

Letters to the Editor

Remarks on sentinel node biopsy in head and neck cancer

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Sir,

The status of the regional lymphatics is one of the most important prognostic parameters in patients with head and neck cancer, and the presence or absence, level, and size of metastatic neck disease are crucial for treatment and survival. Due to the limited sensitivity and specificity of the usual diagnostic tools like ultrasound, CT, MRI, and PET (Stuckensen *et al*, 2000), a pathohistological staging of the neck was generally adopted to remove and detect occult metastases, which could not be detected by these imaging techniques. A large number of elective neck dissections (ND) where the pathohistological examination of the surgical neck specimen did not reveal any positive nodes was accepted. This surgical procedure was associated with risks and morbidity of the patients concerned.

In the last years, beginning with a case report by Alex and Krag (1996), sentinel node biopsy (SNB) in head and neck cancer became a very interesting field of clinical investigation. Other investigators followed, and the recent article of Höft *et al* (2004) mentioned some of them. Because the method of SNB was interlaced with the N0 neck, that is, a neck without clinically detectable nodal metastasis, the procedure generally adopted by investigators like Höft *et al* (2004) was to carry out an elective ND parallelly to SNB. The pathohistological results were compared, with the sentinel nodes carrying metastasis being the false-negative results of the imaging techniques. Experience still is limited, follow-up too short. We felt, however, that Höft *et al* (2004) did not discuss some relevant topics in depth.

The first problem is the definition of the N0 neck, in other words the method of examination on which the clinical diagnosis was based. Höft *et al* (2004) based staging of the neck on ultrasound examination and had a rate of 24% positive sentinel nodes in 50 patients. Contributors to the first multicentre study on sentinel node biopsy in head and neck cancer (Ross *et al*, 2004) based their staging on either clinical palpation or radiological imaging techniques like CT and had an upstaging rate of 34% in 134

patients. Kovács *et al* (2001, 2004a, c) had an upstaging rate of 5–15% following neck staging based on PET in 15 and 38 patients. Thus, SNB reflected the accuracy of the clinical and radiological staging methods, and the ideal diagnostic prerequisite for SNB is not yet found.

The second problem is the dimension of the primary. Höft *et al* (2004) stated that 'if a complete peritumoral injection of the tracer is not possible, the patient is not eligible for the sentinel node method'. We agree that peritumoral accessibility is more important than T classification, but large T3 and T4 primaries pose problems due to destroyed lymphatic drainage. Local intra-arterial induction chemotherapy, however, did not seem to alter lymphatic drainage (Kovács *et al*, 2004b) and might be a modality of treatment that can be added prior to SNB reducing tumour size.

The third and main problem is the omission of an elective ND, which would potentially achieve a benefit for the patient concerning risk, morbidity, and life quality. This would depend on the reliability of SNB. In the study of Höft *et al* (2004), 'no patient with tumor-free sentinel nodes was found to have a metastasis in a nonsentinel lymph node'. False-negative results have been very rare in all previous studies, too. This would encourage the omission of elective ND in favour of SNB. However, Höft *et al* (2004) falsely stated that 'So far, only Ross *et al* (2002) have reported on a study of a true biopsy of the sentinel lymph node without elective neck dissection'. Kovács *et al* (2001) reported on true biopsy of the sentinel node without elective ND, and all consecutive patients have been treated that way (Kovács *et al*, 2001, 2004a–c). Diagnostics using PET in combination with SNB considerably reduced the number of elective ND, and the inconspicuous follow-up time of 80 patients to date surpassing a median of 2 years makes it not likely that this will be paired with hazard. Some contributors of the mentioned multicentre study also adopted this procedure, and there is hope that SNB without elective ND will be the staging procedure of the future in a large number of head and neck cancer patients.

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Reply: Remarks on sentinel node biopsy in head and neck cancer

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Sir,

Thank you for giving us the opportunity to respond to the commentary letter by Dr Kovacs.

In the third paragraph, Dr Kovacs is referring to staging methods. He compares four publications (Kovacs *et al*, 2001, 2004a, c; Ross *et al*, 2004) to our present publication in the *British Journal of Cancer* (Höft *et al*, 2004). One of the four studies was published after ours (Ross *et al*, 2004). Two are not published yet, but are in press (Kovacs *et al*, 2004a, c). Dr Kovacs' conclusion that 'sentinel lymph node biopsy reflected the accuracy of the clinical and radiological staging methods, and the ideal diagnostic prerequisite for SNB is not yet found' is quite similar to ours, namely the 'better the staging methods are in detecting small metastases the less occult metastases will be overlooked and the more valuable will be the impact of an additional sentinel lymph node procedure'. However, the rate of positive sentinel lymph nodes is not only influenced by the staging procedure but also by the pathohistologic work-up. The more the intensive sentinel lymph nodes are examined, the more the occult metastases will be detected, raising the percentage of patients with occult disease (Höft *et al*, 2002; Höft *et al*, 2004). In our study, we applied ultrasound examinations for staging of the neck as a radiological method and also performed fine-needle aspiration cytologies. The accuracy of US-guided aspiration cytology has been shown to be significantly better than that of CT or MRI (van den Brekel *et al*, 1991).

The fourth paragraph concerns the obstacle of performing a sentinel node biopsy on large tumours. In our group of patients, this is due to the fact that it was difficult to perform an endoscopic peritumoral injection on large tumours located in the pharynx and the larynx (Höft *et al*, 2004). Dr Kovacs adds that large tumours

pose problems due to destruction of the lymphatic drainage, but he fails to provide data or literature on which his opinion is based. As we did not perform histologic studies of the lymphatics, we cannot add new information whether large tumours are more aggressive in destroying lymphatic vessels on their rim than are small tumours. However, the technique of the peritumoral injection is to inject the tracer adjacent to, and not into, the tumour. Thus, it does not really matter if a tumour destroys lymphatic vessels within its borders, as there will be intact lymphatics surrounding the tumour to take up the tracer even in large carcinomas.

In his last sentence of the fourth paragraph, Dr Kovacs suggests that an intra-arterial induction chemotherapy might be a modality in reducing tumour size prior to sentinel node biopsy. It is an interesting suggestion we would have liked to discuss in our article. However, Dr Kovacs' results were still in press when his letter of comment was written. Thus, the information he refers to was not accessible to us. Yet, although Dr Kovacs states that intra-arterial chemotherapy did not seem to alter lymphatic drainage (Kovacs *et al*, 2004b), there is ample evidence that preoperative chemotherapy affects lymph nodes. Cohen *et al* (2000) describe lymph nodes showing areas of fibrosis, fat necrosis, histiocytic accumulation and granulation formation after neoadjuvant chemotherapy. Furthermore, metastatic foci can be completely obliterated by chemotherapy. Accordingly, Nason *et al* (2000) concluded in their study that preoperative chemotherapy is associated with an unacceptable high false negative rate for sentinel lymph node detection. If these changes are evident in chemotherapy, we would expect to find them in patients with intra-arterial chemotherapy, too. We are looking forward to the publication of Dr Kovacs' results and histologic findings of the lymphatics.

In the fifth paragraph, Dr Kovacs refers to the omission of an elective neck dissection potentially achieving a benefit for the

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patient in respect to risk, morbidity and quality of life. He complains that Ross *et al* (2002) were not the first to publish a true sentinel node biopsy, but Dr Kovacs himself (Kovacs *et al*, 2001). Furthermore, he is citing three articles by himself that have not been published yet (Kovacs *et al*, 2004a,b,c), mentioning 80 patients who underwent a sentinel node biopsy. At the point of time we wrote and published our article, only the first publication was available in the German literature (Kovacs *et al*, 2001). Dr Kovacs' method included a therapy of the primary tumour prior to sentinel node biopsy by performing an intra-arterial chemotherapy in 12 of 15 patients. In his article, the author did not discuss the problem of chemotherapy causing changes in the lymphatic drainage of the tumour. Yet, as discussed above, there was literature pointing out the disadvantages of prior chemotherapy. Therefore, we are of the opinion that unless proven otherwise, the methodical approach of treating the primary tumour prior to sentinel node biopsy bears the risk of false negative results.

If an elective therapy of the neck such as neck dissection or radiotherapy is omitted in favour of a true sentinel node biopsy, it is with the intent of causing less morbidity and achieving more quality of life for the patient. However, since a true biopsy of the

sentinel node is not yet established for head and neck cancer, we formulated as a prerequisite that patients with a mere biopsy of the sentinel nodes should have equal regional control rates as patients after elective therapy of the neck. This mandates that no additional elective therapy is performed before or after sentinel node biopsy. Otherwise the rate of recurrences after mere sentinel node biopsy does not only present the quality of staging by sentinel node biopsy but also the quality of elective therapy of the neck. In his group of patients, Dr Kovacs performed an elective radiochemotherapy of the neck after sentinel node biopsy applying 51.3 Gy and docetaxel (25 mg m^{-2} once a week) over a period of 5 weeks (Kovacs *et al*, 2001). It is our opinion that the method designed by Dr Kovacs will result in biased data. His method does not represent a true sentinel node biopsy and is likely to discredit the sentinel node concept. Therefore, we cited Ross *et al* (2002) as they indeed were the first to publish a study on a true sentinel node biopsy without prior therapy of the primary tumour and postoperative radiotherapy of the lymphatics in the international literature.

We are still cautious about a true sentinel node biopsy in head and neck cancer and are looking forward to long-term results in comparison to elective selective neck dissection.

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