Editorial

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What is the impact of sentinel node biopsy in the management of cancer?

Sentinel node biopsy (SNB) is a surgical/histopathological diagnostic tool that is increasingly used but still being evaluated in surgical oncology.

The concept of sentinel node biopsy (SNB) was first established in melanoma of the skin [1]. It is based on the observation that from a given area of the skin, lymphatic spreading of melanoma cells proceeds following sequential steps, in an orderly fashion. The first lymph node encountered by floating melanoma cells is called the sentinel node (SN) and SN is specifically (95%) the site of micrometastases if they exist. In case of unpalpable regional lymph node (N0), the histological status of the sentinel node is a prognostic criterion superior—in multivariate analysis—to Breslow's thickness [2].

Survival correlates with the size of lymph node metastasis. Roughly, one single palpable lymph node (N2) results in 5-year survival of 50%, one sentinel node (N1) histologically invaded, 5-year survival of 60%, and one sentinel node (N0) not histologically invaded but PCR positive, 5-year survival of 70%. There is still a debate on the therapeutic value of SNB in melanoma. Indeed, the better survival of patients with early diagnosis of lymph node metastasis followed by selective lymph node dissection (SLND) can be interpreted as the result of better tumour eradication compared with a watch-and-wait policy that consists of doing a radical lymph node dissection when lymph node metastases appear clinically. However, randomized trials in high risk primary melanoma comparing immediate elective lymph node dissection (ELND) to deffered complete lymph node dissection (CLND) -that is when palpable metastatic node appeared- failed to show any difference in overall survival. However, SN is not the exclusive site of micrometastases. If one considers the first metastatic events occurring within 5 years of adequate removal of high risk—>1.5 mm thickness—primary melanoma, only 20–30% will appear in regional lymph nodes, 8–10% as in transit and 20–40% as distant metastases. This means that the status of SN is a window on the metastatic potential of the melanoma that is also correlated with metastases at other sites, in case of positivity. The Sydney Melanoma Unit reviewed 836 SNB-negative melanoma patients. With a median of 42.1 months, melanoma specific survival at 5 years was 90%, compared with 56% for SN-positive patients ($P<0.001$). Eighty-three patients with negative SNB (9.9%) had a recurrence. Twenty-seven patients developed recurrence in the regional node field, and in 22 of these, it was the first recurrence site. Six developed local recurrence, 17 an in-transit metastasis, and 58 distant disease. The false-negative rate was then 13.2%. A very recent third interim analysis of a worldwide randomized trial, the Mslt-1 trial, on SNB shows that melanoma patients who had wide excision followed by SLND ($n=1204$) had a survival similar to patients where a watch-and-wait policy had been followed ($n=797$), with CLND in case of pathological lymph node development [3]. In this study, the disease free survival was superior after SNB [4].

A recent study on 146 high risk primary melanoma cases demonstrated that the metastatic deposits in the SN were subcapsular in 26.0% of patients. None of these patients had any sentinel nodes involved on CLND. In the patients whose sentinel node metastases had a different microanatomic location, the rate of no sentinel node involvement was 22.2% overall. The authors concluded that in patients with only subcapsular deposits in the SN, it is possible that CLND could safely be avoided [5].

Therefore, we can consider SNB as a diagnostic tool with an acceptable false negative rate that detects early lymph node metatases, a clinical condition that appears optimal for adjuvant immunotherapy protocols [6, 7].

Historically, the second indication was breast cancer where SNB appeared useful for the selection of patients to adjuvant treatment with a method that avoids the sequellae of axillary dissection such as oedema [8, 9]. In the management of breast cancer, systemic treatment has a proven impact on survival, in contrast to melanoma. In case of positive SNB, the consensual attitude is currently to submit the patient to partial lymph node dissection. This does not avoid significant side effects. It seems that it is possible to spare some patients from lymph node dissection by detecting those who have a very low risk to harbour metastases in non-SNs. A recent study on 814 patients with breast cancer less than 3 cm diameter [10] revealed 35.1% positive SNs. Subsequent axillary dissections revealed tumours in non-SNs in 188 (65.7%) of these patients. Tumour exhibiting high nuclear grading, ER-, PR-, Erb-2/neu overexpression, lymphovascular invasion, increasing tumour size, multiple positive SNs, and macrometastatic size in SNs (>2 mm) were all significantly correlated with non-SN metastases. Multivariate analysis showed that tumour size, the number of positive SNs, and the metastatic size in SNs were independent factors predicting the presence of positive non-SNs. As for melanoma, it seems that it will be possible to restrict lymph node dissection in selected patient population.

Other indications were investigated: colon cancer, vulva and penis carcinoma, thyroid cancer, lung cancer, gastric carcinoma, pancreas carcinoma, and cervix cancer.

In this issue of *Annals of Oncology*, Barranger et al. [11] explored SNB in 23 patients with various stages of cervical cancer who were first submitted to SNB and thereafter to lymphadenectomy associated to appropriate surgery. No false

negative SNB was found in the patients with early cervix carcinoma—stageIA, IB1—whilst nearly 43% of locally advanced cervix carcinoma had false negative SN.

These results underline the fact that the concept of SNB holds true in primary high risk cancers but not in locally advanced cancers where alterations in the lymph flow and lymph node biology are expected.

Taken together, the results of the extensive studies in melanoma and breast cancer indicate that SNB is a valuable tool for early diagnosis of micrometastases, with a clear prognostic value. However, up to now, there is no evidence that SNB improves the overall survival. It is hoped that SNB patients will be found to benefit the most from adjuvant treatment because of the small burden of putative systemic micrometastases. It remains to be studied whether this can be applied to other cancers such as cervix carcinoma where HPV virus immunisation seems to be a potential treatment.

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