Lymph node procedure controversies in breast cancer patients

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LYMPH NODE PROCEDURE CONTROVERSIES IN BREAST CANCER PATIENTS

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Abbreviations:

ALND – Axillary Lymph Node Dissection

BCS – Breast-Conserving Surgery

DCIS – Ductal Carcinoma In Situ

FNAC – Fine-Needle Aspiration Cytology

FNR – False Negative Rates

IBC – Inflammatory Breast Cancer

IDC – Invasive Ductal Carcinoma

ITC – Isolated Tumor Cell

IMN – Internal Mammary Nodes

LABC – Locally Advanced Breast Cancer

LS – Lymphoscintigraphy

NACT – Neoadjuvant Chemotherapy

SLN – Sentinel Lymph Node

SLNB – Sentinel Lymph Node Biopsy

SPECT - Single-photon Emission Computed Tomography

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1. Abstract

Title: Lymph Node Procedure Controversies in Breast Cancer Patients

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Axillary lymph node status is a major prognostic factor in early-stage breast cancer. It provides information important for the following surgical procedures. Since imaging techniques have limited sensitivity for the detection of metastasis in axillary lymph nodes, the axilla must be surgically explored. The histology of all resected nodes at the time of axillary lymph node dissection (ALND) has traditionally been regarded as the most accurate method for assessing metastatic spread to regional lymph nodes. However, ALND is often connected to life-quality-reducing side-effects such as lymphedema, dysesthesia, shoulder dysfunction, and other short-term and long-term complications. Sentinel lymph node biopsy (SLNB), introduced in the 1990s, was a milestone that permitted avoidance of axillary dissection if the sentinel node was disease-free. SLNB is less invasive and it has been verified that there is decreased morbidity and less negative side-effects when compared to axillary lymph node dissection (ALND). SLNB relies on the notion that tumor drains in an orderly manner through the lymphatic system. The sentinel lymph node (SLN) should, therefore, be first affected, and a tumor-negative SLN makes it highly unlikely for the other lymph nodes to be affected.

SLNB has been established as the gold standard for regional axillary staging. Its use in breast cancer has been evaluated in several randomized controlled trials and validated in multiple prospective studies. However, even today, there are some unresolved questions concerning SLNB and ALND that are still being debated.

2. Sažetak

Naslov rada: Kontroverze kod operacija na limfnom sustavu kod bolesnika s karcinomom dojke
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Status aksilarnih limfnih čvorova je važni prognostički faktor kod raka dojke u ranom stadiju. Pruža informacije važne za daljnje kirurške procedure. S obzirom na to da tehnike snimanja imaju ograničenu osjetljivost za detekciju metastaza u aksilarnim limfnim čvorovima, aksila zahtjeva kiruršku eksploraciju. Histologija svih reseciranih čvorova za vrijeme disekcije aksilarnih limfnih čvorova (ALND) je tradicionalno bila smatrana kao najpreciznija metoda utvrđivanja metastatskog širenja u regionalne limfne čvorove. Međutim, ALND često povezujemo s ozbiljnim nuspojavama kao što su limfedem, disestezija, disfunkcija ramena i ostale kratkoročne i dugoročne komplikacije. Biopsija limfnog čvora stražara (SLNB), uvedena 1990-ih, predstavlja prekretnicu koja je omogućila izbjegavanje aksilarne disekcije ako je čvor stražar bez bolesti. SLNB je manje invazivna i potvrđeno je da nosi manju smrtnost i manje nuspojava u usporedbi s disekcijom limfnih čvorova aksile. SLNB se oslanja na ideju da se tumor širi po redoslijedu kroz limfni sustav. Limfni čvor stražar (SLN) je, prema tome, prvi zahvaćen i tumor-negativni SLN ukazuje na malu vjerojatnost da su ostali limfni čvorovi zahvaćeni. SLNB je uspostavljen kao zlatni standard regionalnog aksilarnog stupnjevanja. Korisnost kod raka dojke je procijenjena kroz nekoliko randomiziranih kontroliranih pokusa i potvrđena u višebrojnim prospektivnim istraživanjima. Međutim, postoje neka nerazjašnjena pitanja u pogledu SLNB i ALND oko kojih se i danas debatira.

3. Introduction

Axillary nodal status is a significant prognosticator in breast cancer patients, next to tumor size and grade. It provides information important for individualized surgical treatment. Sentinel lymph node biopsy (SLNB) has been established as the gold standard for axillary staging, surpassing axillary lymph node dissection (ALND) which has traditionally been regarded as the most accurate method for assessing the metastatic spread of disease to regional lymph nodes. SLNB provides adequate nodal staging information while sparing the patient the increased risk of complication associated with ALND, such as lymphedema, dysesthesia, and motor deficit. More than 20 years after its introduction, questions concerning SLNB and ALND are still debated. Furthermore, SLNB remains an unstandardized procedure, surrounded by controversies including those concerning the technique itself. In this article, we review the main indications, contraindications, and controversies surrounding the techniques and procedures in SLNB and ALND.

4. Radiopharmaceuticals

Several Technetium-99m (99mTc)-based tracers are used for radioguided detection of SLNs in breast cancer (1). According to the size of the particle, the drainage, distribution, and clearance of radioactive colloids vary. Smaller particles reach SLNs sooner but also clear quicker. Large particles are drained and cleared last but may be retained longer. There is a general agreement that a good radiocolloid should exhibit a right balance between optimal lymph node retention and fast lymphatic drainage (2,3). The timing of the preoperative scintigraphy also depends on the size of the particle. SLNs are generally visualized within 1-2 h, and the patient should be in the operating room 2-30 h from the injection of the radiocolloid (2,4,5). However, studies have shown that the result and success are not significantly affected by the particle of choice (6–8). That means that the selection of the tracer probably depends more on the availability in a particular facility than on differences in characteristics. Hypersensitivity reactions to radiopharmaceuticals have been reported but are rare.

5. Modalities of radiocolloid injection

Anatomical and physiological knowledge is useful when considering the appropriate sentinel lymph node biopsy technique. The transmural pressure gradient in lymph vessels can be influenced by the fluid volume, so it is important that patients enter the operating theatre in a well-hydrated state. Administration of ample fluid increases the probability of finding a sentinel lymph node. The volume of the injected radiotracer is also a subject of debate, however, detection rates are good with both smaller and larger amounts. Massaging the injection site is also useful since external pressure

stimulates lymphatic flow. Humoral and neural mechanisms play a role, but they are beyond our control. Anesthetics can hamper the intake of dyes, and halothane has shown to decrease lymph flow by 25% to 59% (9). The size of the injected particle also matters. Smaller particles allow the visualization of channels leading directly to the sentinel node; however, they could move on to lodge in secondary nodes. With larger particles, the channel is visualized less often, but the chance to go to secondary nodes is lower. It is estimated that the ideal size would be somewhere between 10 and 100 nm (1). The main topic of controversy is the site of injection. Despite numerous research starting from the 18th century, the lymphatic drainage of the breast has still not been completely elucidated. Ludwig (10) demonstrated two types of lymph node and lymph vessel relations. The first type is an afferent duct that drains into the node where the lymph is filtered and then discharged into the efferent channel. In the second type, the afferent duct can pass through or along the nodal surface without discharge into it. This could be one of the reasons for a false- negative sentinel lymph node. It is accepted that drainage from the breast can occur to lymph nodes at a number of different sites, and the consensus is that the axilla is the main basin for drainage from the breast. Subcutaneous contralateral drainage is unlikely to occur unless the ipsilateral drainage is impaired by a mass, previous surgery or radiation. Retrosternal contralateral drainage occurs sporadically. Subcutaneous drainage to the contralateral axilla is unlikely to occur unless the ipsilateral drainage is impaired by lymphatic obstruction caused by tumor growth, previous surgery, or irradiation (11). We can divide the injection sites into two types: superficial (intradermal, subdermal, periareolar, subareolar) and deep (peritumoral, intratumoral). The superficial group relies on the hypothesis that the breast and overlying skin share the same lymphatic drainage since the mammary glandular tissue derives from the ectoderm (12).

Lymphatic density is greater in the skin than in the breast parenchyma so the tracers clear more rapidly. Despite the appeal of intradermal injection techniques, there is still insufficient evidence that the lymphatic drainage of the skin reflects drainage from cancer. A superficial injection technique may be good for sparing patients without lymph node metastases in the axilla and unnecessary axillary node dissection. A deep injection technique could be useful for determining the stage of the tumor and the identification of sentinel lymph nodes elsewhere.

6. Preoperative imaging

Nuclear medicine offers assistance in SLN visualization (13,14). Lymphoscintigraphy (LS) can improve accuracy and reduce surgical morbidity (2,15). In order to avoid confusion between SLNs and stasis of the radiocolloid in ducts, there should be an appropriate time window between injection of the pharmaceutical and the procedure. Other variables should be taken into account; for example, in elderly or overweight patients, the lymphatic drainage can be slower. A combination of views helps better detection of SLNs in planar LS. The main basin for breast lymphatic drainage are the axillary lymph nodes. In some cases, however, alternative pathways may occur. Drainage to the internal mammary chain occurs in up to 20% of patients, intramammary (prepectoral) in 6%, interpectoral in 2%, and infraclavicular in 3% (16). Therefore, an additional second radiocolloid injection could improve visualization of SLNs. Intraoperative blue dye is recommended in case of failed identification (17). SPECT/CT has proved to be beneficial in several ways. It can provide a more precise anatomical location and potentially shorten the duration of the surgical procedure. False positives on planar imaging have been detected. Alterations

in surgical plans have been made in patients with nonvisualization on planar imaging (18). Ultrasound is another modality that could yield benefit in preoperative imaging. The presence of adipose tissue in the axillary cavity may represent a limitation. However, simple handling, increasing expertise, low costs, absence of radiation, and the use in conjunction with Fine Needle Aspiration and Cytology (FNAC) make it an attractive option for assessment before surgery.

7. Intraoperative imaging

International guidelines lack a unique definition for surgical detection of radioactive SLN. Some data suggests that all blue staining nodes should be harvested for optimal staging (19–21). There have been several operational definitions of the SLN, with the goal to better decide exactly which nodes should be removed to maximize the probability of locating the “true” biologic SLN and to reduce the unnecessary removal of multiple non- SLNs. Some authors base SLN identification on the absolute number of counts in the nodes, whereas others consider the ratio of the in vivo or ex vivo radioactive counts in the SLNs relative to background or to neighboring non-SLNs (22). It is reported that all blue nodes and all nodes that show 10% or more of the ex vivo radioactive activity of the hottest sentinel node should be harvested for optimal detection of metastases (23). Intraoperative detection of SLNs is usually radio guided by a γ-probe. Recently, various portable γ-cameras have been developed to provide an overview of the radioactive “hot nodes" so as to verify the completion of SLN excision (24,25). These new portable technologies are generally oriented to better localize surgical targets in complex anatomical areas. Recent advancements include the combining of the conventional γ-probes with position and orientation tracking

systems such as the so-called free-hand SPECT, which permits a virtual reconstruction in a 3-dimensional environment. All these technologies will play an increasing role in the future extension of the Guided Intraoperative Scintigraphic Tumor Targeting (GOSTT) concept to provide a more precise plan for radio-guided surgery (26,27).

8. Internal Mammary Chain

The internal mammary nodes (IMNs) are, the same as the axilla, a first echelon nodal drainage site in the breast. They are, however, rarely the primary site of occurrence and randomized trials have not demonstrated a survival benefit from internal mammary chain dissection (28–34). The Early Breast Cancer Trialist's Collaborative Group has given high levels of evidence that post-mastectomy radiotherapy to the chest wall and nodal basins (including IMNs) reduces recurrence and breast cancer mortality in women with one to three positive lymph nodes, even with systemic therapy (35). It is necessary to define patients who may benefit from this irradiation since cardiac and pulmonary toxicity of lymph node irradiation is well known. The indication of internal mammary chain irradiation depends on the benefit to risk ratio (36). Lymphoscintigraphic studies have shown that approximately 30% of medial tumors and 15% of lateral tumors have a primary drainage to IMNs. Studies using IMN biopsy showed that 20% of sentinel IMNs were metastatic (37). IMN metastases have a prognostic significance and seem to have similar prognostic importance as axillary metastases, which lead to their inclusion in the American Joint Committee on Cancer Staging Criteria (17,38). IMN evaluation is not routinely performed, one of the reasons possibly being the difficulty to demonstrate IMN drainage. Peritumoral

radiocolloid injection under ultrasound guidance, as well as an adequate learning curve of the team, could lead to satisfactory IMN visualization (39). The fused SPECT/CT images could increase the identification rates and consequently reduce the FNR of the technique.

9. Ductal Carcinoma In Situ

Ductal Carcinoma In Situ (DCIS), also known as intraductal carcinoma is a precursor, non-invasive lesion. Abnormal epithelial cells are found in the lining of the terminal lactiferous ducts (40). "In situ" refers to the fact that the cells are confined within the basement membrane of the ducts. Invasive ductal carcinoma (IDC) is the ultimate result of the sequential progression of hyperplasia, atypical ductal hyperplasia, and DCIS. The progression to IDC will occur in 13% to 50% of cases (41). DCIS - associated mortality is low with the expected cumulative breast cancer mortality ten years after DCIS estimated to be 2.3% for women younger than 50 years of age and 1.4% for women younger than 50 years of age after treatment (42). The incidence of DCIS has increased in the last 20 years as a result of increased screening by mammography (43). Controversies surrounding DCIS pertain to avoiding undertreatment and overtreatment. SLNB is not recommended for patients with DCIS at biopsy, except when mastectomy is planned (44). It could also be considered in women treated with breast-conserving surgery (BCS) with a high risk of invasive cancer at final diagnosis - palpability of the lesion, presence of a mass on mammography, and calcifications without a mass (spread, ≥5 cm) (44,45).

10. Large tumors and locally advanced or inflammatory breast cancer

Evidence regarding the efficacy of sentinel lymph node biopsy is widely based on studies done on T1 and T2 tumors. Reports suggest that FNR and axillary recurrence in larger tumors are similar (20). The updated American Society of Clinical Oncology (ASCO) guidelines from 2016 recommend against SLNB in T3 breast cancers (44). However, data from non-randomized studies suggest that SLNB is accurate in patients with T3 cancers and a clinically negative axilla (46). In most breast cancer centers, SLNB is considered acceptable in cT3N0 patients. In locally advanced (LABC) or inflammatory breast cancer (IBC), SLNB is not routinely recommended. This is based on the hypothesis that locally advanced or inflammatory changes may yield unacceptable FNRs of sentinel node retrieval (44). In patients with non-inflammatory LABC who have an excellent clinical and radiological response to neoadjuvant chemotherapy (NACT), SLNB instead of ALND may be considered and is moderately recommended by the most recent edition of the National Comprehensive Cancer Network (NCCN) guidelines (47). In order to increase the sensitivity and accuracy of the procedure, at least 3 SLNs should be retrieved and complete ALND is advised even if only one SLN is found to be positive (48,49).

11. Pregnancy

Pregnancy is not an absolute contraindication to SNLB. Certain conditions involving host factors, as well as tumor biologic characteristics, may have negative impacts on the overall success of the procedure (50). However, according to multiple studies, the prenatal doses from LS and SLNB are low enough to not significantly increase the risk of radioactivity-induced effects such as malformation, mental impairment, or death (51–53). It is recommended to reduce the time interval between LS and surgery (by using a single-day protocol) to reduce the injected activity. Lactation should also be suspended for 24 hours after administration of the radiopharmaceutical since small quantities could be excreted with breast milk (20). The current consensus is that radiocolloid mapping is the preferred method as fetal exposure to isosulfan blue may have an effect on the fetus in the first trimester and could cause an anaphylactic reaction in the mother. Severe anaphylaxis is rare. In selected patients with unclear radiocolloid mapping, however, the use of blue dye may be safe in the second and third trimester. Careful monitoring must be performed during anesthesia (51). It is not always possible to find a good balance between the maximum benefit to the mother and minimal harm to the baby, and it takes a multidisciplinary approach to find the right solution (54).

12. SLNB in multisite BC

It has been suggested that drainage from different primaries in the same breast may complicate and impair sentinel node identification and lead to suboptimal axillary staging. However, studies have not shown a difference in axillary recurrence or

survival between patients with unifocal and multisite disease (55,56). An unplanned subgroup analysis in the ALMANAC trial did not show lower FNRs or lower identification rates in SLNB performed for multifocal as opposed to SLNB performed for unifocal lesions. In the AMAROS trial, the identification rates for multisite and unifocal breast cancer were 96% and 98%, respectively. The difference was not statistically significant (57). Currently, SLNB appears to be a feasible and safe option for patients with multiple breast cancer.

13. Suspicious palpable axillary nodes

Palpable axillary nodes may be tumor negative in up to 40% of cases. The widely accepted practice for assessment is preoperative axillary ultrasound scan with fine-needle aspiration cytology or core-needle biopsy of the palpable node. Another accepted practice is to perform SLN biopsy if palpable nodes are negative following preoperative evaluation. Palpable nodes should be harvested and histopathologically evaluated, even when neither hot nor blue (20).

14. Previous surgery

Lymphatic drainage is usually changed in patients who have undergone breast surgery. Nonaxillary drainage has been identified more often in reoperative SLNB than in the primary setting. There is evidence that a successful SLNB can be performed in proximity to the site of the previous biopsy. SLNB can be performed following local recurrence after breast conservation in DCIS patients. Plastic surgery with breast reduction or augmentation is not a contraindication for SLNB. According

to the ASCO guidelines, SLNB is feasible and has acceptable accuracy in patients who have undergone prior nononcologic breast/axillary surgery (44).

15. Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy (NACT) is established for locally advanced breast cancer and is increasingly used for early-stage disease as well (58). The timing of axillary surgery in the neoadjuvant setting is controversial. According to the ASCO guidelines, SLNB may be offered before or after NACT, but the FNR is higher afterward (44). Indications for NACT include tumor downsizing to increase breast tissue conservation, conversion of large unifocal tumors requiring mastectomy to smaller ones manageable with breast-conserving surgery (BCS), and making large, locally advanced or inflammatory cancers operable (59). The idea of SLNB instead of ALND in patients receiving neoadjuvant chemotherapy was controversial (60). Sentinel lymph node biopsy performed after NACT may lead to underestimation of the initial stage of the disease because lymphatic drainage from the breast could be impaired and also because the tumor regression pattern in the axilla is unknown. There was a concern for high false negative rates due to tumor emboli and chemotherapy-induced fibrosis, causing a non-uniform response across the axillary nodal basin.

15.1. SLNB after NACT (cN0 patients at diagnosis)

Subsequent studies proved SLNB after NACT in node-negative patients reasonable, and FNR is comparable to pre-chemotherapy SLNB. In the GANEA study, among the 130 patients with cN0 disease, the SLN identification rate was 95% with an FNR of 9% (61). A study from MD Anderson Cancer Center looked at 3171 cN0 patients who underwent SLNB before and 575 cN0 patients that underwent SLNB after NACT. The results were similar between the pre-chemotherapy and post-chemotherapy SLNB - identification rate 99% and 97%, FNR 4% and 6% respectively (62). Meta-analyses involving more than 5000 patients showed SLN identification rates from 90% to 94% and FNRs from 7% to 12% in treatment with SLNB after NACT (63). Currently, SLNB in the clinically node - negative patient is recommended after NACT, given that clinical palpation and imaging suggest no evidence of progression and the nodes remain clinically normal. Other trials are in progress to further address the need for ALD in node-positive patients after NACT (64).

15.2. SLNB after NACT (cN+ patients at diagnosis)

The GANEA study included 65 cN+ patients who underwent SLNB after NACT and back-up ALND after NACT. The SLNB identification rate was 81.5%, and the FNR was 15% (61). The SENTINA trial looked at patients who converted from cN+ to cN0 following NACT. The SLN identification rate was 80% and FNR 14%. Three subgroups with 3 or more, 2, and only 1 lymph node harvested showed FNRs of 7%, 19%, and 24%, respectively (49). In the ACOSOG Z1071 trial, the pre-defined FNR was set to 10%, but the conversion from cN+ to cN0 was not mandatory, and only

patients with more than 2 harvested lymph nodes were included. The FNR was 13%, but an unplanned exploratory analysis showed that with 3 or more harvested lymph nodes, the FNR dropped to 9% (65). The SN-FNAC study also followed cN+ patients who underwent SLNB post-NACT. Immunohistochemical detection of isolated tumor cells (ITCs) was mandatory. The FNR was 8% when patients with ITCs after NACT were considered node- positive, and the FNR was 13% when they were considered node-negative (66). A Swedish group reported results of 195 node-positive patients who underwent SLNB after NACT. The FNR was 14% but dropped to 4% when 2 or more SLNs were harvested (64). To summarize, the studies demonstrated SLNB to be feasible if there is a good clinical and radiological response to NACT. It is important to note the fact that FNRs are unacceptably high unless 3 or more nodes are harvested (49,65–67). SLNB after NACT for cN+ patients is implemented in the last edition of the NCCN guidelines as a Level 2b recommendation(47).

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18. Biography

I was born in Zagreb, Croatia, on May 20, 1993. My father Dražen Ileković is an economist and mother Antoaneta Ulaga - Ileković, a tourism worker. I grew up in Zagreb, where I finished both primary and high school (Private Classical Gymnasium).

Since I was a small child, I have been training and competing in various sports, most notably football and wrestling. My affection for competition is still allive, and I still actively participate in wrestling.

After finishing gymnasium, medicine prevailed over architecture, and I enrolled in the English program at the Medical School in Zagreb. Apart from the obligatory clinical curricula, I regularly did summer rotations at the Department of Cardiosurgery at Clinical Hospital Center Dubrava. In the summer of 2018, I was part of a team that provides medical care in overlooked remote areas called Team5. We offered help to the indigenous people of Guatemala. In 2019 I finished my medical school education by doing my clinical rotations in Zagreb at the Department of Emergency Medicine and the Department of Surgery at Zagreb University Hospital Center (Rebro).