How to analyze the diagnostic value of sentinel node biopsy in head and neck cancer

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In an attempt to more reliably select the lymph nodes that potentially contain metastases, the sentinel lymph node (SLN) concept has been introduced. This has been studied extensively in melanoma and breast cancer, but was recently introduced in the staging of oral squamous cell carcinoma (OSCC). The SLN is likely to be the first lymph node to harbour metastasis and can be used to provide information on the rest of the nodal basin. The SLN is usually identified by peritumoural injection of radioactive colloid and a blue dye. Preoperative lymphoscintigraphy, intraoperative visualization of blue coloration and intraoperative radionuclide detection using a gamma probe allow identification of the SLN. After surgical removal, this SLN is investigated by meticulous histopathological examination using stepped serial sectioning and immunohistochemistry. If the SLN contains metastatic tumour cells, treatment of the neck is recommended, usually in a second procedure [1]. The SLN procedure is considered to be more precise than imaging procedures and less invasive than elective neck dissection. Moreover, it is associated with significantly less postoperative morbidity and better shoulder function as compared with elective neck dissection [2]. Current best practice guidelines for the provision of SLN biopsy (SLNB) in early OSCC patients have been outlined, which provide a framework for the currently evolving recommendations for its use [3].

The sentinel node concept in OSCC has been validated in several studies in which in all patients after SLNB, a

neck dissection was performed. The histopathological examination of the neck dissection specimen was used as reference (gold) standard. Although several European studies had validated the sentinel node concept in OSCC, an American multicenter validation study was initiated in which routine histopathological examination of the neck dissection specimen was used as gold standard. This American College of Surgeons Oncology Group (ACOSOG) Z0360 validation study with 140 patients in 25 institutions showed a sensitivity of 90 % and a negative predictive value (NPV) of 96 % [4]. Because routine histopathological examination (and not step-serial sectioning and immunohistochemistry) of the neck dissection specimen was used as the gold standard occult micrometastases might have been missed [5], potentially contributing to higher figures for sensitivity and negative predicting value.

After initial studies to validate the SLN concept in early OSCC patients, several small prospective observational studies have been reported. In these studies, a neck dissection was performed only when the SLN contained a metastasis and a watchful waiting strategy was followed when the SLN was tumour-free. Two larger single centre studies found sensitivities and NPVs above 90 % [6, 7].

In an European multicenter study [8] of 134 cT1/2N0 OSCC patients 79 patients underwent SLNB as the sole staging tool, while 55 patients underwent SLNB followed by elective neck dissection (END). For the two groups together, using a reference standard of 5 years follow-up after SLNB staging, a sensitivity of 91 % and a NPV of 95 % were found. The better performance of the SLNB-assisted END group (sensitivity 96 %, NPV 97 %) compared to the SLNB-alone group (sensitivity 87 %, NPV 94 %) can be explained by the use of standard (routine) histopathological examination of the neck dissection specimen versus 5 years follow-up as a gold standard for metastasis [8].

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In 2005, Paleri et al. [9] reported on a meta-analysis of 19 pilot validation studies (histopathological examination of neck dissection specimen as gold standard) with a total of 347 oral and oropharyngeal cancer patients and found pooled sensitivity of 92.6 %. In this issue of the *European Archives of Otorhinolaryngology* ... et al. [10] reported a pooled sensitivity of 95 % and a NPV of 96 % in a meta-analysis of 25 validation studies (SLNB followed by concurrent neck dissection as gold standard) with totally 738 head and neck cancer patients. In their meta-analysis studies in which no concurrent END was performed after a negative SLNB were not included, but summarized in Table 3 [10]. The pooled sensitivity and NPV of these studies in which observation was the gold standard were 86 and 94 %, respectively, which is slightly lower than the studies using histological examination of the neck dissection specimen as gold standard. This suggests that observation is probably a better gold standard, because micrometastasis and single tumour cells which may be missed during (routine) histopathological examination of the neck dissection specimen and would, if left untreated, proliferate gradually and be detected sooner or later as overt metastases [5].

In both meta-analyses and the ACOSOG Z0360 study, the number of patients per center is below 30. Civantos et al. [4] reported better results of experienced surgeons in the ACOSOG Z0360 study. Ross et al. [11] reported on the first international conference on SLNB in head and neck cancer that centers who had performed 10 or less cases had a lower sensitivity (57 %) in comparison with centres that had performed more than 10 cases (sensitivity 94 %). In small series the contribution of the first 10 patients on the results may be substantial. If only larger studies would have been included in the meta-analyses the pooled sensitivity and NPV may have even been higher.

Three large multicenter prospective studies with the SLN procedure as staging technique of the neck in early oral cancer [Sentinel Node European Trial (SENT), the Danish national group trial (DAHANCA 22) and the Brazilian head and neck group] have been started. The observational multicenter SENT study with more than 300 patients, has completed accrual and is waiting for long-term follow-up [12]. In this study, centres were only allowed to include patients after a learning curve of ten sentinel node procedures with concurrent neck dissection.

Histopathological examination is often considered to be the best gold standard. However, histopathological examination may miss minimal disease especially if routine techniques and not step-serial sectioning and immunohistochemistry are used [5]. Therefore, long-term observation of the untreated neck (no neck dissection or radiotherapy) is the best gold standard for determining the value of diagnostic techniques (e.g. the SLN procedure) for detection of occult lymph node metastases.

Another factor influencing the accuracy of a diagnostic technique is the incidence of the disease. In the detection of occult lymph node metastases, if the incidence of metastasis is low the NPV will be high almost regardless of the performance of the diagnostic technique. An upstage by a positive SLN of 30 % as reported in [10] shows that the studied patient population reflects the daily clinical practice and the results of the study can be implemented in routine clinical practice.

Many factors may influence the report of the SLN procedure. Step-serial sectioning and immunohistochemistry of the SLN can significantly improve the sensitivity and NPV. Histopathological examination of the surgical specimen (especially if no step-serial sectioning and immunohistochemistry are used) in stead of long-term observation without treatment of the neck (if SLN is tumor-free) may results in (unreal) higher sensitivity and NPV. Also a low incidence of occult lymph node metastases is easily accompanied by a higher NPV. Surgeons more experienced in SLNB produce probably better accuracy data. The best study design to analyze the real diagnostic value of SLNB in head and neck cancer includes a large number of patients who underwent SLNB by experienced surgeons in multiple centers, with step-serial sectioning and immunohistochemistry and long-term observation without treatment of the neck if the SLN is negative. Since, the results of this kind of studies are not available yet, meta-analyses as published in this issue of the *European Archives of Otorhinolaryngology* provides valuable information on the potential diagnostic value of SLNB in patients with early oral carcinoma.

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