Current issues in breast surgery

Ph. D. Thesis

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LIST OF FULL PAPERS THAT SERVED AS THE BASIS OF THE PH.D. THESIS

I. **Maráz R**, Boross G, Ambrózay E, Svébis M, Cserni G.
Selective ductectomy for the diagnosis and treatment of intraductal papillary lesions presenting with single duct discharge.
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II. **Maráz R**, Boross G, Pap-Szekeres J, Rajtár M, Ambrózay E, Cserni G.
Internal Mammary Sentinel Node Biopsy in Breast Cancer. Is it indicated?
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III. **Maráz R**, Boross G, Pap-Szekeres J, Markó L, Rajtár M, Ambrózay É, Bori R, Cserni G.
The role of sentinel node biopsy in male breast cancer.
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IV. Cserni G, **Maráz R.**
Regional disease control in selected patients with sentinel lymph node involvement and omission of axillary lymph node dissection.
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1. INTRODUCTION

Breast cancer is the most common malignant tumor in women. Currently, the majority of cases of breast cancer are detected at an early stage, with relatively small size and limited or no lymph node involvement.

Single duct nipple discharge, especially when the fluid is blood stained, is a typical but not general or specific initial symptom of breast cancer and can be caused by papillary prolierations too. The majority of solitary papillomas are benign, although they can be associated with atypia, in-situ or invasive malignancy. Their diagnostic work-up includes mammography and ductography. A potential diagnostic procedure is the histological verification of intraductal lesions following selective ductectomy (SD), a conservative surgical excisional procedure aiming at the removal of the discharging duct with a minimal rim of periductal breast tissue.

From the mid-1990s, sentinel lymph node biopsy (SLNB) has become a widely used staging procedure.Sentinel lymph nodes (SLNs) are visualized by lymphoscintigraphy, which can show the presence of not only axillary but also internal mammary SLNs (IM-SLNs). Biopsy of these latter has not become a routine procedure.

Although studies of lymphatic drainage patterns report internal mammary chain (IMC) involvement in 13–35%, the value of an SLN procedure for the IMC is still controversial. In addition to the axillary lymph node status, the internal mammary (IM) lymph node status also provides prognostic information in breast cancer patients. If positive, the prognosis is less favourable.

The same reasoning as the one leading to the introduction of SLNB has lead to questioning the need to perform axillary lymph node dissection (ALND) in all cases with SLN involvement.

Omission of ALND has been a trend in at least a subset of SLN-positive patients for several years, even before the publication of the results of the American College of Surgeons Oncology Group trial Z-0011. Recent guideline recommendations acknowledge that limited SLN involvement does not necessarily require ALND in all

patients, and suggest that there is no need for ALND if the SLN involvement is at most micrometastatic.

Nomograms devised for the prediction of non sentinel lymph node (NSLN) metastasis in patients with micrometastatic SLNs suggest over 30% risk of NSLN involvement at their extreme. Therefore, the omission of ALND in all micrometastatic SLN patients might be negligent. This is why follow-up data of patients with limited SLN involvement but no ALND is still important.

Compared to female breast cancer male breast cancer (MBC) is a rare disease representing less than 1% of all malignancies in men and only 1% of all incident breast cancers. Because of the low number of affected patients, treatment for MBC has been extrapolated from treatment protocols relating to breast cancer occurring in women. Mastectomy with axillary dissection is still the most commonly recommended procedure for MBC. There have been several reports on the use of SLNB in men, although the numbers of patients and length of follow-up have been limited.

2. AIMS

1. To analyze the role of selective ductectomy for the diagnosis and treatment of intraductal lesions presenting with single or rarely dual duct discharge and ductography suggestive of intraductal (papillary) lesions. To investigate the incidence of neoplastic proliferations or malignancy in this group.
2. To investigate in what percentage lymphoscintigraphy visualized IM-SLNs during the axillary SLNB (A-SLNB) operations performed in patients with invasive, clinically node-negative breast cancer. To analyze in what proportion the IM-SLNB was successful in these patients, what was the rate of metastatic IM-SLNs and what were the factors influencing the presence of metastatic involvement. To assess to what extent IM-SLN involvement led to a change in treatment.
3. To investigate the role of SLNB in MBC.

4. To assess the impact of omitting ALND in breast cancer patients with low volume SLN metastasis on locoregional recurrence and disease-free and overall survival.

3. PATIENTS AND METHODS

3.1

Files of patients presenting with single (or rarely dual) duct discharge and undergoing SD were evaluated in this retrospective analysis. Bilateral two-view-mammography, ultrasonography and ductography were performed in all patients. Nipple discharge cytology was evaluated in all cases. Surgical excision was recommended on the basis of suspected intraductal papilloma (IP) or other papillary lesions. SD was performed in the following steps. At the beginning of the operation, the nipple was compressed in order to visualize the duct with the discharge. One ml of Patent blue dye, was injected into the pathologic duct. Following this vital labelling of the duct, an infraareolar incision was made and the areolar flap was raised. The pathological duct was identified and the dyed 3 or 4 cm long part was removed with a small rim of surrounding breast tissue and oriented.

3.2

Between January 2001 and June 2012, 1542 patients with clinically node-negative operable primary breast cancer gave an informed consent and underwent SLNB. Except for pregnancy and T4 tumors, no patients were excluded. The preoperative diagnosis of breast cancer was established by mammography, ultrasonography and fine needle aspiration cytology (FNAC) or core needle biopsy (CNB) in all patients. Prior to surgery, axillary ultrasound (AXUS) was performed routinely and if suspicious lymph nodes were identified, FNAC was also done. When this revealed an axillary lymph node (ALN) metastasis, ALND was performed, whereas in case of negative cytology findings, A-SLNB was the staging procedure done. Lymphoscintigraphy was done in all cases. Two ml Patent Blue dye was injected

intraparenchymally above the tumor after the induction of general anaesthesia, 10–15 min before the incision. Harvesting both axillary and IM-SLNs was attempted in all patients, when visualized on lymphoscintigraphy.

The IM-SLNB technique can usually be performed using the mastectomy incision. In breast conserving operations, a small additional horizontal incision (2.5– 3 cm) over the desired interspace was used to sample IM-SLNs. The pectoral major muscle was exposed for 2 to 3 cm directly over the desired interspace. The muscle fibers were then separated to expose the posterior intercostal space. The external and internal intercostal muscles was divided transversely from the sternal border in a lateral direction for 3 to 4 cm. When cutting the internal intercostal muscle, particular care must be taken to avoid injury to the inferior parietal pleura or the internal mammary artery. Intraoperative identification of the A-SLNs and IM-SLNs was based both on blue dye mapping and gamma probe detection.

Statistical analysis for the comparisons included the chi-square test for categorical variables and the student t test for continuous variables. The significance level was set at $p<0.05$.

3.3

Twenty-five MBC patients were operated on between January 2004 and August 2013. At the beginning of the study period, mastectomy was performed with immediate ALND, without attempting SLNB. From 2004 the preoperative diagnosis of MBC was established similarly to breast cancer in women. When this revealed an A-SLN metastasis, ALND was performed, whereas in case of negative axillary findings, A-SLNB was the staging procedure done.

3.4

Patients were routinely offered SLNB from October 2000. The methods used were similar to those described in section 3.2., A-SLNs were removed following vital dye and radiocolloid labeling. Their pathological work-up included imprint cytology, step sectioning of the sliced SLNs and cytokeratin immunohistochemistry (IHC) at multiple levels. All patients with positive SLN findings on intraoperative or final

histology were offered ALND. Isolated tumor cells (ITCs) were considered negative nodal findings in this respect, according to the Tumor Node Metastases (TNM) recommendations, and patients with minimal nodal involvement belonging to this category were generally not offered ALND. Later a number of micrometastatic patients were also spared ALND, and a few patients with larger metastases also skipped completion ALND by not consenting to this operation.

Radiotherapy (RT) and systemic therapy was given according to national guidelines valid at the time of their management. Patients lost to follow-up within the first 12 months were not considered suitable for this retrospective analysis. The Kaplan-Meier survival estimates were used for overall, disease free and breast cancer specific survivals. Patients with SLN metastatic involvement not larger than 2 mm were analyzed for the risk of NSLN involvement with 3 nomograms devised for micrometastatic disease. A low risk of NSLN involvement was defined as a nomogram predicted risk not greater than 10%. Accordingly, a nomogram based risk of more than 10% was classified as high risk. Disease related events of patients classified as having high versus low risk were compared with the Fisher exact test, and the significance level of the two sided test was set at $p<0.05$.

4. RESULTS

4.1

The retrospective review of records between January 2004 and January 2011 revealed 100 patients with suspected intraductal papillary proliferations removed by ductectomy. Nipple discharge was the main clinical symptom in all of them. Mammography was normal in 83 cases and showed microcalcifications in 17 cases. Ultrasound described a mass in 23 cases. A single duct discharge was identified in 98 cases and dual duct excretion was seen in 2 cases.

Of the 100 patients presenting with single (dual) duct discharge and ductographic changes suggestive of intraductal (papillary) proliferations, 6 (6%) proved

to have malignant disease (4 in situ and 2 invasive carcinomas), further 10 (10%) were associated with neoplastic changes, atypical hyperplasia found in 5 and around 5 of them. The initially performed selective ductectomy was complemented in 6 proved malignant cases with Radioguided Occult Lesion Localization (ROLL) and breast conserving surgery plus SLNB. The SLNs were negative in all cases.

4.2

IM-SLNs were visualized on preoperative lymphoscintigraphy in 83 of the 1542 patients (5.4%) who had an attempted A-SLNB between January 2001 and June 2012 and IM-SLNB was successful in 77 cases (93%). The IM-SLN stained blue in only 11 patients (14%). A total of 86 IM-SLNs were dissected (mean1.1). IM-SLN involvement was identified in 14 cases, i.e. 18% of the patients who underwent IM-SLNB. This included macrometastases (MAC) in 5 cases, micrometastasis (MIC) in 2 cases, ITC in 7 cases. Axillary involvement was found in 16 cases (20% of the 77 patients) and consisted of ITC in 3 cases, MIC in 6 and MAC in 7. In 10 cases (13% of the IM-SLNB patients) the IM-SLN was involved without A-SLN involvement. Of these patients, the IM-SLN involvement has lead to new therapeutical indications in 2 cases (3% of all IM-SLNB patients), both of them due to MAC in the IM-SLN. One patient had a change in chemotherapy and one had a change in RT with the addition of irradiation of the IMC. Median follow-up time was 46 month (range: 2–121 month).

IM-SLNB had few complications. Out of the 83 patients in whom IM-SLNB was attempted, minor complications were seen in 8 cases (9.6%). There was one major complication (1.2%): a retrocostal leak of the IM artery requiring partial resection of two adjacent ribs to allow its restauration. The latter patient is well and alive with no evidence of disease after 12 months of follow up at the time of writing.

4.3

A total of 25 consecutive MBC patients were included in this review. Sixteen of them (64%) had SLNB. The SLNB was successful in all cases. The remaining 9

patients (36%) had primary ALND. The only significant difference between patients with SLNB or ALND was in tumor size with larger tumors in ALND patients. Breast conserving surgery was performed in only 1 patient.

All patients underwent mastectomy in the ALND group (n = 9). Preoperative AXUS was used in 5 patients (55%) and it showed pathologic lymph nodes in 2 cases. There was no axillary metastasis in 3 cases (33%). The median follow-up in this group was 5 months (range 1–84). Four patients died due to distant metastases and the progression of the disease after one, three, five and seven postoperative years, respectively.

All male patients patients undergoing SLNB (n = 16) had a negative axillary status on physical examination. Preoperative AXUS was used in 12 patients (75%) and it was negative in all of them. Preoperative lymphoscintigraphy was performed in all 16 patients. Of the 16 cases with successful SLNB, the SLN was involved in 12 patients (75%); 9 patients had MAC, 2 patients had MIC, and 1 patient had ITC. In the case of SLN ITC, we could not find NSLN involvement. In the MIC group, we found NSLN involvement in one of the 2 patients. In the MAC group, NSLN involvement was present in 4 of the 9 patients.

The median follow-up time in the SLNB group was 68 (range: 6-137) month. None of the patients who underwent SLNB alone had an axillary recurrence during this time. Five of the 16 SLNB patients of this study died, one of distant metastases of breast cancer in the lung five years after the operation, and four of unrelated causes. The median follow-up time for all 25 patients was 48 (range: 1–140) months. Finally, ALND was performed in 21 patients.

4.4

Between October 2000 and December 2012, 111 patients with demonstrated SLN involvement did not undergo an ALND and had at least 12 months of follow-up. The majority of the patients had only ITC involvement of the SLNs, but 30% had MIC and 2 patients had metastasis larger than 2 mm. All patients undergoing breast

conserving surgery had adjuvant whole breast irradiation complemented with boost irradiation when the margins were close.

Axillary RT was given to 29 patients (9 with SLN ITC, 19 with SLN MIC and 1 patient with axillary MAC). Systemic therapy involved hormonal therapy (HT) in 75 patients, chemotherapy in 13 patients, and their combination in 19 patients. Seven patients with human epidermal growth factor receptor 2 (HER-2) positive tumors also received trastuzumab as part of their adjuvant treatment.

The median follow-up was 37 (range: 12-148) months. During this period, 6 patients died, 3 of disseminated disease with multiple distant metastases, and 3 of unrelated causes. All the 3 patients who died of disease had only ITC category SLN involvement. Eight further patients had breast cancer related events: 1 local breast recurrence in a patient with initial ITC involved SLN, managed surgically with repeated SLNB and 2 negative SLNs, and 7 distant metastases. Of the latter patients with distant metastasis, the SLN originally harboured ITCs (n=3), MICs (n=3) and MACs (n=1). No axillary regional recurrence was detected in any of the 111 patients. The 5-year estimates for disease free survival, overall survival and breast cancer specific survival were 85.7% (standard error, SE: 0.06), 100% (SE: 0.0) and 100% (SE: 0.0), respectively.

The used nomograms predict for further nodal involvement beyond the SLN, but since there were no regional recurrences, local and distant relapses were analyzed in this setting. There was no significant difference in the rate of relapse in patients classified as having a high or a low risk of NSLN metastasis, independently of the nomogram or predictive tool used.

5. DISCUSSION

5.1

Although nipple discharge is a relatively common symptom and is usually benign in origin, it can also be a feature of intraductal carcinoma of the breast (DCIS).

On the basis of previous reports, the incidence of DCIS in patients with nipple discharge varies from 1% to 16%. In our hospital, the general work-up of single duct discharge through the nipple includes mammography, ultrasonography, ductography and discharge cytology. Image guided FNAC or CNB are also used for cases with identifiable mass lesions. When these examination suggest intraductal proliferations (papillomas in general), SD, a conservative surgical excision of limited extent was our method of choice for diagnosing and treating the lesion behind the symptom. When malignancy was proven preoperatively, breast conserving surgery with the ROLL technique or mastectomy with SLNB were advocated. In six cases, malignancy was discovered in the surgical specimens removed by SD and initiated a second operation in all but one patient who had a mastectomy in a third step.

Our data suggest a 6% (95% CI: 3–12%) in situ or invasive malignancy rate for patients presenting with single rather than multiple duct discharge, and a suspicion of intraductal proliferation (papilloma) on ductography. For the histopathological entity 10 patients had precursor neoplastic lesions, atypical ductal hyperplasia, atypical papilloma or lobular intraepithelial neoplasia. The rate of neoplastic changes was 10%. Therefore, the clinical presentation we discuss in our series was associated with neoplastic epithelial changes in 10 cases and 6 cases were associated with DCIS or invasive carcinoma.

Whether surgery is needed for a disease or a symptom associated with such a low incidence of malignancy, and low grade neoplasia in general can be questionable. However, after meeting the patients, it became clear, that nipple discharge can be very unpleasant and this minimal diagnostical operation promptly cease the symptom. Considering the possibility of the oncological overtreatment (94% of the patients had no malignant lesion, and the importance of the four in situ carcinomas is unclear) it is very important to inform the patients about the magnitude of the risk of malignancy.

5.2

IMC lymph node dissection was part of the standard surgical treatment in some centers in the 1950s and 1960s. This radical surgical procedure was abandoned in the

1970s because patient outcome studies showed that radical dissection did not improve survival.

Since the introduction of SLNB, there has been a renewed interest in the IM-SLNs. As a consequence, IM-SLNB can refine staging in breast cancer patients and offers the possibility of providing tailored treatment in cases of proven metastases to the IMC. The rate of identification of SLNs in the IM region is generally lower than in the case of A-SLNB. IM-SLNB is not performed routinely, as opposed to A-SLNB, because many breast surgeons have concerns about the rate of complications of the procedure, due to the lack of technical expertise and familiarity with the route of access. In our series the success rate of A-SLNB was 96% and that of IM-SLNB was 93%.

The overall risk of IM-SLN metastasis in breast cancer patients is well known and reported to be 18–33%. Metastases exclusively situated in the IM nodes, without concurrent axillary metastases, occur in 2–11% of patients. In our study, no significant differences were found between patients with and without IM-SLN involvement in terms of age, tumor location, tumor size, axillary involvement, tumor grade or estrogen receptor (ER) status.

A possible role of nodal positivity detected by IM-SLNB may be the indication of more aggressive systemic treatment in axillary node-positive patients. Adjuvant locoregional RT has proven to be beneficial after mastectomy, but the contribution of radiation to the IMC to improve survival and recurrence rates is still unclear. Although RT of the parasternal region does not seem to improve survival, the value of this treatment in IM-SLN-positive patients detected by IM-SLNB has not been assessed in prospective studies.

As for today, there is insufficient data to determine a positive effect of parasternal radiotherapy on survival in patients with proven IM metastases. The systemic treatment strategy was rarely influenced by IM metastases in this series of patients. Due to axillary metastases and unfavourable primary tumor characteristics, a lot of patients would have already received adjuvant chemotherapy and even more of them would have had adjuvant HT.

Adjuvant chemotherapeutic treatment and IMC irradiation is however indicated when a tumor-positive IMC lymph node is found. IM-SLNB may be associated with some additional morbidity in about 3–10% of the cases, according to the literature: pleural lesions or injury of the IM artery. Recovery is usually uneventful in the case of pleural lesions, after simple vacuum drainage. The injury of the IM artery poses more serious challenges. In our study we recognized minor complications in 8 cases (9.6%), and one major complication (1.2%) also occurred. Recovery was uneventful in both the minor and the major complication group.

On the basis of recent publications, arguments for performing IM-SLNB are the following:

It helps the correct staging of patients with breast cancer, IM-SLN involvement is a prognostic factor. In case of IM-SLN-positive patients, the treatment can be altered (chemo- or radiotherapy). Studies evaluating the effect of the IM-SLNB on the treatment strategy in patients with an IMC drainage pattern report a change of treatment in 2–9%. Since adjuvant systemic treatment in this small but substantial patient group is likely to improve prognosis, authors of these studies recommend routine biopsy of IM-SLNs.

There are also arguments against IM-SLNB, and these are listed as follows:

IM-SLN metastases occur only in a small proportion of patients undergoing SLNB. Overall, isolated IM-SLN involvement is rare (2–9%). If the A-SLNs are negative, then IM-SLNs are also negative in 41%–57%. The IM node status resulted in a change of the adjuvant treatment plans in only 3% of the patients

The impact of IM-SLNB on altering adjuvant systemic therapy was relatively small in our series. We have found IM-SLN involvement in 14 cases, which represents 18% of the patients who underwent IM-SLNB, but in 7 cases, only ITC were found, and these are not considered metastasis at present. Neither ITC, nor MIC nor MAC of the IM-SLN has lead to further surgical therapy. Micrometastases in A-SLNs or IM-SLNs were not an indication for adjuvant chemotherapy. In our series, only 1 patient received RT to the IMC, and a new indication for chemotherapy was also established in only 1

patient because of MAC of the IM-SLN. Therefore in our series consisting of 77 patients, only 2 of the IM-SLNB patients (2.6%) had therapeutic consequences.

5.3

The majority of MBC patients undergo mastectomy because of the small breast size and subareolar location of most malignancies. Because of the low incidence, treatment for breast cancer in men has been extrapolated from the experience of treatment of breast cancer in women, without the benefits of randomized trials.

Since the experience was published in 2004, SLNB has been routinely offered to all male patients with breast cancer and clinically negative axillary nodes, according to the standard policy applied to women with breast cancer at the European Institute of Oncology, Milan, Italy. Frequently, breast cancer in men is diagnosed at an advanced stage, making SLNB inappropriate, but still a considerable proportion of patients present with a clinically negative axilla, therefore making them candidates for a less invasive method of axillary staging. At the beginning of the study period, mastectomy was performed with immediate ALND, without attempting SLNB. The reasoning behind this policy was as follows: the size of tumors in males is typically larger compared to females, larger tumors are more often accompanied by lymph node metastases, and there were insufficient data on the role of SLNB in male patients. This approach was used in 9 patients.

The final histological examination of the ALND specimen proved a negative nodal status in 3 of them. In our experience, 4 of 16 patients (25%) who underwent SLNB were spared an unnecessary axillary dissection. Should SLNB been performed in all male patients with clinically negative axillae, 3 further men could have been spared the potential morbidity of ALND, and this rate could have been 7/25.

If an SLN is positive for metastatic disease, complete ALND has been recommended. Owing to the relatively high rate of nodal involvement, intraoperative SLN examinations are of value. Compared to female patients, a larger proportion of

male patients (75%) have positive nodes, but for patients with clinically negative nodes, SLNB may reduce morbidities associated with ALND.

5.4

The involvement of NSLNs is influenced by several factors among which the size / degree of the SLN involvement is one of the most important. Low-volume SLN metastases of the micrometastatic category are associated with NSLN positivity in 10-15% of the cases, a proportion which is confirmed by the data of recent clinical trials, but depending on the combination of several factors, this may double or triple in a minority of patients . In this respect, ITCs do not seem much better, as on average, they are suggested to be associated with NSLN involvement in about 12% of the cases according to a meta-analysis.

It must also be remembered that until recently, the distinction between ITC and MIC by pathologists was far from perfect. Taking all this together, analyzing patients with SLN MIC or ITC together makes sense. Although current trends favor the omission of ALND in many patients with minimal SLN involvement including all with SLN MIC, this approach may ignore a small minority of patients who could potentially benefit from further axillary treatment. This makes follow-up studies of patients with involved SLNs but no ALND important.

One of the first studies of the kind reported no axillary recurrence for a selected group of SLN micrometastatic patients with favorable prognostic profile during a median follow-up period matching the present one. Likewise, this series also included mainly patients deemed to have a low risk of further nodal involvement, including many with SLN ITC only. Unlike in other studies, some patients with omitted ALND and receiving RT to the breast following breast conservation, also got irradiation of the axillary region, which we believe to constitute an overtreatment in patients with low risk of axillary NSLN involvement. In keeping with the results of the first similar report,

no axillary recurrence occurred during the follow-up period, but 11 breast cancer related events were noted, including 3 deaths from metastatic disease.

The results of clinical trials looking at the safety of omitting ALND in patients with minimal SLN involvement, also point to a very low rate of axillary recurrence after a somewhat longer median follow-up, and the occurrence of local (in breast) and systemic disease recurrence. This seems unrelated to the manifestation of recurring axillary cancer, and also to the predicted risk of NSLN involvement on the basis of predictive tools devised for low volume SLN metastasis patients.

6. CONCLUSIONS

6.1 Single duct nipple discharge with no obvious mammographic or ultrasonographic lesions, but a ductographic finding suggestive of intraductal proliferation was associated with malignancy (most of the time in situ carcinoma) in 6% of the cases and atypical hyperplasia in further 10% of the cases. For such a low risk and generally low grade of malignancy, simple follow-up could be offered from a surgical and an oncological point of view, but in some cases, considering the patients' request to get rid of the symptoms, SD could be applied. Whenever associated mass lesions or microcalcifications are identified, these require separate work-up, including non-operative guided biopsies or surgical excisions for both high risk lesions on non-operative diagnostics and lesions with inconclusive non-operative assessment. Our retrospective analysis suggests that SD is well tolerated, has no major complications and might be a realistic diagnostic and therapeutic approach in the clinical situations described above.

6.2 Based on our own series and information from the literature, we conclude that the indication for an IM-SLNB procedure is very limited, and its routine use should not be recommended. A failure to identify an A-SLN is an indication for ALND in general, but it is felt that if there is no lymphatic drainage towards the axilla on lymphoscintigraphy, and even vital dye guided A-SLNB fails to identify an A-SLN, but an IM-SLN is visualized on the lymphoscintigram, IM-SLNB could be considered

for nodal staging, and the omission of ALND could also be envisaged. In the studied setting, the data point more to abandoning routine IM-SLNB in patients with IMC drainage and potentially restricting its use to a very small subset of patients.

6.3 We conclude that SLN operations in male patients with clinically node-negative BC are feasible and accurate, and appear to be an appropriate alternative to routine ALND. Intraoperative evaluation of the SLN should be strongly considered in the surgical management of MBC patients.

6.4 The presented retrospective data suggest that omitting ALND in patients with low volume SLN metastasis may be a safe procedure, and support the observation that systemic disease recurrence may not be associated with axillary recurrence or the risk of NSLN involvement predicted by nomograms.

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