The role of sentinel node biopsy in breast cancer management: an overview

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Abstracts

Regional lymph nodes surgical management is an integral part of breast cancer therapy. One of the most important therapeutic problems is the risk of surgical treatment which is too wide or inadequate due to the lack of correct presurgical information on the conditions of regional lymph nodes. For melanoma the problem was solved combining surgical accuracy with the slightest surgical resection, using sentinel node biopsy.

In breast cancer the removal of axillary nodes proved to be unnecessary in more than 50% of cases. The first international studies on the use of sentinel node biopsy in breast carcinoma for the identification of patients who do not need axillary clearance suggest the high accuracy of the technique. Some practical problems still exist, however, and the optimisation of the method is not yet complete.

The use of sentinel node biopsy in breast cancer treatment might be able to provide distinctive clinical information, which can improve our knowledge about the disease's biological behaviour and about its treatment.

Key words: breast, axillary nodes, sentinel node, dye, lymphoscintigraphy, γ-probe

The first surgical attempts to achieve control over breast cancer were just a tumour resection: it was soon obvious that this treatment was not sufficient. To avoid local recurrences with their severe relative complications total mastectomy also needed to be completed, including removal of the thoracic wall muscles. The need to remove the axillary nodes at the same time was suggested by clinical and pathological considerations. Radical mastectomy, applied in the last years of the nineteenth century by Halsted (1), achieved two goals: it reduced the number of local recurrences and improved patients' chances of survival. As most of the patients treated at that time had advanced cancer, the removal of metastatic axillary nodes was of the utmost importance.

Moreover, it soon become evident that axillary dissection was useful in forecasting disease prognosis and in achieving local control of the axilla.

Then there were some attempts to improve the results by widening the surgical boundaries to include supraclavicular and internal mammary nodes en bloc with part of the thoracic wall (2, 3). Nevertheless, these superradical procedures were not able to achieve any therapeutic improvement compared to Halsted's classic mastectomy (4). On the contrary, it was weighed up if or how much it was possible to reduce surgical resection without worsening long term results of therapy. Surgeons started to perform a modified radical mastectomy that allowed the preservation of the pectoralis major, sacrificing just the pectoralis minor to make easier lymphoadenectomy, which had much better cosmetic and functional results than radical mastectomy (5). Then Auchincloss — after proving that a two level axillary lymph node resection was as effective as a three level one — suggested a radical mastectomy with preservation of both pectoralis major and minor and resection of just the first two lymph nodal levels in the axilla (6).

By the Seventies modified mastectomies had nearly replaced radical mastectomy according to Halsted.

In the following decade all studies were aiming towards discovering if a surgical treatment that allowed the patient with a small carcinoma to preserve her breast could be able to control the disease as well as — if not better than — a wider resection. This smaller resection (just the quadrant that contains the cancer with first and second level axillary lymph nodes) should be followed by radiotherapy on the remaining breast tissue (7, 8).

In the last few years the greater awareness of people, a better diffusion of screening programmes and the improvement of diagnostic procedures have led to a progressive and rapid reduction of breast cancer mean size at the diagnosis. In the period 1989–95

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this value reached about 1.5 cm: by extrapolation, we can foresee that within ten years the mean size of diagnosed breast cancer will be about 1 cm (9). Therefore in most cases the so-called QUART — which is performed by removing the lesion with a 2 to 3 cm margin of healthy tissue with the respective skin, the underlying muscles fascia and axillary lymph nodes of all levels and completed with radiotherapy of residual breast tissue — is an adequate therapy and is used, with minimal variations, all over the world. The current trend is to get a further reduction of the breast tissue that has to be resected to reach a simple lumpectomy, completing the procedure with further chemo- or radio therapy. The results for this kind of procedure are conflicting and depend on the number of data to be considered: the most important of these factors seems to be the presence of cancer cells in the resection margins. This occurrence, however, seems to affect just local recurrence rate, not survival or distant metastasis (10, 11, 12, 13, 14).

Anyhow, this search for procedures is oriented to improve the quality of patient life by taking into consideration the cost-effectiveness of these techniques, steering clinical choices to a better use of disposable resources while maintaining the same therapeutic effectiveness, and is supported by clinical observation that often the nodes resected with primary tumour are healthy.

But, even in the early Seventies, it was doubtful if axillary lymph nodes resection was so effective for survival. A study of the National Surgical Adjuvant Breast Project published in 1985 (15) compared ten years survival of randomised groups of breast cancer patients with clinically negative axillary nodes treated respectively with: radical mastectomy, total mastectomy with axillary dissection just at lymph nodes metastasis appearance and total mastectomy with regional nodes irradiation. Significant statistical differences were not found in any group survival in spite of the fact that about 40% of patients who underwent lymphoadenectomy had axillary metastasis and, presumably, in patients of both the other groups the rate of lymph nodes metastasis was the same. So for the first time Halsted's principle of surgical radicality, which had influenced breast cancer treatment for almost a century, was placed in doubt.

These new changes in breast cancer treatment were important because they demonstrated it was not necessary to use maiming operations, with dramatic effects on both patient body and mind. They showed breast cancer as systemic and not an organ disease from the beginning, with axillary metastasis in the role of the first sign of a special biological behaviour of that certain tumour.

We are arriving now at modern surgical oncology, which does not regard widening the extent of surgical resection as the main way to achieve a better prognosis, but recognises as its main aim the maintenance of the highest quality of life jointly with the greatest therapeutic efficacy by means of a rational modulation of the operation.

There exists a well known linear relationship between primary tumour size and axillary nodes metastasis rates. This rises from a 0% rate for Tis tumours, to a 3% rate in T1a, to 7% in T1b, to 32% in T1c, and as high as 44% and 60% for T2 and T3 (16). Altogether, for tumours smaller than 2 cm, axillary metastasis rate is about 28% with a trend, over time, to diminish in accordance with median size reduction of diagnosed cancers (17).

At present, when performing an axillary lymph nodes resection on two or three levels, in two thirds of cases the surgeon removes healthy nodes doing an unnecessary operation and exposing the patient to risk of secondary complications. These complications are often mild and temporary but sometimes go on for a long time and worsen patient quality of life even though they do not put their survival at risk. Among these complications the most frequent and persistent is lymphedema, which shows severely in 2–8% of patients who underwent level III axillary clearance (18), in a soft but perceptible way in 15–20% of patients who underwent level II axillary dissection and just as a different arm size in 40% of cases (18, 20, 21).

Some other complications which can follow axillary lymph nodes dissection are: seroma formation in post-operatory course, restriction of shoulder movements, numbness and pain that appear respectively in 9% and 78% of cases. Altogether in 15% of patients symptoms attributable to axillary surgery are severe enough to interfere with their daily lives (21).

Considering all these data, it could seem correct to perform full axillary lymph node clearance just in case of axillary metastasis. Local axillary recurrence, if not treated, leads to unfavourable prognosis, is often difficult to treat surgically and has disappointing developments (22). In all other patients it was stated that axillary clearance of healthy nodes does not improve long term survival.

Nevertheless axillary nodal status is one of the most important prognostic factors, together with primary tumour size, and cannot be substituted by other factors even if considered all together. Unfortunately, the only clinical examination has false negative results in about 35% of cases (23) and more complex instrumental examinations are also not able to determine undoubtedly that a certain node, especially if very small, is the site of metastasis. The only technique able to identify lymph nodes metastasis at present is Positron Emission Tomography (PET), with a sensitivity that ranges from 90 to 100%, but just for lymph nodes 2 cm or more in size (24).

Axillary clearance remains currently the most accurate predictor of overall axillary node status and was recommended by the Consensus Conference of the National Institute of Health at Bethesda in 1992 to stage the disease and control regional diffusion of cancer.

Nevertheless, the attempts to find a less aggressive alternative to full axillary clearance are progressing. From Veronesi et al., it results that cancer cells follow a well known way in the progression through the nodes and they seldom deflect from their route, going on tidily from I° to III° level. The so-called „skip metastases" occur in less than 2% of cases (17). So, if it was possible to know beforehand that there were no nodal metastases at level I°, it might be reasonably safe to avoid II° and III° level removal. On the other hand, when level I° has metastases, the other levels are involved in 41% of cases. Moreover, about 10% of patients with one I° level involved node and about ñ of patients with two I° level nodes involved have metastases in other levels. Altogether, about 16% of breast cancer patients have metastases in all three axillary levels, whereas II° and III° level metastases are present in about 40% of patients with one axillary involvement and in 28% of patients with breast cancer 2 cm or smaller in size.

From these data it is clear that resection of just I° level nodes could be inadequate in a great number of patients with I° level involvement and that, in the same patients, it could shorten the disease-free interval and overall survival too because it was dem-

onstrated that survival is directly related to the number of removed axillary nodes.

Since nodal metastases are rare in cancers smaller than 2 cm (10–13%), it was proposed that in these cases the resection could be limited just to level I° nodes (23). This way of acting is in conflict with Mustafa et al. (25) whose data showed — in a large series — the reduced prognostic value of tumour size. The paper demonstrated an increase in importance of other two factors: patient age and histological grading of cancer. Among young women, nodal metastases occurrence can be greater than expected in very small cancers and lead to underestimating the extent of disease.

Partial or „sampling" lymphoadenectomy has a high likelihood of false negative results that reach even 40%; facing this fact the smaller incidence of surgical complications loses any importance (26).

Although total axillary clearance with a complete histological examination is the golden standard to which all other procedures are compared, an alternative to take into consideration is sentinel node biopsy, first applied by Morton in melanoma.

Sentinel node is the first node where lymphatic flow coming from the neoplastic region arrives. It is identified trough intradermic administration of vital dye: this rapidly enters the lymphatics and leads to a blue-staining of the nearest node that is assumed to be most likely to harbour metastases, because it is the node which first drains the region in which the tumour exists. Using this technique, Morton et al. (26) were able to identify in melanoma a sentinel node in 80% of cases. Later this rate grew to 85% by some other AA (27).

Of course, the procedure's major issue was if sentinel node was able to predict lymph node status of all the draining region. In Morton's original series, histological examination, performed on surgical resected nodes, demonstrated a direct relation between sentinel node and whole regional lymphatic basin status in 98% of cases. The false negative rate was reduced to only 1%.

With such encouraging results, all efforts were made to improve the technique using Tc-labelled sulphur colloid injected in the region which contains the tumour and a γ-camera (lymphoscintigraphy) or a manual probe used during surgical operation to map regional lymph nodes. Using both blue dye and lymphoscintigraphic methods, sentinel node identification was possible in 97% of cases (28).

Scintigraphic method is simpler than the blue dye one because this could be difficult to follow, especially when lymphatic drainage is deep and to apply it correctly the physician has to be very familiar with it. At present, sentinel node scintigraphic identification is commonly employed in melanoma with practically no errors (30, 31).

In breast cancer too both sentinel node detection techniques are employed. An intra or subdermal injection of blue dye is performed in the tumour or tumour surrounding area. The dye rapidly enters the lymphatics and 5–10 min later some blue stained lymphatic vessels that lead to a node coloured in blue — sentinel node — can be visible. This technique is not entirely simple because of the propensity of the dye to pass through lymphatic vessels walls and spread all over, making it hard for the surgeon sentinel node identification (26, 29). Nevertheless, identification rates improve rapidly after a short period of operator's experience: familiarity with this technique raises identification rates from 65% to 94% for an experienced surgeon (32).

The second technique employs Tc-labelled colloids whose particles are small enough to rapidly enter lymphatic vessels and large enough to be phagocytosed in the first node entered. From experimental studies, the best size for the particles seems to be about 80 nm. (33). Thus the particles are not able to enter the bloodstream and assure a high node-to-background uptake ratio. As the sentinel node is identified, with images acquired firstly at 10 min and later every 15 min until visualisation, the overlying skin is marked.

During the surgical operation, performed some hours later, the radiotracer still in the node is revealed by a hand held detector (γ-probe) that guides the surgeon onto the sentinel node and confirms the uptake.

In a recent trial by Veronesi et al. this technique allowed for the correct diagnosis of axillary lymph nodes status in 97.5% of patients while an American multicentric trial performed in more than 400 patients refers a 97% diagnostic accuracy (34).

If we compare both methods, it appears evident that the lymphoscintigraphic technique gives higher sensitivity and more diagnostic accuracy than the blue dye one in melanoma (35) and in breast cancer (36).

Using sentinel node technique in breast cancer allows the surgeon to apply less invasive surgical management with a better cost-benefit ratio both for the patient and for the community. The pathologist too can get a more accurate study on the resected node. It would be impracticable to subject all nodes from a total axillary clearance (certainly more than 10, if the clearance is accurate) to serial sections (3 to 5 each node), immunohistochemical examinations and molecular analysis, but the same techniques can be easily applied on just one node. Some recent papers highlight the value of evaluations performed employing monoclonal antibodies against epithelial antigens on serial node sections as well as standard hematoxylin-eosin staining: with these more sensitive analyses the rate of diagnosed node metastasis rises from 8 to 41% (38, 39).

These micrometastases, diagnosed with more refined techniques, seem to have some clinical implications: retrospective studies show that those patients who have axillary micrometastases will have a worse prognosis than those who have no axillary metastases at all (37, 38).

On the basis of these considerations, we can easily understand that sentinel node immunohistochemical analysis could not be carried out on frozen sections during surgery but must be performed after definitive surgery, putting off full axillary clearance if sentinel node biopsy is positive. Immediate examination by frozen section, actually, has a sensitivity of 80–85% even though with a specificity of 100%. The absence of false-positive cases allows the surgeon to perform an immediate complete axillary clearance in those patients whose nodes are positive at a first standard examination on frozen sections and to put off till a second operation those patients whose nodes will result positive just at a post-operative examination (about 10%). Recently, Veronesi et. al. described a quick immunohistochemical method performed on frozen sections able to be employed for intraoperatory diagnosis on sentinel node biopsy (40). This technique — still to be evaluated — seems to require just one hour but it is complex, it needs 2 or 3 pathologists at work at the same time and it makes the operation longer (41). Apposition methods with cytological studies are simple and quick but have a low sensitivity (60–65%) and do not add anything to the accuracy of frozen sections (42).

In conclusion, early experiences on sentinel node technique use in breast cancer therapy seem promising: the first data col-

lected confirm that it can be employed in early breast cancer to identify those patients who, free of axillary nodes metastases, could get from axillary clearance just complications and discomfort without any therapeutic advantage.

At the same time sentinel node biopsy seems to be able to properly predict axillary node status and can provide the same prognostic and therapeutic indications as the total axillary clearance. Surprisingly this method, which consists in resecting just one node, seems to be able, because this only node is accurately examined, to diagnose otherwise occult micrometastases. The prognostic and therapeutic value to be attributed to these data is still to be assessed but there is no doubt that somehow they will lead to a deeper knowledge of the biological behaviour of this cancer.

The problem remains still unresolved of patients (luckily rare) whose lymphatic vessels drain into the internal mammary chain or into supraclavicular nodes: in this case axillary clearance would be useless and should be replaced by different surgical procedures.

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