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Sentinel node biopsy for breast cancer: yes, less surgery is better surgery

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Summary

Breast surgery evolves towards always more precise, but less invasive techniques. The *halstedian* concept of radical surgery has been abandoned and the majority of patients are now allowed to preserve their breasts provided they receive radiation therapy after surgery. In many institutions standard axillary lymph-node dissection is being replaced by the less invasive and probably also more accurate staging technique known as sentinel-node dissection. Nevertheless, the procedure requires interdisciplinary collaboration and rigorous quality control monitoring to provide optimal results. Many issues, some of which will be discussed in the light of our personal experience, still need to be tested in clinical controlled trials.

Key words: Breast cancer; Sentinel node dissection; Axillary node dissection.

Introduction

Several theories regarding the dissemination of breast cancer through the lymphatics have been derived from experimental and clinical observations. More than a century ago, the understanding of the biology of the disease focused the medical community on the usefulness of complete regional lymph-node dissection for all invasive breast cancers. Nevertheless, with the recognition that breast cancer is frequently systemic from the beginning, elective lymph-node dissections became controversial. In the meantime, more breast awareness and the diffusion of mammography contributed to increase the quote of node-negative patients suffering from the associated morbidity of axillary dissection without gaining any survival benefit.

It has been the development of sentinel lymph node dissection (SLND) and its demonstrated accuracy of detection of metastatic nodal disease to set new fuel to the debate. After a few years from its introduction, it is now common sense that complete axillary dissection for staging purposes is no longer necessary. In this paper, after a brief review of the current understanding of the metastatic process through the lymphatic system, we will discuss some of the emerging data in light of our personal experience on the performance of SLND.

The role of lymphatics in the metastatic process

The lymphatics as a distinct anatomic entity were first described in the mid of the 17th century, but it was only 200 years later that *Virchow* formulated the theory according to which lymph nodes filter particulate matter from the lymph and function as a barrier to tumour spread [1]. This assumption formed the basis of the idea that "en bloc" excision of the tumour with its efferent lymphatics could lead to definitive cure of breast cancer patients (*dissemination theory*).

In 1894, *Halsted* [2] described radical mastectomy, reporting improved local-regional control and survival rates. Nevertheless, it was the author himself who was the first to recognise that the removal of the axillary lymph nodes, if involved, did not affect survival. Furthermore, even more extended lymph-node dissections (*i.e.* supraclavicular, internal mammary, and mediastinal) did not produce any positive effect on

prognosis; on the other hand, modifications of the procedure by Patey and Madden, although diminishing the number of lymph nodes, were shown to be associated with the same survival rates as compared with the standard radical mastectomy.

These observations suggested that less aggressive surgery was indeed able to confer a similar survival benefit as compared to the more radical approaches, but it was only in the 1960's that this clinical observation received a plausible biologic explanation. It was *Fisher* who suggested that nodal involvement was not due to an orderly contiguous extension, but was rather a marker of distant disease [3]. He produced experimental data supporting the view that the outcome of the disease was pre-determined by the extent of micrometastases disseminated via the microvasculature of the tumour very early on in its natural history (*systemic theory*) [4]. This theory shifted the attention from the chronology ("early" versus "late") to the biology ("good" versus "bad") of the disease. The important therapeutic consequence was the development of adjuvant systemic therapies using cytotoxic drugs or endocrine agents; one example of the major impact of this strategy is proven by a relative reduction of recurrence rates approaching 50% in breast cancer patients with estrogen-receptor positive disease [5]. Nevertheless, it cannot be overlooked that in absolute terms the benefits in disease free and overall survival are considerably lower and that no real major progress has been made over the last 20 years.

This disappointing finding and other inconsistencies of the "systemic theory" prompted *Baum* to reconsider the whole matter and to describe one alternative biological model. He regards metastases as complex organisms existing in a state of dynamic equilibrium close to a chaotic boundary, whose future is determined by the balance of angiogenesis, epithelial proliferation and apoptosis (*chaos theory*) [6]. In his view, distant metastatic sites can live indefinitely if their steady state is not perturbed by stimulating events (surgery, traumas, infections, etc.). Thus, the state of "activation" of the tumour's microenvironment (*i.e.* during the follicular versus luteal phase of the menstrual cycle) or anti-angiogenetic therapies administered before the operation, could be paradoxically more important than current surgical or cytotoxic interventions, since they could limit the possibility that occult micro-metastases are awaked from their "dormant" condition.

A more pragmatic approach stems from the clinical observation that many patients are actually cured after adequate loco-regional treatment, although others are not. Therefore, breast cancer may be considered a spectrum of diseases with increasing inclination towards metastasising as a function of tumour growth and progression (*spectrum theory*) and a nodal metastasis may either be the only site of dissemination or a marker of distant disease [7].

The development of the sentinel node hypothesis

Thirty years ago Cabañas was the first to observe the existence of a sentinel node (SLN) in the lymphatic drainage of the penis [8], but the concept of lymphatic mapping was not introduced until the end of the 20th century for staging patients with melanoma [9]. The concept was based on two basic principles: the existence of an orderly and predictable pattern of lymphatic drainage to a regional lymph-node basin, and the functioning of a first lymph node as an effective filter for tumour cells. These principles are based on the *halstedian* vision of ordinate tumour spread, but are not in contrast with the other theories depicted above, which consider lymph-node involvement to be an indicator of distant disease.

The first article of blue dye mapping in breast cancer was published by Giuliano et al in 1994 [10], whereas the injection of radiolabelled colloids with intraoperative detection of the SLN using a gamma-ray detection probe was introduced later [11]. These two lymphatic mapping strategies are now applied all over the world, with SLN detection rates approaching 100%, and have received extensive scientific validation from clinical controlled trials.

A crucial parameter is how much the absence of tumour cells in the SLN is indicative of the absence of tumour cells in the other lymph nodes of the regional basin, usually expressed by the false negative rate. It has been calculated that, if the SLN is tumour free, the probability of involvement of a non-SLN is one in 1,087 [12] and available data on SLND in breast cancer suggest a diagnostic accuracy of more than 95% [13].

Standard of care and research areas in SLND

A consensus conference was held in Philadelphia in the spring of 2001, where scientific evidence and opinions of major experts in the field of SLND from all over the world were discussed and summarised [14].

The conclusions of that conference are generally considered as the current standard of care and it is not within the aim of this paper to review them in detail. Nevertheless, new data are emerging at rapid pace, some of which will be discussed in light of our personal experience with the procedure.

Tumour diameter

SLND has been attempted for tumour sizes ranging from T1 to T3, but most of the data pertains to lesions measuring up to 3 cm. Two recent studies have specifically looked at larger tumours, and these showed no difference in either the identification or the false-negative rate in a group of patients undergoing complete lymph node dissection [15, 16]. We believe that the major drawback of performing SLND in patients with large lesions is that in the end they will need complete axillary lymph-node dissection (ALND) in the majority of the cases. If intraoperative evaluation is not performed or if it gives false negative results, having to wait for histology on permanent sections and rescheduling for surgery will delay the administration of adjuvant therapies. This could have adverse consequences on patient prognosis and does certainly increase the economic costs for the community.

Patient age

One exception to the general attitude of reserving SLND to patients with tumours measuring ≤ 3 cm could be represented by older patients who generally have slow growing, endocrine-sensitive tumours. Their likelihood of harbouring nodal metastases for a lesion of a certain diameter is in fact lower as compared to younger patients and, indeed, the opportunity of performing ALND is questionable in view of the higher morbidity, limited range of adjuvant treatment, and shorter life expectancy which characterise this group of patients. This is why in our institution elderly patients with clinically node-negative primary lesions always undergo SLND irrespective of tumour size and, in case of positive SLN, a decision is taken on the performance of completion of ALND on a patient basis. With this regard, it has been reported that the older the patient, the lower the identification rate of SLN [17]. Nevertheless, our experience with subdermal injection, which is characterised by a higher identification rate, reveals that older women have similar identification rates as compared to younger women.

Prior surgery of the breast

Since it was initially believed that a previous open biopsy of a tumour was a contraindication to SLND [18], until recently this has also been our practice. Nevertheless, several studies have documented no difference in the results of SLND for breast cancer in patients that had a prior breast biopsy [19]. Consensus panellists in Philadelphia agreed that this should no longer be considered a contraindication to SLND, unless extensive excision or complex procedures of plastic surgery had been previously performed. In particular, failures of lymphatic mapping after excisional biopsies are typical of lesions of the upper outer breast. Kern et al. provide an anatomical explanation to this clinical observation, attributing such failures to the interruption of the major lymphatic pathway in this location [20]. Our initial experience with subdermal or periareolar radiotracer injection in these cases is promising, although in our practice the almost universal utilization of fine needle aspiration or core biopsy devices to reach a preoperative diagnosis, makes this one only a minor issue.

Type and Site of injection

Both blue dye and radiocolloid can be used as tracers, although the latter technique is generally felt to be superior because it allows preoperative localisation of the SLN, detects SLN outside the axillary basin (intramammary, supraclavicular, internal mammary), requires less surgical training and, overall, is generally associated with a superior detection rate. A combined technique of blue dye and radioisotope mapping is associated with a 97% SLN identification rate, and may be appropriate during the learning phase, but with experience a declining marginal benefit for blue dye has been reported [21].

A subdermal injection is associated with excellent detection rates [22] and is now considered superior to a peritumoral injection. In our institution, colloidal particles of human albumin (*Nanocoll®*) labeled with 300 μCi of Tc^{99m} in a 0.15 ml volume are injected subdermally on the day before surgery. With this technique,

our detection rate is 97% in a series of almost 300 cases. In order to investigate the correspondence between peritumoral and subdermal injections, we have conducted a small pilot study on 20 patients. We first injected subdermally the radioactive tracer, located the SLN by dynamic lymphoscintigraphy and assessed its radioactivity after 30'; we then injected peritumorally the radioactive tracer, verified if other SLN(s) appeared on lymphoscintigraphy and quantified the radioactive activity of all SLN(s) after 180'. Correspondence between the two types of injection was confirmed as the second (peritumoral) injection never identified a different SLN as compared to the first (subdermal) injection, although radioactivity of the SLN was always increased.

We are now conducting a similar study to verify the correspondence between subdermal over the tumor and subareolar injections. The latter are particularly useful for patients with upper outer quadrant lesions, where significant shine through can occur from the injection of the radiocolloid, making identification of a SLN difficult, and also for patients with occult lesions when stereotactic or ultrasound localization is problematic. Early reports seem to confirm that the subareolar (into the Sappey's plexus), peritumoral and subdermal injection sites drain most of the times to the same SLN [23].

Lymphoscintigraphy

The utility of lymphoscintigraphy in detecting internal mammary sentinel nodes (IMSLN) is debated. A recent review of all the available evidence shows that after peritumoral injection of the radiotracer, the lymphoscintigram demonstrates mapping to the IMSLN in 0% to 35% of patients. Combining all studies, IMSLN contained metastases in 18% of patients, of whom only two were axillary node negative (2.4%). These data clearly suggest that only a small number of patients could benefit from IMSLN biopsy [24].

According to the literature data, we have never identified migration to the IMSLN after subdermal injection in our series of patients. Nevertheless, we also found that lymphoscintigraphy contributes to lymphatic mapping as it helps to locate the SLNs and can reveal SLNs that are hidden by a shine-through effect. Finally, the presence of more SLNs on the lymphoscintigram may prompt the surgeon to look for additional hot nodes once the first SLN has been taken out. For example, when two or more SLNs are visualised by limphoscintigraphy, only one is positive for metastatic disease in over 70% of our SLN positive cases. Clearly, this raises the possibility of understaging if not all SLNs are excised. Conversely, the examination of clinically suspicious but "cold" nodes during a SLN procedure never led to the identification of otherwise undiscovered metastatic disease.

Intraoperative histologic evaluation

Intraoperative assessment of SLN is especially important, as it allows us to conclude the surgical treatment with a one-step procedure in the majority of the cases. Frozen sectioning and imprint cytology are the two most widely used methods of intraoperative SLN assessment. There is large variation in the reported ranges of sensitivity (55-93%) and negative predictive value (74-98%) [25], which is partly the result of the differences in the methodology involved. In any case, as several undetected metastases should be expected with both techniques, permanent sections should complement all negative intraoperative investigations.

In our experience the combination of cytology and frozen sectioning on a limited (usually 5) number of sections is associated with a sensitivity of 67.3% and a negative predictive value of 90.4%; this strategy appears to offer the best compromise and allows all negative intraoperative investigations to be complemented with an optimal examination on permanent sections.

Management of micrometastatic SLN

It can be assumed from several large series that no further axillary dissection is necessary for patients who have a tumour-free SLN. A review of the literature shows that axillary recurrence rate is as low as 1.4% in breast cancer patients who undergo SLND; accordingly, we have seen just one single axillary recurrence after 255 procedures (Table 1) [26-30]. However, for patients with a positive SLN, the current standard is a completion ALND. The rationale for this is that metastatic disease may still remain in the axilla and the total number of nodes involved with tumour is unknown.

Table 1. — *Incidence of axillary recurrence after SLND in breast cancer patients.*

Series	Time period	Number	Length of follow-up (months)	Nodal recurrences	Method of evaluation
Shrenk *et al.* [26]	1996–2000	83	22	0% (0/83)	IHC
Roumen *et al.* [27]	1997–2000	100	24	1.0% (1/100)	IHC
Giuliano *et al.* [28]	1995–1997	67	39	0% (0/67)	IHC
Veronesi *et al.* [29]	1996–1999	285	–	0% (0/285)	IHC
Chung *et al.* [30]	1998-2001	208	26	1.4% (3/208)	Serial sectioning
Our series	1999-2002	255	15	0.4% (1/255)	Serial sectioning + IHC

IHC: immunohistochemisty with pan-cytokeratin antibody; serial sectioning: sectioning of lymph nodes at 100 micron intervals.

Modified from Chung et al. [32]

Several investigators have examined the risk of non-SLN tumour involvement for patients with a tumour-involved SLN by looking at the size of the primary tumour and metastasis. In two studies [31, 32], patients with a primary tumour > 2.0 cm had an increased incidence of non SLN-tumour involvement when compared to patients with a primary tumour $\leq$ 2.0 cm. Similarly, cases with a SLN metastasis > 2.0 mm were associated with an increased rate of non SLN metastasis when compared to cases with a SLN metastasis $\leq$ 2.0 mm. No other clinical or histopathologic factor examined by multivariate analysis in these studies was found to be predictive of non SLN-tumour involvement. In our series, although the likelihood of harbouring other positive nodes in the axilla was significantly higher in cases of macrometastatic as compared to micrometastatic SLN and, although not significantly, for larger (> 2 cm) as compared to smaller tumours ($\leq$ 2 cm), we could not detect any subset of SLN positive patients for whom ALND might be safely spared.

As far as the significance of SLN micrometastases detected only by immunohistochemistry (IHC) is concerned, no definitive data exist to clarify the issue. That is why in our institution IHC of the SLN is reserved for equivocal findings on conventional hematoxylin and eosin stain, until two open clinical trials (ACOSOG Z0010, NSABP B-32) will help to answer this important question.

Conclusions

The modern paradigm of cancer therapy is to eradicate the disease while minimising unnecessary trauma. Radical mastectomy for breast cancer has been almost entirely abandoned in favour of breast preserving operations. Less mutilating surgery is now possible by combining surgical, physical and medical treatments and they often also result in improved overall survival. New surgical techniques hold the promise of further improvements; one example is provided by SLND that will likely replace and hopefully increase the prognostic information provided by ALND in breast cancer patients.

Once the multidisciplinary team has demonstrated a high success rate with SLND, we believe that there is sufficient evidence suggesting that ALND is required only in patients with a positive SLN. Although follow-up is short, axillary recurrences after a negative SLND are very rare, whereas complication rates are considerably lower as compared to ALND. Our results are in line with those in the literature, but only the completion of large American and European studies will clarify the safety of SLND as far as local control and long- term survival are concerned.

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References

[1] Tanis P. J., Nieweg O. E., Valdés Olmos R. A. *et al.*: "History of sentinel node and validation of the technique". *Breast Cancer. Res.*, 2001, 3, 109.
[2] Halsted W. S.: "The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 to January 1894". *Johns Hopkins Hosp. Bull.*, 1894, *4*, 297.
[3] Fisher B.: "Seminars of Bernard Fisher 1960 – nature of cancer as systemic disease?". *Bull. Soc. Int. Chir.*, 1972, *31 (6)*, 604.
[4] Fisher B., Fisher E. R.: "Barrier function of lymph node to tumor cells and erythrocytes". *Cancer*, 1967, *20*, 1907.
[5] The ATAC Trialist Group: "Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial". *Lancet*, 2002, *359*, 2131.

[6] Baum M., Chaplain M. A. J., Anderson A. R. A. *et al.*: "Does breast cancer exist in a state of chaos?". *Eur. J. Cancer*, 1999, *35*, 886.
[7] Hellman S.: "Natural history of small breast cancers". *J. Clin. Oncol.*, 1994, *12*, 2229.
[8] Cabañas R. M.: "An approach for the treatment of penile carcinoma". *Cancer*, 1977, *39*, 456.
[9] Morton D. L., Wen D. R., Wong J. H. *et al.*: "Technical details of intraoperative lymphatic mapping for early stage melanoma". *Arch. Surg.*, 1992, *127*, 392.
[10] Giuliano A. E., Kirgan D. M., Guenther J. M., Morton D. L.: "Lymphatic mapping and sentinel lymphadenectomy for breast cancer". *Ann. Surg.*, 1994, *220*, 391.
[11] Krag D. N., Weaver D. L., Alex J. C., Fairbank J. T.: "Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe". *Surg. Oncol.*, 1993, *2*, 335.
[12] Turner R. R., Ollila D. W., Krasne D. L., Giuliano A. E.: "Histopathologic validation of the sentinel lymph node hypothesis for breast carcinoma". *Ann. Surg.*, 1997, *226*, 271.
[13] Hsueh E. C., Turner R. R., Glass E. C., Brenner R. J., Brennan M. B., Giuliano A. E.: "Sentinel node biopsy in breast cancer". *J. Am. Coll. Surg.*, 1999, *189*, 207.
[14] Schwartz G. F., Giuliano A. E., Veronesi U. and the Consensus Conference Committee. *Breast J.*, 2002, *3*, 126.
[15] Tafra L., Chua A., Madigan M. *et al.*: "Sentinel node biopsy for breast tumors 4 cm or greater". *Eur. J. Nucl. Med.*, 1999, *26* (suppl.), 93.
[16] Bedrosian I., Reynolds C., Mick R. *et al.*: "Accuracy of sentinel lymph node biopsy in patients with large primary breast tumors". *Cancer*, 2000, *88*, 2540.
[17] Krag D., Weaver D., Ashikaga T. *et al.*: "Sentinel node biopsy and breast cancer: a multicenter validation study". *N. Engl. J. Med.*, 1998, *339*, 941.
[18] Feldman S. M., Krag D. N., McNally R. K. *et al.*: "Limitation in gamma probe localization of the sentinel node in breast cancer with large excisional biopsy". *J. Am. Coll. Surg.*, 1999, *188*, 248.
[19] Haigh P. I., Hansen N. M., Qi K., Giuliano A. E.: "Biopsy method and excision volume do not affect success rate of subsequent sentinel lymph node dissection in breast cancer". *Ann. Surg. Oncol.*, 2000, *7*, 21.
[20] Kern K. A.: "Lymphoscintigraphic Anatomy of Sentinel Lymphatic Channels after Subareolar Injection of Technetium 99m Sulfur Colloid". *J. Am. Coll. Surg.*, 2001, *193*, 601.
[21] Derossis A. M., Fey J., Yeung H. *et al.*: "A trend analysis of the relative value of blue dye and isotope localization in 2,000 consecutive cases of sentinel node biopsy for breast cancer". *J. Am. Coll. Surg.*, 2001, *193*, 473.
[22] Veronesi U., Paganelli G., Viale G. *et al.*: "Sentinel lymph node biopsy and axillary dissection in breast cancer: results in a large series". *J. Natl. Cancer Inst.*, 1999, *91*, 368.
[23] Donahue E. J.: "Sentinel node imaging and biopsy in breast cancer patients". *Am. J. Surg.*, 2001, *182*, 426.
[24] Klauber-DeMore N., Bevilacqua J. L. B., Van Zee K. J. *et al.*: "Comprehensive review of the management of internal mammary lymph node metastases in breast cancer". *J. Am. Coll. Surg.*, 2001, *193*, 547.
[25] Cserni G.: "Axillary staging of breast cancer and the sentinel node". *J. Clin. Pathol.*, 2000, *53*, 733.
[26] Schrenk P., Hatzl-Griesenhodfer M., Shamiyeh A., Waynad W.: "Follow-up of sentinel node negative breast cancer patients without axillary lymph node dissection". *J. Surg. Oncol.*, 2001, *77*, 165.
[27] Roumen R. M., Kuijt G. P., Liem I. H., van Beek M. W.: "Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection". *Br. J. Surg.*, 2001, *88*, 1639.
[28] Giuliano A. E., Haigh P. I., Brennan M. P. *et al.*: "Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer". *J. Clin. Oncol.*, 2000, *18*, 2553.
[29] Veronesi U., Galimberti V., Zurrida S. *et al.*: "Sentinel lymph node biopsy as an indicator for axillary dissection in early breast cancer". *Eur. J. Cancer*, 2001, *37*, 454.
[30] Chung M. A., Steinhoff M. M., Cady B.: "Clinical axillary recurrence in breast cancer patients after a negative sentinel node biopsy". *Am. J. Surg.*, 2002, *184*, 310.
[31] Chu K. U., Turner R. R., Hansen N. M. *et al.*: "Do all patients with sentinel node metastasis from breast carcinoma need complete axillary node dissection?". *Ann. Surg.*, 1999, *229 (4)*, 536.
[32] Reynolds C., Mick R., Donohue J. H. *et al.*: "Sentinel lymph node biopsy with metastasis: can axillary dissection be avoided in some patients with breast cancer?". *J. Clin. Oncol.*, 1999, *17 (6)*, 1720.

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