superficial nodes, e.g. along the external jugular vein, in the parotids or nuchal area occur more frequently than in mucosal squamous cancers [13-15]. Furthermore, regional metastatic patterns from melanomas are more variable and less predictable than metastases from skin squamous carcinomas [16,17]. The parotid gland is a major nodal echelon for all skin tumours of the face and scalp anterior to a vertical plane through the ear. Tumours behind this line mainly spread to the posterior neck nodes, nuchal, retro-auricular and occipital nodes [15, 18]. This pattern of metastasis has important consequences for the extent of surgery and radiotherapy and explains the popularity of the sentinel node procedure in skin melanoma.

Imaging of the neck

The risk of occult metastases can be diminished by more accurate detection techniques.

In patients with high risk SCC, Merkel cell carcinoma and melanoma, the risk of occult lymph node metastases warrants preoperative assessment of the neck.

To assess the neck non-invasively, several authors and some systematic reviews have shown that ultrasound (US)and especially US guided fine needle aspiration cytology (US-FNAC) is the modality of choice, more reliable than palpation, MRI, CT or PET-CT [19-22]. Recent advances in MRI, such as diffusion weighted MRI are promising. However, so far these techniques cannot compete with US-FNAC [23]. In a recent systematic review, Sun et al did not find a difference between CT or MRI in accuracy [24]. In melanoma patients, we previously reported a sensitivity of 87% for CT, but these patients were not all clinically N0 [25].

PET–CT scanning is very promising as an imaging technique as it does not rely on morphological criteria for metastasis but rather on biologic markers, currently mainly glucose metabolism. FDG PET-CT is nowadays widely used in melanoma staging. Swetter et al found that PET is superior to CT in detecting both regional and distant metastases in melanoma patients [26]. However in this study very few regional metastases in the neck were studied. For the assessment of occult nodal metastases the sensitivity of PET-CT is in the range of 50-70%, comparable to CT or MRI and cannot compete with US-FNAC or sentinel biopsies [27-31]. Sohn et al recently showed that PET-CT is not better than CT or MRI in detecting occult metastases in the neck in mucosal SCC [32] and Ozer showed that the sensitivity in this group was only 57% [33].

In staging patients with known neck node metastases, and also in stage 3 melanoma patients (in conjunction with MRI of the brain and S100), it has been shown that PET-CT changes treatment in 37% of patients [34,35]. However, in patients with a positive SNB, PET-CT is not very useful in detecting distant metastases as in general these are too small at the time of the SNB [36].

Ultra sound and especially US-FNAC is currently the most reliable technique to stage the neck. In a recent meta-analysis from Ulrich et al, a sensitivity of US-FNAC in melanoma of 65% was reported [21].Blum et al reported that US was more reliable than palpation in a large series of melanoma patients undergoing US in the follow-up [37]. In their study of 235 patients, US had a sensitivity of 89%, and 29% of the detected metastases were not palpable. In other studies on US, Voit et al reported a sensitivity of 71%,Hocevaret al found a sensitivity of 21% and Rossi et al of 39% [38-40]. This wide range of sensitivities might reflect differences in rates of micrometastases (and the pathologic technique used to detect these micrometastases in the neck dissection specimens), but also the skill of the ultrasonographer plays an important role [41, 42]. The main advantage of adding FNAC to the US is that false positive cytology is very rare and thus the specificity is in general (almost) 100%. In general, cytology of metastatic SCC, Merkel cell carcinomas as well as melanomas is very reliable [40] as atypical cells can be distinguished from reactive lymphatic cells. However, in desmoplasic and spindle cell melanomas this is not always easy without additional staining techniques. Thus false negative US-FNAC is mainly caused by aspirating from the wrong lymph node or lymph nodes with very small metastases (sampling error) [43]. Unfortunately, no currently available imaging modality can reliably detect small tumour deposits in lymph nodes [44, 45].

Another application for US and US-FNAC might be selection of patients to undergo or not undergo SN procedure: only patients with negative US-FNAC are scheduled for SN procedure. This selection makes sense because US-FNAC is less invasive, less complex to perform and cheaper, but with a lower sensitivity as compared to SN procedure. In a study by van Rijk et al [46] from our institute in 107 patients, in 22 a suspicious node was detected at US. In 13 of these (59%) this proved to be a metastasis at SNB. However, only 2 of these were correctly diagnosed using US guided aspiration cytology. Of the 85 patients with no suspicious nodes at US, 25 (29%) were shown to have metastases. The main reason for the very low sensitivity of US-FNAC in this study was the high number of micrometastases. From this study, we concluded that US-FNAC is able to detect only a minority of clinically occult metastases and rarely obviates the need for SNB. However, several authors have shown much higher sensitivities of US-FNAC in melanoma patients. In the study of Testori on 88 patients undergoing SN procedures, it was shown that if US (without aspiration) is negative, the chance that the SN was positive was only 1% (one of 818 basins studied) but the false positive rate was high: f US was positive, the chance of a positive SN was only 64% [47]. The sensitivity of US alone was 94% with a specificity of 90%.

Apart from initial assessment, US-FNAC can be used during follow-up if the risk of regional recurrence is considered high or if SN biopsy is not employed. In the study of Voit et al, only 61 of the 242 regional recurrences in his series of 829 patients were detected by palpation, whereas 240 were detected using US. There were 48 false positive US results [48].

Sentinel node biopsies

Early metastases are too small to detect clinically or with imaging [45,49]. Because of that, and because many melanoma metastases are micrometastases, the SNB has gained widespread acceptance in melanoma [50]. There has been a continuing controversy in the prognostic significance of the SNB procedure. In 2004 Doubrovsky et al did not find a difference in prognosis between either a SNB or and elective node dissection, although more micrometastases were detected using the SNB [51]. It has been shown, that in case of a positive SNB, it is of prognostic value to detect these metastases in an early stage [52]. For the head and neck area, the accuracy of the sentinel node procedure is less than for other parts of the body. In a study from New York, a false negative rate of 30% was reported [53], and Teltzrow found a sensitivity of only 68% [54]. Also, there are uncertainties in the reliability of the procedure as some authors have reported discordant drainage patterns in repeated scintigraphy procedures [55]. So technically the SNB is difficult, and the technique is crucial to obtain reliable results. Recent improvement in detection techniques, using pre-operative anatomical mapping with integrated SPECT/CT, and intraoperative imaging with mobile scintigraphy cameras and fluorescence have greatly facilitated and improved lymph node detection, especially in difficult areas such as the parotid glands and in close proximity to the administered depots around the primary tumour [56,57].

In Merkel cell carcinoma's, the SNB procedure is reported to be of value and reliable in lesions over 1 cm, as in these tumours the neck assessment and management is a crucial factor [58-61]. Recently, Sadeghi as well as Tseng reported a prognostic benefit of SNB over a wait and see policy [61,62]. However a high false negative rate (12.9%) has been reported as well, clearly illustrating the technical challenge of this procedure [63]. Sentinel lymph node mapping to determine the extent of elective radiotherapy has recently been reported and is a promising new development [64].

In high risk SCC of the skin, SNB is rarely used as the risk of occult metastases is rarely over 15-20%. However, when a risk of 10% is accepted as an indication, it can be used to detect occult metastases reliably [65]. Reports are scarce though.

Elective treatment of the neck

Elective treatment of the neck and parotid has the advantage that occult metastases are treated in a very early stage, possibly improving prognosis. The disadvantage is that both surgery and radiotherapy have morbidity and many patients are treated unnecessary. Furthermore, because of the less predictable patterns of metastases, inadequate elective treatment might miss the involved lymph nodes. The cut-off for the risk of occult metastasis that warrants elective treatment is disputed in the literature. In a recent study on the value of elective neck treatment, Okura showed that using meticulous follow-up and adequate salvage, a risk of 44% of occult metastasis can be used as a cut-off in selecting oral cancer patients for either a wait and see policy or elective treatment [66]. In a recent study on the value of elective neck dissection in oral cancer from India, in which a risk of more than 40% was reported, indeed a prognostic benefit was reported of elective neck dissection[67]. However, this high percentage of occult metastases is rarely reached in skin cancers.

Some authors have advocated elective neck dissection in high-risk subgroups with SCC of the skin. However the definitions of high risk not well defined and in general a combination of multiple poor prognostic factors is used (periauricular, larger than 2 cm, deeply infiltrating, recurrences, perineural growth, immunosuppressed)[68,69]. There are no data on the prognostic benefit of elective neck treatment in these high-risk patients, and in general elective neck treatment is not advocated. When postoperative radiotherapy is anticipated, elective treatment of the first nodal basins is often performed when these are in proximity to the primary tumour.

With a higher incidence of occult metastases, especially in melanoma and Merkel cell carcinoma, elective neck treatment becomes more of an issue [70]. In melanomas, some centres advocate or have studied elective neck dissection [71] or irradiation [72]. Although older studies reported positive results of elective neck dissection in younger patients [73] , in most studies no prognostic benefit was found in elective neck treatment of melanoma [71,74, 75]. In fact, it is surprising that elective neck dissection in general is not found to be beneficial whereas it has been shown in a large trial by Morton the sentinel node procedure has a positive impact on prognosis in intermediate thickness melanoma [52].Although the final report of the MSLT-1 did not provide analysis per melanoma site, it seems that these data are without major restriction applicable to head and neck melanomas [76]. In patients with parotid metastases of melanoma, but also squamous cell carcinoma, elective neck dissection of at least levels II and III is common practice, whereas levels I, IV and V are at a much lower risk [77].

Several authors have reported a high incidence of occult metastases in Merkel cell carcinoma, which is a neuroendocrine tumour with high loco regional recurrence rates [8, 9]. To date the role of (neo)adjuvant chemotherapy has not been definitively determined [78], but postoperative radiotherapy, including elective neck irradiation has a positive impact on recurrence and survival [79]. Because of the high rate of regional metastases in but the very small ones, the neck should be addressed in these patients by either elective treatment (radiotherapy or surgery) or a sentinel node procedure [61, 80, 81].

CONCLUSIONS

In conclusion, the indication for assessing the neck in skin cancer is only present in deeply infiltrating or extensive SCC in the high risk areas of the face, all Merkel cell carcinomas and all melanomas infiltrating more than 1 mm. US-FNAC is the preferred techniques to use for these indications, but the sensitivity is dependent on the skill of the ultrasonographer.US-FNAC should be used in the first years during follow-up of patients with a high risk of occult metastases not treated electively. Ultrasound (with or without FNAC) can also be used to select for SN procedures in melanoma and Merkel cell carcinoma as a positive US-FNAC examination is already an argument to perform a neck dissection and refrain from a SNB. PET-CT, frequently already performed for screening on distant metastases, plays a major role in staging patients with clinically involved lymph node metastases, but cannot compete with US-FNAC or SNB in assessing the N0 neck. A SNB is the most accurate technique to stage the neck and is also prognostically advantageous in intermediate thickness melanoma. In Merkel cell carcinomas and possibly large SCC it can be employed as well. SNB is however technically demanding and dependent on the technical support and surgical techniques. Elective neck treatment by neck dissection or radiotherapy is a valid alternative in Merkel cell carcinoma, but is rarely indicated in any other skin malignancy.

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