Is Completion Axillary Dissection Necessary For This Patient?

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Case Discussion

A 70-year-old female patient presents to the breast clinic for annual screening. She has no family history of breast cancer. Her physical examination is normal, however an area of 0.5cm in size located in the lower inner quadrant of the right breast has microcalcifications and the adjacent area of approximately 2cm shows structural distortion on mammography (BIRADS 5). The core biopsy reveals high grade, solid ductal carcinoma in situ that contains areas of comedo necrosis and invasive ductal carcinoma in one border. The estrogen receptor (ER) (+), progesterone receptor (PR) (-), Her 2 (-) and Ki-67 is reported as 12%. The patient undergoes segmental mastectomy with wire guide and sentinel lymph node biopsy (SLNB). A 1% isosulfane blue and gamma probe is used for the detection of SLN. One SLN that was not macroscopically suspicious is sent to the pathology department peroperatively, without a request for frozen section evaluation. The paraffin section examination shows a grade 3, ER (+), PR (-) and HER- neu2n (-) invasive tumor with a 2 cm integrity diameter. Lymphovascular invasion (LVI) is positive, and comedo necrosis that surrounds the invasive tumor and forms 15% of the tumor volume are determined, as well as a nuclear grade 3 ductal carcinoma in situ containing microcalcifications. The nearest margins to DCIS are 0.3cm at the medial and 0.2cm at the lateral borders, with negative surgical margins. The pathologic evaluation of the aforementioned single lymph node shows an 8mm metastasis with 0.2 X 0.2 cm extracapsular extension by hematoxylin and eosin (H&E).

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Axillary lymph node dissection (ALND) has been recognized as the most important factor in local recurrence and survival of breast cancer for many years. Although more conservative approaches for excision of the primary tumor in the breast has been suggested since the second half of the twentieth century, until recently there had been no change in ALND (1, 2). The aim of surgical intervention to the axilla in breast cancer is: to provide local control, to reduce the local-regional recurrence and thus contribute to overall survival, to stage the disease, and to direct adjuvant therapy. However, the technique's not being so innocent and the fact that significant survival advantage is not achieved in the majority of patients with breast cancer by axillary treatment has brought ALND into question, especially in early stage breast cancer (3). Therefore, in the last decade, SLNB technique was introduced instead of ALND in patients with invasive breast cancer who are clinically negative in the axillary region. The current standard approach in SLNB positive patients is completion axillary dissection. However, in 40-70% of patients with positive SLN lymph node, no other node is affected. In other words, in 40-70% of SLN -positive patients, an unnecessary complementary ALND is being performed (3, 4). Predictors of metastatic non-SLN are characteristics of the primary tumor and those of the metastatic SLN's. The most powerful independent predictive factors for non-SLN metastases are; the diameters of the primary tumor and the SLN metastasis. The non-SLN metastasis risk is higher in patients with tumor diameter >2 cm than in patients with tumor size <2 cm. The number and size of metastatic SLN are also important predictive factors for positive non-SLN. If the SLN metastasis diameter is <1 mm, the incidence of non-SLN metastases is 0-27%. If the SLN metastasis diameter is >2 mm, the incidence of the non-SLN metastases is 75%. In addition, the presence of lymphovascular invasion in the primary tumor is an important factor that increases the rate of non-SLN metastasis. If lymphovascular invasion is not present in the primary tumor the incidence of non-SLN metastasis is 12-43%, while in the presence of lymphovascular invasion the
incidence of non-SLN metastasis is 30-60% (5, 13). Travaglini and colleagues (14) reported that the presence of lymphovascular invasion in the primary tumor was the only significant predictive factor among studied parameters. Until very recently, completion axillary lymph node dissection (CALND) was recommended all SLN-positive patients except the presence of micrometastases and isolated tumor cells. However, the ACOSOG Z0011 study offers important suggestions in this regard. This study is a randomized study that evaluates the effectiveness of axillary lymph node dissection in clinical T1-2 N0 M0 breast cancer patients with SLN-positivity. Ego were treated with breast-conserving surgery followed by radiotherapy and adjuvant systemic therapy. It was concluded that axillary dissection in such patients does not contribute to local recurrence and survival (3, 15). While there are controversial aspects of this study, it is one of the highly reliable studies on this subject. Although it is a very important study that will help in clinical practice, it fails to address the implementation of CALND in patients with clinically positive axillary lymph nodes and locally advanced disease who received neoadjuvant chemotherapy and underwent mastectomy. According to the ACOSOG Z0011 study, if the patient is SLNB (+) and will not receive either partial breast irradiation, mastectomy, or neoadjuvant chemotherapy, ALND may be omitted, and radiotherapy and systemic chemotherapy may be implemented. The formulations and scoring systems that aid in determining the likelihood of metastasis in other nodes in the axilla, in patients with positive SLN, is called the nomogram. The success rate of existing nomograms in estimating non-sentinel lymph node metastasis (NSLNM) varies in different patient groups. In this patient, the probability of NSLNM is 81% according to the world’s most proven nomogram developed at Memorial Sloan-Kettering Cancer Center, and is 53% by the Turkish model developed for our country (MF08 -01 model). According to both of these results from nomogram models, CALND should be done in this patient. The presence of one positive lymph node in SLNB may suggest that additional assessment of the axilla is required. Although approximately 27% of patients in the ACOSOG study had NSLNM, it had no effect on either local recurrence or survival. Another subject that should be considered in the discussed patient is the presence of extracapsular extension of the SLN metastases, however this issue has not been addressed in the study. Many studies showed that extracapsular extension is predictive for NSLNM. CALND is not required in the patient according to the American College of Surgeons Oncology Group study. However, it should be kept in mind that the general approach to SLN-positive patients in current guidelines including the NCNN guideline, except for patients with good prognostic features, is implementation of CALND. The high nomogram values of this patient and extracapsular extension of the SLN suggest that CALND should be done (16). However, taking tumor size and patient age to consideration, it should also be discussed whether axillary radiotherapy can be used instead of CALND?

References

Our patient is 70 years old; lumpectomy and SLNB is applied upon detection of a tumor in the right breast lower outer quadrant at screening mammography. Pathological diagnosis: Invasive ductal carcinoma, grade 3, ER-positive (percentage rate is not clear); PR negative and HER2 negative. Ki-67 is 12% and lymphovascular invasion (LVI) is positive. Tumor diameter is 2 cm; high-grade ductal carcinoma in situ (DCIS) is present in 15% around the tumor. Surgical margins are negative, and the closest surgical margin is 2 mm away from the focus of DCIS. Axillary lymph nodes are not palpable on physical examination, however gross metastasis and extracapsular spread is determined in the single SLN. We have no information on the status of our patients’ overall health status. We do not know whether she has additional medical problems.

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According to the given data, our patient has T1 N1 M0 (assuming that metastasis screening had been done and found negative) breast cancer. The aim of axillary dissection is to improve local regional control, and to identify the correct staging and prognosis of the disease. The importance of molecular sub-grouping is increasing in the selection of adjuvant systemic therapy and the significance of axillary lymph nodes is decreasing. Our patient has a luminal type B breast cancer. The tumor’s being Grade 3 and LVI positivity are adverse prognostic factors that show the necessity of chemotherapy (CT) (1). The number of positive ALN does not alter the choice of treatment (2). There is a mismatch between Ki-67 and grade in the pathology report. In such cases, a second pathology consultation may be required if treatment selection would be altered.

The ACOSOG Z0011 study (1900 patients with T1 and T2 tumors, who received breast conserving surgery, had metastasis in 1 or 2 SLNs, without gross extracapsular extension in the SLN were randomized to tangential RT and systemic therapy, and ALND groups) and Amarosa study (1425 patients with T1 and T2 tumors, with clinical N0 disease but SLN positive were randomized to ALND and axillary RT (ART) arms) have been published in the last 5 years (3-5). In the ACOZOG Z0011 study, after a median follow-up of 6.3 years, the 5-year overall survival (OS) and disease-free survival (DFS) was 91.8%, and 82.2% in the ALND arm and 92.5% and 83.9% in the SLND arm, respectively, and no significant difference was found between arms. Similarly, there was no difference in terms of local regional recurrence between arms. Lymphedema, paresthesia, seroma, and wound healing problems were significantly more frequent in the ALND group than the other group (p<0.001). In this study, an average of two SLNs was removed. The effect of presence of extracapsular extension in the SLN is unknown. The median 6.1-year follow-up results of the AMAROS study have been reported in 2013 ASCO (American Society of Clinical Oncology) (5). The axillary recurrence rate, 5-year OS and DFS were 0.54% and 1.03%; 86.9% and 82.6%; and 93.3% and 92.5% in the ALND and ART arms, respectively, with no significant differences between the two groups. Lymphedema was observed significantly higher in the ALND arm (40% and 28% at 1 year, 22% and 14% at 5 years, p<0.0001). In this study, information regarding presence of extracapsular extension in the SLN is not available. In these studies, systemic therapy and RT application had a positive impact on both OS and DFS.

The implementation of completion axillary dissection in our patient, and detection of lymph node metastasis as a result of this dissection would change the expected 10-year OS and DFS rather than the choice of treatment. When our patient’s information is entered in to the Adjuvant online version as a patient with no additional health problems (HER2 and PR, Ki-67 is entered) 10 years, the risk of relapse at 10 years is calculated as 43% and the risk of death as 24% (6). With adjuvant 3rd generation chemotherapy regimens and adjuvant aromatase inhibitor, the risk of relapse is decreased by 58% and mortality risk is reduced by 55%. In case of detection of more lymph node metastasis by ALND, the benefits of combined therapy do not change. Prognostic information regarding recurrence and death varies; the 10-year recurrence and mortality rates are calculated as 65% and 45% if 4-9 ALNs are positive for metastasis and as 85% and 68% if ≥9 ALNs are positive, respectively. If the patient has significant co-morbidities, the benefit of adjuvant systemic therapy decreases accordingly. Hormonal therapy alone may be recommended in such patients.

Another point to be considered in our patient is the localization of the tumor in the inner quadrant. The likelihood of internal mammary lymph node metastasis increases in tumors of the inner quadrant; this rate is 2% in tumors localized at the outer quadrant whereas it may raise up to 17-20% in tumors localized at the inner quadrant (7). Localization does not affect the choice of systemic treatment. It will be important in planning adjuvant radiotherapy (RT).

As a result, ALND does not change the selection of adjuvant systemic therapy in our patient. According to the results of two studies, it does not affect the OS or DFS (3-5). However, the special information of our patient is that extracapsular spread is detected in lymph nodes. In these two studies, information is not available on this topic.

References

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The number of axillary metastatic ganglia is considered both scientifically and traditionally when determining radiation therapy indication for treatment of breast cancer (1). The decision to use peripheral lymphatic irradiation area in addition to breast or chest wall irradiation is also made according to the number of ganglia with metastasis (2, 3). Leading authors suggest, not relying on published data but as "expert opinion", the planning of supraclavicular/axillary radiotherapy field in addition to breast area in patients with SLN metastasis who did not have completion axillary dissection and if their risk of having more than four metastatic ganglia is higher than 30% according to nomograms (4, 5). If the patient is going to be treated according to the results of the Z0011 study (see above in surgical opinion) (ie, without dissection and without additional regional lymphatic irradiation field application), and if only breast radiation is to be conducted, it is recommended that the patient should completely fulfill the Z0011 study inclusion criteria. In this case, the presence of extracapsular spread does not fit to the Z0011 criteria (gross extracapsular spread is accepted as exclusion criteria in the study). According to nomograms, the risk of additional axillary metastasis in this patient is reported as 53-81%. Axillary lymph node dissection is recommended based on these two data. However, if additional surgery is not considered due to the patient’s clinical condition, then regional lymphatics can be controlled with radiation therapy. In clinical N0 patients and in patients with a positive axilla but insufficient dissection, application of axillary radiotherapy instead of additional surgery to the axilla enables equal success in terms of control (6, 7). We would recommend radiotherapy of the breast and axilla/supraclavicular areas to this patient because she partially does not fit the Z0011 criteria and the risk of more than four metastases is higher than 30% according to Katz nomogram.

The most remarkable result of the Z0011 study is the axillary recurrence rate of less than 1% in 27% of patients with 1-2 SLN metastases, without direct radiotherapy to the axilla. The Z0011 study is criticized due to recruitment of less patients than planned, the low statistical power, and its being the only study, and its results are not accepted as "treatment/application altering study" by some clinicians. If experience of clinics in managing SLN positive axilla increase in the direction of being more conservative (act like in Z0011, not use axillary dissection and direct radiation) and no negative consequences of this approach is detected, the Z0011 approach will gain widely acceptance. While adopting Z0011 results, it should be remembered that axillary surgery/radiotherapy is not performed only if all patient characteristics (histopathologic findings of the tumor and SLN metastasis) meet the Z0011 inclusion criteria. If the Z0011 study approach is confirmed by other clinics, using nomograms that determine the rate of additional ganglion metastasis in SLN positive cases will not be needed; since regional recurrence rate is less than 1% even in the presence of 27% additional histopathologically proven metastases. The Z0011 study has shown that the local method treating the axilla is not tangential breast irradiation (8, 9). The breast radiation area used in Z0011 does not cover the axilla sufficiently. In other words, there are no regional recurrences even in conditions where axillary surgery or radiotherapy are not used. The axilla may have been controlled by systemic treatment or the patient’s immune system (10, 11). Therefore, in the coming years, if confidence in Z0011 study results increase, in patients who meet the study criteria, the patient may be assessed for systemic therapy and only breast irradiation without considering risk ratios by nomograms and without any local treatment directed to the axilla (axillary lymph node dissection and/or axilla radiotherapy). On the other hand, if the benefit of adding peripheral lymphatic irradiation in the presence of even one ganglion metastasis is proven in the newly closed randomized trials, addition of lymphatic radiotherapy from a specific area may again become popular in SLN positive patients (12, 13).

References


The decision to perform systemic therapy in this patient can be made without axillary dissection. In principle, chemotherapy is recommended to node-positive patients, nevertheless its benefits are more limited in patients over the age of 70 years and the decision should be made by considering individual properties (1). The use of Oncotype Dx and other genomic predictive and prognostic tests in axilla positive patients is not yet recommended in routine clinical practice. Adjuvant therapy with aromatase inhibitors is an option in patients who are older than 70 years and are receptor positive, considering other comorbid factors (2).

**References**
