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ARTICLE

Estimating the Overlap Between Sentinel Lymph Nodes and Axillary Node Samples in Breast Cancer

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Management of the axilla in breast cancer patients is a controversial issue. Axillary sampling and sentinel lymphadenectomy are both conservative surgical approaches which aim to stage the disease. These procedures target selective treatment of node-positive patients and seem to allow the omission of axillary clearance in node-negative ones. In this way, they reduce the rate of complications in an otherwise overtreated subset of patients. Forty consecutive patients with palpable T1 and T2 breast carcinoma underwent sentinel lymphadenectomy following mapping with Patent blue dye, with subsequent axillary clearance and excision of the tumor or mastectomy. Then the largest/firmest 3,4,5 and 6 nodes were selected from all the lymph nodes in order to model an axillary sample. It was suggested that these are the nodes that are the most likely to be included in the specimen during sampling, because of their size and consistency. The probability of the sentinel lymph nodes falling into the sample of the 3-6 largest/firmest nodes was calculated. The sentinel nodes predicted the axillary nodal status in 95%, while the samples of the largest 3, 4, 5 and 6 nodes were predictive in 95, 96, 98 and 98%, respectively. The two methods of evaluation displayed a considerable overlap, as the sentinel node would have been included in the 3–6 largest/firmest nodes in 79–92% of the cases, depending on the number of largest nodes evaluated. The overlap was greater after fine needle aspiration of the primary tumor. Although the two alternative staging procedures of 3, 4, 5 or 6 node sampling and sentinel lymphadenectomy with the vital blue dye technique cannot be simultaneously done without one influencing the other, and the first method was only modeled, the results suggest that there is a considerable overlap between the two; axillary sampling may often remove the sentinel lymph nodes. (Pathology Oncology Research Vol 5, No 2, 129–133, 1999)

Keywords: breast cancer, axillary clearance, axillary sampling, staging

Introduction

Management of the axilla in the treatment of breast cancer is a matter of debate. Most surgeons argue that axillary clearance is the best choice, since it is both a staging and a therapeutic intervention.[4,9,19,26] On the other hand, most medical oncologists regard axillary surgery mainly as a staging procedure, [4,24] as the axillary lymph node status is still the most important single prognostic factor in breast cancer. Theoretically, only a small percentage of patients would benefit from axillary clearance,[17] while an increasing proportion of breast cancer patients[6] are overtreated with this procedure as they have no demonstrable metastases in the axilla. Most of the complications and morbidity of current breast cancer treatment result from axillary lymph node dissection[5] or radiotherapy.[28] The exposure of node-negative patients to these complications is unjustified. Management of the axilla should therefore be an intervention influenced by the current status of the patient and her disease. These considerations have implemented the search for alternative methods of evaluating the axilla adequately without proceeding to its clearance.

Clinical examination and the use of imaging techniques to assess the nodal status are not reliable enough procedures because of the high rates of false-positivity and false-

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Table 1. **Distribution of the tumors studied according to pathologic T and N (pT and pN) categories**

	pN0	*pN1a*	*pN1bI*	*pN1bIII*	*pN1bIV*	*pN2*
pTx	0	0	0	1	0	1
pTis	1	0	0	0	0	1
pT1miv	1	0	0	0	0	1
pT1b	1	0	0	0	0	1
pT1c	5	2	1	1	0	9
pT2	6	4	6	9	1	27
	14	6	7	11	1	40

negativity. Histopathological assessment has rather been considered the "gold standard" for the evaluation of lymph nodes. Surgico-pathological methods alternative to axillary clearance have also emerged. Axillary sampling[11,13,16,22,30] and lymphatic mapping with sentinel lymph node biopsy (SLNB)[1,15,23,33] are such alternatives. Axillary sampling is not a uniformly defined and performed operation. It is likely that authors challenging the reliability of sampling[10,21,25,27] used a blind approach defined by anatomical boundaries, and poorly performed surgery could possibly account for their less than optimal results.[16] Sampling aiming to remove all enlarged and firm nodes and a minimum of 4 to 6 nodes,[12,18] as also suggested by current guidelines,[3,31] is reported to be an adequate approach. On the other hand, lymphatic mapping and SLNB coupled with more sensitive methods of detecting metastases (serial sectioning and immunohistochemistry) seem to be superior to a routine histopathologic work-up of the total number of axillary nodes.[14] This minimally invasive staging method has been validated,[32] and has a very low false-negative rate.[34] It seems to permit the omission of axillary clearance in (sentinel) node-negative patients. In the present pilot study, the possible overlap between axillary samples and sentinel lymph nodes (SLNs) has been estimated in order to check on the possible overlap between the two staging procedures.

Materials and Methods

The study population comprised 40 patients with palpable and operable breast cancer in categories N0 and N1 of the UICC/AJCC common staging system.[2] Two further patients were excluded from the consecutively operated cases because their axilla contained 14 and 30 metastatic nodes, respectively, most of which were enlarged and firm, as identified during surgery; these patients were only possible candidates for axillary clearance despite the fact that SLNB was completed in them.

Lymphatic mapping was performed after peritumoral injection of 4–5 ml of diluted Patent blue dye (Patentblau V2,5%, Byk Gulden, Konstanz, Germany). A blue lymphatic vessel was identified from an anterior axillary incision and was carefully dissected till the first blue node. Additional blue lymphatics and/or nodes were then searched for. All blue nodes were considered SLNs. Axillary clearance followed the SLNB, while the tumor was excised or in some cases treated by mastectomy.

Table 2. **Detials of the size of individual SLNs and their probability of being included in the 3–6 largest/firmest nodes**

Patient No.	*Rank of the SLN*	*3 nodes*	*4 nodes*	*5 nodes*	*6 nodes*
1	5–7.	0	0	0.3	0.7
2	6–8.	0	0	0	0.3
3	1–3., 9–13.	0.5	0.5	0.5	0.5
4	2., 6–7.	0.5	0.5	0.5	0.8
5	1.	1	1	1	1
6	1.	1	1	1	1
7	1.	1	1	1	1
8	1.	1	1	1	1
9	2.	1	1	1	1
10*	3–4.	0.5	1	1	1
11	1.	1	1	1	1
12	1–3.	1	1	1	1
13	2.	1	1	1	1
14	1–2., 1–2.	1	1	1	1
15	2–3., 2–3.	1	1	1	1
16	2–4.	0.8	1	1	1
17	1–2.	1	1	1	1
18	3.	1	1	1	1
19	2–3., 2–3.	1	1	1	1
20	2–3.	1	1	1	1
21	9–10.	0	0	0	0
22	1.	1	1	1	1
23	2., 7.	0.5	0.5	0.5	0.5
24	2.	1	1	1	1
25	4.	0	1	1	1
26	2–5.	0.5	0.8	1	1
27	1.	1	1	1	1
28	1–2., 3.	1	1	1	1
29	2.	1	1	1	1
30	1–2.	1	1	1	1
31	1.	1	1	1	1
32	1.	1	1	1	1
33	1–4., 5.	0.4	0.5	1	1
34	4–5.	0	0.5	1	1
35	1–2.	1	1	1	1
36	1–2.	1	1	1	1
37	3.	1	1	1	1
38*	1.	1	1	1	1
39	1–2.	1	1	1	1
40	1.	1	1	1	1
Overall	–	31.7	34.3	35.8	36.8
(%)	–	(71%)	(86%)	(90%)	(92%)

(The rank of the SLNs refers to the serial numbers given to each SLN; * marks the false negative SLNs.)

The histopathology of the SLNs, submitted separately, included serial sections through the whole node after cutting the blocks to extinction, and immunohistochemistry to cytokeratin and epithelial membrane antigen for nodes negative on haematoxylin and eosin (HE) staining. The rest of the nodes were recovered from the axillary fat without clearing and were processed separately. In all cases, the largest cut surface was sectioned and studied under the microscope after HE staining.

All lymph nodes (including the SLNs) were numbered consecutively in sequence of size, the first being the largest one. Lymphoid and metastatic neoplastic tissue content was also considered on the basis of the blue area (more nuclear staining) seen macroscopically on the HE-stained slides. It must be noted that patent blue vanishes during tissue processing, and the blue colour investigated here was purely due to haematoxylin staining. In this way, the largest node was not necessarily the one with the largest diameter, but the one with the largest estimated haematoxylin stained blue area – corresponding to either lymphoid or metastatic neoplastic tissue or both. These are the tissues most likely to influence the consistecy (firmness) of lymph nodes. Nodes with similar estimated blue areas received the same sequential numbers (e.g. 3 nodes each numbered 2–4 would indicate that these 3 nodes were the 2nd, 3rd and 4th largest ones, but that their estimated sizes were too similar for a distinction to be made between them). Nodes were then studied microscopically for the identification of metastases. The serial numbers of SLNs were recorded.

The probability that the first 3, 4, 5 or 6 largest nodes included the SLN(s) was calculated, differentiating the results with regard to those with fine needle aspiration cytology (FNAC) in their preoperative work-up and those without. The size and number of the SLNs were also considered in the calculation. In each individual case the probability that SLNs were included in the sample of the "n" largest/firmest lymph nodes ("n" = 3, 4, 5 or 6 in the four different estimations) was 1 (maximal) if all the SLNs were larger than, or equal to the size of the"(n)th" node. It ensues that the probability was <1 if any of the SLNs were smaller than the "(n)th" node, or there were more nodes of the same size as the "(n)th" node and any of these were not included within the modelled sample of "n" node.

Results

Table 1 demonstrates the distribution of the tumors according to the pT and pN categories of TNM system.[2] All tumors were M0.

The results of SLNB can be summarized as follows: 1 or 2 SLNs (mean 1.3) were removed per patients. The number of non-SLNs ranged between 10 and 38 (mean 20). 16 SLNs were negative for metastasis (2 of them were false-negative). The SLN(s) was(were) the only positive node(s) in 10 (42% of all node-positive patients) of the remaining 24 SLN-positive patients. Micrometastases were disclosed with immunostains in 2 SLNs. The 3, 4, 5 or 6 largest/firmest nodes gave an adequate qualitative axillary nodal status in 95%, 96%, 98% and 98%, respectively. The overlap between the SLNs and the largest/firmest lymph nodes (and probably the two staging procedures) is expressed in *Table 2. and 3.*

Discussion

Axillary sampling requiring a non-blind surgical approach that considers lymph node location, size and consistency has been reported to be a reliable means of staging breast cancer.[12,16] In a previous study involving 499 breast cancers, we demonstrated that sampling the 3–6 largest/firmest axillary lymph nodes led to the detection of 93–98% of node-positive patients and gave a correct qualitative axillary nodal status in 96–99%.[8] Lymphatic mapping and SLNB have also been and continue to be intensively studied. This approach seems reliable for staging with low rates of false-negativity. Our 2 cases of false-negativity could both be explained on the basis of clinical data or a technical failure. One patient had had a contralateral breast cancer 6 years before the SLNB, followed by two local recurrences in the same breast, one 2 years previously and one at the same time as the detection of the 1.8 cm cancer operated on together with the SLNB. This might have been a case where SLNB was unjustified because of possible multifocality and altered lymphatic drainage.[29] The relative and absolute contraindications of SLNB are not yet set established, and require further investigation.

Table 3. **Probabilities of the SLN(s) falling in the samples of the 3, 4, 5, or 6 largest/firmest axillary lymph nodes**

			Number of lymph nodes assessed			
		No. of cases	*3 nodes*	*4 nodes*	*5 nodes*	*6 nodes*
FNAC +	Node-negative	8	0.81	0.88	0.94	0.94
	Node-positive	24	0.84	0.91	0.94	0.95
	All	32	0.83	0.90	0.94	0.95
FNAC –	Node-negative	7	0.57	0.64	0.69	0.79
	Node-positive	1	1	1	1	1
	All	8	0.63	0.69	0.73	0.82
FNAC +/–	Total	40	0.79	0.86	0.90	0.92

(FNAC +: with fine needle aspiration cytology on the tumor prior to SLNB, FNAC –: without fine needle aspiration cytology on the tumor prior to SLNB.)

The SLN of the other patient was improperly stained due to a technical failure. Both these patients had only 1 micrometastasis in one non-SLN, serially numbered 3–4 and 2–3, respectively. The only SLN was the largest node in 11 cases (27.5%) and at least one of the SLNs was one of the largest nodes in 21 cases (52.5%).

From the present study, it emerges that the sample of the 4-6 largest/firmest nodes would include the SLNs in 86–92% of the cases. It is important to note that the nodes draining the tumor usually enlarge as a consequence of reactive hyperplasia resulting from the preoperative diagnostic interventions (aspiration or core biopsies), and this makes them easier to palpate during sampling.[16]. This procedure may be considered a kind of physiological lymphatic mapping. Accordingly, we separated our results into two groups: those on patients with preoperative FNAC and those without. The inclusion of the SLN in the 3 to 6 largest/firmest lymph nodes was slightly greater in the patients with FNAC of the primary tumor in the short-term anamnesis and in the case of node-positivity. However, a larger number of cases would be needed for a reliable statistical difference.

The model used here considers that the size and firmness of a lymph node are the qualities related to its palpability and chances of being sampled, what must be the case most of the time. So our results suggest that non-blind sampling of the axilla, removing at least 4,[3,31] but preferably 6 nodes,[18] can be an adequate staging method and may often overlap with the removal of the SLNs.

The lymph nodes in the axillary pyramid are not equivalent and interchangeable. Mathematical models requiring a minimum of 10 nodes for adequate identification of category pN0 fail to consider the location, size and consistency of the nodes.[7,20] This is why they can be challenged. Fewer nodes may also give an adequate qualitative nodal status without the possible complications of the clearance procedures.

While staging can be achieved by both sampling and SLN biopsy and a decision on the quality of adjuvant systemic therapy can be made by using the nodal status established by them and the characteristics of the primary tumor, the loco-regional treatment of node-positive patients is still subject to some controversy.

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