Pathol. Oncol. Res. (2008) 14:117–121
DOI 10.1007/s12253-008-9052-x

REVIEW

Minimal Disease in Sentinel Nodes

Gábor Cserni

Received: 29 March 2008 / Accepted: 10 April 2008 / Published online: 21 May 2008

Abstract Isolated tumor cells and micrometastases represent low-volume or minimal disease in the regional lymph nodes of breast cancer patients as compared to macrometastases. Sentinel lymph node biopsy is a functional selection and removal of the most likely site of regional metastasis, and gives pathologists the opportunity to concentrate detection techniques on a limited number of lymph nodes. Consequently, more lesions belonging in the two mentioned staging categories are discovered in sentinel lymph nodes. Despite some publications contradicting stochastic models of breast cancer, micrometastases seem to reflect a prognosis intermediate between the node-negative and macrometastatic nodal status, and they also reflect a risk of non-sentinel node involvement slightly higher than that associated with a node-negative status. Data are more contradictory as concerns isolated tumor cells. This minireview summarizes the definitions, their inconsistencies, pathological protocols aiming at the detection of minimal nodal disease, the prognostic impact and non-sentinel node involvement related risk of such nodal lesions, and their therapeutic consequences.

Keywords Breast cancer · Sentinel lymph node · Micrometastasis · Isolated tumor cells

Abbreviations

ACOSOG	American College Of Surgeons—Oncology Group
ITC	isolated tumor cells
NSABP	National Surgical Adjuvant Breast and Bowel Project
SLN	sentinel lymph node
SLNB	sentinel lymph node biopsy
RT-PCR	reverse transcription polymerase chain reaction
TNM	tumor, node, metastasis

G. Cserni (✉)
Bács-Kiskun County Teaching Hospital,
Nyíri út 38.,
H6000 Kecskemét, Hungary
e-mail: cserni@freemail.hu

Micrometastases and Isolated Tumor Cells

It has been known for a long time that conventional histological examination of lymph nodes leaves some metastases hidden [1]. These occult metastases are generally small, and often belong in the so called micrometastasis category. With more extensive sampling (more levels examined) and/or a more sensitive method of detection (e.g. immunohistochemistry) the proportion of cases with detected metastatic involvement can be increased. Since lymph node metastasis is considered an important prognosticator of breast cancer [2], which to some extent also influences treatment decisions, the aim of identifying these occult metastases seems logical.

At the upper end, an increasing number [3] or ratio [4–6] of metastatic lymph nodes is paralleled by a worse outcome. It may therefore be logically hypothesized in this stochastic concept that at the bottom end, a decreasing nodal load infers a less ominous outcome. When micrometastases where introduced in the literature of breast cancer by the Hungarian born pathologist Andrew Huvos, they were reported to have the same impact as negative lymph nodes after a minimum follow-up of 8 years [7]. Fisher and colleagues reported similar findings from a National Surgical Adjuvant Breast and Bowel Project

(NSABP) trial [8]. However, it must be noted that neither of these studies from 30–40 years ago would be considered of sufficient power for such conclusions today; only 18 and 21 micrometastatic cases were included, respectively [9]. Although the prognostic significance of micrometastases has been continuously challenged, most current reports reinforce that they carry a survival disadvantage [9–12]. On this basis, looking for them makes sense, but looking for them by conventional light microscopy in all lymph nodes removed during axillary dissection is more than pathology departments or health care systems can allow.

During the 90s of the last century, sentinel lymph node biopsy (SLNB) has gained an increasing acceptance in the nodal staging of breast carcinomas. It allows the removal of a few, functionally selected tumor draining lymph nodes, which are directly connected to the tumor site and are therefore the most likely sites of regional metastases. These lymph nodes can be given more scrutiny during histopathological evaluation. Indeed, it has been documented as early as 1995, that SLNB improves nodal staging [13], a finding which has been reinforced by a multitude of publications [14]. The entry of SLNB in the armamentarium of breast surgeons and pathologists has resulted in a virtual shift in the proportion of cases diagnosed with node-positive disease, and this has led to a stage migration [12, 15]. Partly in order to compensate this statistical artefact [9], the term "isolated tumor cells" (ITC) was introduced in 1999 by the Union International Contre le Cancer tumor, node, metastasis (TNM) committee members [16] and a few years later this was adopted by the 6th edition of the TNM staging books [17, 18].

ITC forms the bottom end of metastatic nodal involvement, and is considered negligible disease, hence is classified as a subset of the node-negative group: pN0(i+). It is suggested that ITCs should be ignored from the points of view of both staging and treatment decisions [19]. The backgrounds for this interpretation are multiple:

- ITC are very small and truly represent the bottom end of nodal involvement that can be detected by microscopy. In the stochastic concept of breast cancer (with larger volumes of tumor cells consisting of greater risk of dying from the disease) such lesions could probably be ignored.
- If ITCs are classified as a subset of the pN0 category breast carcinomas on the basis of the above, the stage migration resulting from SLNB can be decreased, and these very low volume nodal involvement cases can be by authority put back to the "undetected" category.
- Single cells or smaller clusters can be dislodged by diagnostic or therapeutic interventions, and if dislodged into lymphatics they can be passively transported to the sentinel lymph nodes (SLNs) [20, 21]. Such passively displaced tumor cells are often (but not on evidence base) considered of no prognostic significance.
- Sometimes cytokeratin positive non-tumor cells are falsely interpreted as ITC, and with this approach, such cases are not falsely classified as node-positive.

With the introduction of ITC in the staging systems, the term micrometastasis was restricted and was given not only an upper inclusive limit of 2 mm, but also a lower non-inclusive limit of 0.2 mm. The segregation of these two categories of minimal nodal disease is arbitrary and also means an arbitrarily based distinction between node-negative and node-positive breast cancers with potential therapeutic consequences. Before dealing with these consequences it seems reasonable to discuss how reliably minimal disease can be detected in SLNs.

Detection of Minimal Disease in Sentinel Lymph Nodes

Due to the fact that SLNs are the most likely sites of nodal metastases, it has been widely accepted and recommended that they should be submitted to more detailed histopathological analysis than lymph nodes in general. Most, if not all guidelines recommend multilevel assessment of the SLNs either by means of gross slicing or by step-sectioning or by combining these two methods. Cytokeratin immunohistochemistry is also included in some national guidelines [22]. Adhering to these recommendations will obviously increase the rate of nodal involvement, with many of the additional levels disclosing minimal disease. The pathological work-up of the SLNs is very heterogeneous through Europe as reflected by the questionnaire based study of the European Working Group for Breast Screening Pathology [23].

It must be mentioned that at least some micrometastases of the early studies probably reflected smaller macrometastases tangentially or superficially sectioned, as it is very likely (due to the lack of methodological details in the relevant articles) that no further sectioning was done to exclude the possibility of the metastasis becoming greater at deeper levels. The micrometastatic size of an SLN metastasis today is either obvious in some SLN protocols with sufficiently small distances between the levels examined or can be clarified by ordering a few deeper levels of incompletely sectioned blocks; an approach which is recommended.

Owing to the fact that nodal micrometastases reflect some prognostic disadvantage their identification has been advocated by several histopathology protocols. If it is accepted that micrometastases are nodal lesions ranging from 0.2 to 2 mm in maximum dimension, it may be possible to construct models for their all or nearly all inclusive detection [24]. Despite the fact that the detection

of micrometastases can be targeted by the pathology protocols, only few work-up protocols have been implemented with this aim [22, 23]. If the sampling and examination of the SLN is built up with the aim of identifying nearly all micrometastases, it can be trusted that the SLN with negative findings contains no micrometastasis, therefore this form of nodal lesion can be reliably excluded.

On the other hand, a nearly all inclusive detection of ITC cannot be reached by microscopic examination of the SLNs. Therefore the lack of detecting ITC, i.e. the pN0(i−) status can mean either the absence of ITC or their occult presence, or more directly stated can reflect a true-negative as well as a false-negative status for ITCs.

Molecular methods can probably replace microscopy in some respects. However, conventional single-marker reverse transcription polymerase chain reaction tests fail in this respect, as most of them fail to detect some obviously positive SLN cases (probably due to sampling or technical issues) [14]. The use of multiple markers increases the specificity of the tests, but creates problems about the definition of a positive assay (positive with all markers, any markers, or the majority of markers). Quantitative real-time assays seem much more realistic, and with good calibration they seem to allow the identification of clinically significant disease [25, 26]. Whatever the molecular assay used, it is wise to run this with parallel histology in order to exclude the possibility of non-tumoral epithelium (e.g. breast tissue inclusions [27]) and to better quantify and qualify the type of nodal involvement. Otherwise the size correlations might be lost, the micrometastatic nature cannot be documented. Cases negative by histology but positive by a molecular assay are currently labelled as pN0(mol+).

Axillary and Systemic Treatment Related Implications

The first prevalent breast cancer theory of the last century inferred a great role for the locoregional therapy of the disease, an as such gave ground to radical surgical approaches. This theory, often used with the eponym of Halsted was later replaced by Bernard Fisher's systemic one. The systemic concept suggests that breast cancers are systemic (disseminated) from their earliest days, and therefore locoregional therapy has little to do with them, the disease should be treated by systemic therapy. This theory gave ground to breast conserving surgical approaches and to the introduction of adjuvant systemic therapies. The therapeutic role of eliminating local and regional manifestation of disease was shadowed to some extent, although it is now well supported that locoregional therapy also influences disease survival [28–30], as suggested by the spectrum theory of breast carcinoma [31].

Although some considered axillary dissection purely as a staging procedure providing prognostic information, the above considerations lend support to perform axillary dissection in patients with positive SLNs both for more precisely staging and for treating the disease. Nevertheless, it is obvious that dissecting negative lymph nodes makes not much sense, if their negativity can be predicted, and in an optimal setting axillary clearance should be done only in patients having nodal metastases beyond the SLN.

It is widely accepted that axillary dissection can be omitted in patients with negative SLNs. Level V evidence (expert opinion) suggests that ITCs should be considered as pN0, i.e. negative [32]. The same kind of evidence has advocated a node-positive status for somewhat larger volume nodal involvement termed micrometastasis. As a first approach, further axillary treatment is recommended for SLN-positive cases, therefore even those patients who have micrometastases.

If further axillary treatment (either surgical in the form of axillary clearance or radiotherapeutical which seems to emerge as an acceptable alternative) is recommended on the basis of risk assessment, it must be remembered that the majority of patients with minimal SLN involvement will have no further metastases discovered in the non-SLNs, therefore any form of regional therapy represents overtreatment to them. Non-SLN involvement in not only dependent on SLN metastasis size (which is an important predictor on the basis of several studies [9, 33]), but other factors such as lymphovascular invasion, tumor size…etc. also influence it. Therefore, there may be some patients with a set of clinicopathological parameters suggesting a very low risk of non-SLN involvement (e.g. small micrometastasis <1 mm in greatest dimension, small tubular carcinoma without vascular invasion) where axillary dissection (or irradiation) can safely be omitted. On the opposite extreme, larger micrometastases with larger high grade primary tumors can have higher risk of non-SLN involvement favouring axillary dissection on the basis of risk evaluation. Multivariate risk assessing tools are available for axillary treatment decisions [34–39], but it seems that they are less reliable at lower ranges of estimated non-SLN metastasis risk [40–42] and they may specifically fail when micrometastases are considered [43].

It must be noted, that level IV or III evidence regarding axillary dissection for low-volume SLN metastases is lacking. Some retrospective analyses and limited prospective studies suggest a stochastic approach with higher risk of non-SLN positivity with greater size of the SLN involvement (ITC vs micrometastasis vs macrometastases or ITC vs micrometastasis up to 1 mm vs greater micrometastasis) [44, 45], whereas others argue against such a size or volume related relationship [46].

In this latter respect, pathologist should really try to be as consistent as possible in diagnosing or distinguishing

between ITC and micrometastases or between micrometastases and macrometastases. This is currently not the case, as interpretations of these categories are not uniform [23, 47–50].

Similarly to the regional therapy related issues, the literature is also controversial in the systemic therapy area. There are at least a few studies suggesting that even minimal nodal disease classified as ITC reflects a survival disadvantage [11, 51], and the name of nanometastasis has been suggested to label them [51]. Such data, although disputable from some aspects, are compatible with a non-stochastic theory of breast cancer suggesting that not the quantity but rather the quality of the metastases are important. It is therefore proposed that the presence of progenitor cells or stem cells with real tumorigenic capability is important, and this is something that size measurements cannot assess; even minimal disease can be of ominous outcome. For the moment however, more evidence in this direction is required, and it should not be forgotten that most of the recent population based data suggest that minimal nodal metastases (micrometastases) can be translated to reflect a risk between that of macrometastases and that of no metastasis at all.

As concerns systemic treatment decisions, the role of nodal involvement has lost some of its power, since adjuvant treatment is often recommended on the basis of primary cancer and patient characteristics rather than the presence or absence of lymph node metastasis, or the quantitative nodal status. More importantly, factors predictive of the potential success of a given systemic therapy [e.g. estrogen receptor or HER-2 status] have become of prime importance in this decision making process. And in the new era of tailoring treatment to the individual patient and her (his) disease, molecular markers of prognosis and prediction of response to given therapeutic agents may well come in first line for choosing the optimal form of systemic therapy. In this context, lymph node status seems to lose further grounds from its "most significant prognostic factor" [2] status.

Concluding Remarks

The oncological society is awaiting the results of the NSABP-B32, the ACOSOG-Z10 and the underpowered and prematurely closed Z11 trials for having higher levels of evidence as concerns the axillary or systemic therapy related impact of minimal disease in the SLNs. (This evidence may however be of questionable value if the classification rules do not allow a reasonable interobserver reproducibility of the staging categories.)

In the interim, cancer staging requires the distinction between ITC and micrometastases. With this distinction in the heads of both pathologists and oncologists, treatment decisions are being made. Micrometastases will probably infer axillary dissection in most patients, although there are small subgroups with this type of SLN involvement in which clearance of the axilla could rather safely be omitted. ITCs, as chance findings that cannot be recognized in an all inclusive manner by workable histological methods would in most cases be only followed-up without further axillary surgery.

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