A Multidisciplinary Approach to Locoregional Management of the Axilla for Primary Operable Breast Cancer

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Background: Lymph node metastasis is the single most important factor in assessing breast cancer prognosis and planning systemic therapy. However, lymph node dissection portends significant morbidity, with little or no therapeutic benefit if the nodes prove to be negative for cancer.

Methods: The authors review indications for avoiding axillary dissection, and they analyze the results from lower-level axillary lymphadenectomy together with the morbidity from full axillary dissection.

Results: Limited level I dissection depends on surgical technique and limits prognostic information. Three approaches have evolved to identify the sentinel node in breast cancer: peri-lesional breast injection of radiocolloid alone, blue dye alone, or a combination of radiocolloid and blue dye. These techniques provide high diagnostic accuracy, few false-negative results, and less morbidity.

Conclusions: Knowledge of axillary status is critical to current breast cancer management and cannot be foregone in the preponderance of patients with advanced breast cancer. Results from lymphatic mapping and sentinel node biopsy are highly encouraging.

Introduction

The current role of axillary dissection may be the most controversial topic in breast cancer therapy today. While Halsted1 demonstrated the therapeutic benefit and curative potential of the radical mastectomy, Patey and Dyson2 showed that the modified radical mastectomy could yield similar survival with decreased morbidity. Since randomized trials have now proven that many women with limited disease are adequately treated using even smaller operations, increasingly limited surgical procedures combined with adjuvant treatments are being proposed to have the same curative potential as had the more radical surgical interventions from the past.

Polarized and contrasting opinions have been expressed by experts contesting the current role of axillary dissection in the management of primary operable breast cancer. The presence of nodal metastases remains the single most important independent variable in predicting prognosis. However, the diagnostic utility of axillary dissection is decreasing since breast cancer is now diagnosed at earlier stages of disease and because the use of adjuvant chemotherapy is no longer limited to patients with node-positive breast cancer. Advocates of axillary dissection contend that lymphadenectomy has therapeutic benefit for breast cancer patients since axillary dissection renders regional control of axillary disease.3-5 They contend that surgical extirpation of microscopic nodal metastases is curative without adjuvant chemotherapy in a subset of patients.6 Conversely, critics of axillary dissection maintain that overall survival, which depends on the development of distant metastases, may not be influenced by axillary dissection in the majority of patients. They suggest that patients with microscopic axillary metastases might be cured by adjuvant chemotherapy and/or nodal irradiation without axillary dissection.7,8

While some centers advocate abstention from axillary dissection in a subset of patients with "early" breast cancer, we suggest that knowledge of axillary status is critical to current breast cancer management and cannot be foregone in the preponderance of patients with invasive breast cancer. Cancer stage at diagnosis is central to outcome assessment and adjuvant treatment planning. Patients with node-negative T1a/T1b invasive cancers (<1 cm) have an excellent prognosis such that the morbidity of systemic therapy is difficult to justify. However, patients with similarly sized node-positive tumors clearly benefit from systemic treatment and would be undertreated if nodal metastases went unrecognized because node dissection was not performed. Ironically, lymph node dissection, with its potentially serious morbidity, has played the biggest role in decision making among patients with the smallest tumors.

Fundamental changes in breast cancer management warrant careful scrutiny. Breast cancer is a slowly evolving disease in most patients, with recurrences developing up to 20 or even 40 years following primary therapy.9,10 Treatment changes made today may impact on disease outcome many years from now. Thus, the endeavor to minimize surgical morbidity must be tempered by the recognition that new treatment strategies in breast cancer cannot be definitively assessed without many years of follow-up.

Inaccurate or absent pathologic staging could mask the identification of subtle decrements in recurrence and survival rates. Thus, abstention from axillary lymphadenectomy converts pathologic staging from a scientific analysis to a statistical probability. Years from now, investigators who simply avoid the use of axillary dissection could potentially find themselves hindered in their ability to detect outcome changes for lack of adequate primary staging data.

First established as a standard technique in melanoma therapy, lymphatic mapping and sentinel lymph node (SLN) biopsy have recently been applied to breast cancer...
Limited Axillary Lymphadenectomy in Breast Cancer

While the complete axillary dissection (levels I and II) is the gold standard for diagnostic staging in breast cancer, it also conveys significant morbidity in a subset of patients. Investigators have evaluated the use of limited axillary dissection or its avoidance altogether. Unfortunately, clinical assessment of axillary nodal status is an unreliable method for staging breast cancer, with false-negatives and false-positives in at least one third of patients. In the NSABP B-04 trial, 39% of clinically normal axillae were found on pathologic examination to have nodes with microscopic metastases. Of these, 45% had four or more positive nodes and 15% had 10 or more positive nodes. On the other hand, one quarter of patients with clinical lymphadenopathy had histologically benign nodes. Thus, histologic evaluation has remained an important element in staging patients for clinical studies and prognostic evaluation.

Axillary Staging With Noninvasive and Minimally Invasive Breast Cancer

Patients with noninvasive breast cancer (ductal carcinoma in situ, DCIS) are unlikely to benefit from axillary dissection because purely noninvasive breast cancer has very little or no biologic potential for nodal metastases. This appears to be true because noninvasive neoplastic changes remain confined within the basement membrane of the duct and, therefore, do not have access to the blood or lymphatic channels. It is presumed that the reported 1% to 2% incidence of nodal metastases in patients diagnosed with DCIS results from occult invasive disease within the primarily noninvasive process. In general, the histologic finding of DCIS without invasion is an excellent predictor of nodal negativity such that nodal dissection is generally not warranted.

Microscopic invasion identified in DCIS is associated with variable rates of nodal positivity, rates that depend more on the definition of "microinvasion" than with actual differences in invasive histology. The defined depth of invasion with "microinvasion" has varied from one cell thickness in some reports to several millimeters in others. A complete discussion of microinvasion is beyond the scope of this review. To generalize, most reports studying "DCIS with microinvasion" describe nodal positivity rates of less than 5%, with nodal positivity rates directly correlating with depth of microinvasion.

The arguably poor terms "minimally invasive" or "minimal" breast cancers are used by some to describe invasive cancers of less than 1.0 cm in diameter, representing a spectrum of early invasive disease. This heterogeneous population can have lymph node metastases in less than 5% or more than 30%, depending on patient selection. The American Joint Committee on Cancer more rigorously distinguishes T1a invasive breast cancers (less than or equal to 0.5 cm) from T1b invasive breast cancer (0.5 to 1.0 cm) to allow more accurate comparisons. However, even among the T1a cancers, it is difficult to prospectively define a group of patients with invasive breast cancer in whom nodal metastases is consistently unlikely.

At the University of Washington, we have defined a treatment algorithm that guides our surgical recommendations for axillary dissection (Fig 1). This approach is consistent with the National Cancer Center Network guidelines for breast cancer care, which we also helped establish. However, it is our experience that this decision-making algorithm must be handled on a case-by-case basis, particularly when selecting patients with invasive cancer in whom we decide not to perform axillary lymphadenectomy. Most of these patients either have small (T1a) cancers with otherwise favorable tumor characteristics (well- or moderately well-differentiated estrogen-receptor [ER]-positive cancers without HER-2/neu overexpression and/or other immunohistologic evidence of biologic aggression) or have a poor functional status secondary to comorbid disease or advanced age. We are reluctant to avoid axillary lymphadenectomy unless either we estimate the likelihood of metastases to be less than 5% or we project that the patient is unlikely to survive five years due to serious comorbid disease(s). We avoid axillary dissection in elderly patients with 1- to 2-cm (T1c) ER-positive cancers who are undergoing breast conservation therapy. The age at which we avoid axillary dissection (in the absence of sentinel node) has been variable since many patients in their 70s or even 80s can be extremely healthy and appear functionally younger than their stated age. Our rationale is that these patients will be recommended for tamoxifen therapy if they are found to be node-negative or node-negative, and regional control of disease can be obtained with axillary irradiation. Paradoxically, this decision-making algorithm becomes problematic with similar elderly patients having smaller (<1 cm) ER-positive cancers since they would not be given any systemic therapy were they node-negative but would be given tamoxifen were they node-positive.

If proven to be efficacious, SLN biopsy would be an ideal solution for this quandary in patients with the smallest tumors. It has been speculated that SLN biopsy could be used to redefine the need for nodal evaluation in patients with DCIS. Additional information is needed to assess whether the technique could help to identify the 1% to 2% of DCIS patients with positive nodes.
The greatest surgical morbidity following axillary lymphadenectomy is the development of arm lymphedema. It is an incurable, debilitating process that in the worst cases can cause a limb nonfunctional. Its incidence is difficult to quantify because appearance may be delayed for many years following the procedure. Less than 1% of patients who undergo surgical lymphadenectomy alone should have severe complications within the first five years. One might anticipate that a lesser dissection would have a lower incidence of subsequent lymphedema. Although the point has not been proven in any trial, investigators have evaluated the diagnostic efficacy of limited axillary dissection, presuming that the incidence of serious morbidity will be decreased.

For diagnostic purposes, level I axillary lymphadenectomy (dissection limited to nodes lateral to the pectoralis minor muscle and inferior to the axillary vein) may have a reasonably high predictive value for the identification of nodal metastases. Veronesi and colleagues found in a review of 539 node-positive cases treated with total axillary dissection (levels I, II, and III) that 98.5% had nodal metastases within the level I specimen. The first level was skipped by metastases in eight patients (1.5%), and both lower levels were skipped in only two patients (0.4%). Similar statistics were observed in a smaller study in which seven of 80 node-positive patients (8.7%) had metastases that skipped level I but were present in levels II and/or III. These authors point out that the positive predictive value of a level I axillary dissection is actually higher than 91.3% because over half of axillary dissections (60% in their series) prove to have no nodal involvement and hence would have been predicted correctly by the examination of only level I nodes.

Some investigators have studied axillary lymphadenectomy of a lesser scope than a formal level I dissection. Limited level I dissection (removal of the lower axillary nodes in the axillary fat only at the apex of the breast tail) was reported to be accurate for qualitative analysis in one randomized series from the Scottish Cancer Trials. In 417 randomized patients, similar rates of nodal positivity were found with limited level I dissection and with complete levels I and II nodal clearance. Limited level I axillary dissection specimens each contained a mean of four axillary nodes. No difference in rates of nodal positivity were noted between the limited dissection and the nodal clearance groups. Each of the 16 patients who underwent both limited dissection and subsequent axillary clearance were correctly categorized by the limited dissection data. Only one patient in the entire series failed to have lymph nodes identified in the limited dissection specimen.

However, the diagnostic accuracy of limited level I axillary dissection critically depends on surgical technique. An earlier study also from the Scottish data, found no nodes to be identified in 116 (25%) of 473 patients with stage I or II breast cancer treated by limited level I axillary dissection. Another report describes a qualitative error for nodal sampling in 18% of 50 mastectomies in which perioperative sampling preceded axillary node clearance.

A serious limitation of limited level I axillary dissection is that the number of positive axillary nodes does have prognostic significance for patient survival. Patients with four or more positive nodes fare worse than those with one to three positive nodes. In the NSABP, five-year survival proved to be approximately 75% in patients without lymph node metastases, falling to approximately 60% in the presence of one to three positive nodes and falling to 30% or less with four or more metastatic axillary nodes. Thus, the decreased morbidity of a limited level I dissection, even if qualitatively accurate, must be weighed against the loss of information from quantitation of metastatic nodes.

**Axillary Lymphadenectomy as a Therapeutic Procedure**

Axillary lymphadenectomy could potentially impact on two areas of breast cancer therapy: (1) regional control of disease in the axilla (prevention of axillary recurrence and associated complications), and (2) systemic control of disease (prevention of systemic dissemination and survival).

**Regional Control of Disease**

**Axillary Relapse in the Untreated Axilla:** The incidence of axillary failure when neither surgery nor RT is used to treat the axilla in patients with clinically uninvolved nodes has been reported to be between 19% and 37%. If relapse occurs, axillary salvage following relapse using resection and/or RT fails to achieve regional control in approximately one out of four patients. Uncontrolled axillary metastases with neurovascular invasion is extremely morbid. Therefore, lack of axillary treatment is probably unwise except with purely in situ carcinoma or early invasive cancers with extremely favorable prognosis.

**Axillary Relapse Following Lymphadenectomy:** The probability of axillary relapse is inversely correlated with the extent of axillary dissection as reflected by the number of axillary nodes removed. When formal level I and II lymphadenectomy is performed by experienced surgeons, axillary failure develops in as little as 0.7% of patients. By contrast, the Danish Breast Cancer Cooperative Group reported significantly higher failure rates in patients treated by more limited resections in that series, 3,128 women underwent total mastectomy and limited level I axillary dissection. Each patient had originally been classified as node-negative, but a median of only four lymph nodes (range 0 to 30) was identified in each specimen. Ipsilateral axillary recurrences developed by five years in 178 patients (5.7%) with recurrence highest in women who had no nodes found in the specimen (19%) and lowest for women with five or more lymph nodes removed (3%). The likelihood of axillary recurrence continued to rise after five years for patients who had fewer than five lymph nodes removed at the original operation, with the rate of rise being greatest for those who had no nodes removed.

**Axillary Relapse Following Axillary Radiation Therapy:** With current doses and techniques, the incidence of axillary failure in patients treated with axillary RT alone is 0% to 3%. Which is similar to those rates for axillary lymphadenectomy. The incidence of axillary recurrence is higher when RT is used to treat clinically positive axillae (2.9%) than with clinically negative axillae (0.8%). A problem with axillary radiation used as primary treatment for the axilla is that it does not permit staging of the nodes. Thus, even if axillary disease is controlled by axillary radiation, the selection of systemic therapy, which depends in part on the number of positive lymph nodes, is hindered.

**Complications Following Lymphadenectomy And/or Axillary Radiation Therapy:** Axillary RT increases the probability of complications when added to lymphadenectomy. Dewar and colleagues reviewed the Institut Gustave-Roussy experience with axillary management in 587 patients with T1 or small T2 breast cancers treated by breast conservation. Axillae were managed using lymphadenectomy and/or Cobalt axillary RT. The probability of axillary complications at five years was 7.2% for lymphadenectomy alone, 26.1% for axillary RT alone, and 33.7% for combined surgery and RT. Less than 5% of these complications were severe and debilitating, and all occurred in patients who had combined surgical and radiation in the axilla. In this series, the axillary recurrence rate was 1.2% overall at five years. No decrease in axillary recurrence could be attributed to axillary RT when added to combined levels I and II lymphadenectomy.

Larson and colleagues reviewed their experience with lymphadenectomy and axillary RT and found that in patients who had full axillary dissection (n = 49), the incidence of arm edema was increased in patients who were radiated as well (36%) compared with those who were not (12%). The relationship was similar in patients who had a lesser dissection (n = 191), although the incidence of arm edema was less overall (11% with RT vs 6% without RT). In breast conservation patients, the use of axillary RT was associated with a significantly higher incidence of pneumonitis (1.6%) and brachial plexopathy (2%) compared with patients who had RT to the breast alone (<0.2%). The incidence of these complications was heavily influenced by the use of chemotherapy and its temporal sequencing with RT.
Axillary Lymphadenectomy as a Curative Procedure for Regionally Metastatic Breast Cancer: Axillary lymphadenectomy used in conjunction with primary tumor ablation can cure breast cancer, even in the presence of significant nodal metastases. In a retrospective review of 1,458 breast cancers treated by radical mastectomy from the years 1940 to 1943, Adair et al showed that 184 patients were alive with an average follow-up of 30.6 years, and 60 of these women had node-positive disease at operation. Adjunct chemotherapy was not available in that era. Of these long-term survivors, 82% had metastases limited to levels I and II. Eleven patients had metastases in level III nodes (the axillary apex medial to the pectoralis minor muscle up to Halsted’s ligament) at initial operation; despite extensive nodal metastases, these women were alive with a minimum follow-up of 28 years, having been treated with surgery alone.6

Retrospective data suggest that axillary dissection may confer a survival advantage to a subset of breast cancer patients. The Danish Breast Cancer Cooperative Group78 found in their 3,128 women treated with total mastectomy and limited I axillary dissection that survival was decreased (P<0.05) in patients who had four or fewer nodes removed compared with patients who had five or more nodes removed. The biologic significance of these data remain unclear. Despite large numbers of patients, it remained undetermined whether the groups had comparably advanced disease at operation and decreased survival was due directly to failure to treat microscopic axillary metastases, or whether the decrease was an artifact of inaccurate staging (ie, patients with fewer dissected nodes actually had more advanced disease than the group with more nodes removed). This study illustrates the real difficulty in survival analysis among groups that are incompletely staged at the time of the original therapeutic intervention.

Axillary Management Using Minimally Invasive Strategies

Lymph Node Mapping and Sentinel Node Biopsy

SLN biopsy is a technique pioneered by Morton and colleagues35 in the treatment of melanoma in which intraoperative lymph node mapping is used to identify the leading point in lymphatic drainage for a tumor-involved region. The impetus for a less invasive technique to identify lymph node metastases in patients with melanoma was the growing trend away from elective lymph node dissection (ELND). Two past randomized prospective trials,36,37 failed to demonstrate a survival advantage of ELND over observation, and the recently reported Intergroup randomized prospective trial38 showed a survival benefit only in a subgroup of male patients under 60 years of age with melanoma thickness from 1 to 2 mm. Maturation of this technique in the mid-1990s in several centers has led to a growing consensus that SLN biopsy is now the standard of care for management of regional lymph nodes in patients with intermediate-thickness cutaneous melanoma.

Background of SLN Biopsy in Breast Cancer

There has been great interest in the application of the SLN biopsy technique in management of patients with breast cancer. At least three theoretical advantages of a minimal axillary staging procedure are readily apparent. First, identification of patients with negative axillary nodes by evaluation of a single lymph node biopsy eliminates an unnecessary lymph node dissection in these patients without losing the staging benefit of knowing the lymph node status. Second, localization of a node or nodes at highest risk of harboring metastatic disease facilitates a more intensive pathologic evaluation for subtle microscopic disease. One or two nodes can be subjected to serial sectioning, yielding multiple levels of nodal tissue that can then undergo standard hematoxylin–eosin staining, immunocytochemical evaluation with anticytokeratin antibodies, and perhaps polymerase chain reaction evaluation for the presence of RNA expressed by breast cancer cells.39,40 This more intensive nodal evaluation will likely identify a greater percentage of patients with nodal metastases who may benefit from adjuvant therapy. Third, this technique has broad appeal: the patient is spared the morbidity, expense, and recovery of a complete axillary node dissection. If a negative SLN is found, the surgeon still will provide axillary staging information with an overall reduction in patient morbidity, and the medical oncologist will have more accurate information regarding axillary node status to counsel patients regarding a possible benefit of adjuvant treatment. Patients who are SLN positive may undergo a complete axillary node dissection for regional control and to determine the number of positive nodes in institutions where a greater number of positive nodes or the presence of extranodal extension may lead to a recommendation of a more intensive chemotherapy regimen or to adjuvant irradiation.

Experience of SLN Biopsy in Breast Cancer

Early experience with lymphatic mapping and SLN biopsy for breast cancer is encouraging. Three approaches have evolved to identify the SLN in the axilla of patients undergoing axillary node dissection for invasive breast cancer: perilesional breast injection of radiocolloid alone, blue dye alone, or a combination of radiocolloid and blue dye.

Using perilesional breast injection of radiocolloid alone and gamma probe of the axilla, investigators at the University of Vermont identified SLNs in 71% patients undergoing axillary node dissection for breast carcinoma.42 In a larger series, Veronesi et al41 reported finding sentinel nodes in 160 of 163 patients and observing a 97.5% concordance rate between SLN and full axillary histology. The Italian researchers, who were using radioactively labeled albumin, found a 95% negative predictive rate in patients with tumors of all sizes, meaning that one in 20 women could be incorrectly classified as node negative without more stringent patient selection.

At the John Wayne Cancer Institute (JWCI) in Santa Monica, Calif, where perilesional breast injection of blue dye alone was used in 174 mapping procedures, SLNs were identified in 114 (66%) patients and accurately predicted axillary nodal status in 109 (95.6%) of 114 patients.43 In a recent update of the experience at the JWCI of the most recent 107 patients where blue dye alone was used, SLNs were identified in 100 (94%) patients without any false-negative results in the concomitant axillary node dissection.42

At Moffitt Cancer Center in Tampa, Fla, using a combined technique of perilesional breast injection of blue dye and radiocolloid in 62 mapping procedures, SLNs were identified in 57 (92%) of 62 patients without any false-negative results in the concomitant axillary node dissection.43 In a recent update of the Moffitt experience (C. Cox, MD, personal communication, 1997), investigators identified SLNs in 93% of 256 patients with one false-negative (skip metastasis) in a patient who had undergone a previous excisional biopsy. Seventy-five (16%) of 450 SLNs harvested contained tumor. Of these 75 positive nodes, 50 (67%) were blue-stained, 59 (79%) were “hot” by gamma probe, and 45 (60%) were blue-stained and “hot.” They concluded that the two techniques were complementary in identification of the SLN. In a recent experience at Memorial Sloan-Kettering Cancer Center in New York (H. Cody, MD, personal communication, 1997) using radiocolloid and blue dye in 58 patients, SLNs were identified in 56 (97%) patients. The two techniques were complementary in identification of SLNs. One of 46
patients with a T1 (<2 cm) primary tumor had a false-negative result (negative predictive value = 99.6%). Two of 12 patients with a T2-3 (>2 cm) primary tumor had a false-negative result (negative predictive value = 91.5%).

At our center, we have begun to study SLN biopsy as part of an experimental protocol to demonstrate efficacy of the technique in our own hands (Fig 2). SLN biopsy is offered to patients with known invasive breast cancer who would otherwise undergo standard axillary lymphadenectomy as part of their surgical staging. In their operation, patients first undergo SLN biopsy using both blue dye and technetium-labeled sulfur colloid techniques. The purpose of this protocol is to verify that the mapping approach works in our own hands and that the false-negative SLN biopsy rate is minimal.

The recurring message from the leading centers currently performing SLN biopsy for breast cancer is the plea for caution before changing practice patterns and adopting SLN biopsy alone in axillary lymph node staging. Each center and individual surgeon should seek and obtain training in the current techniques of SLN biopsy and determine personal and institutional rates of SLN identification and false-negative results. The rapid and premature use of this innovative technique is likely to result in missed positive axillary nodes that may take months to years to become clinically apparent and may lead to misleading adjuvant treatment recommendations in patients with breast cancer.

Integration of SLN Biopsy Into Standard Surgical Planning for Breast Cancer

If SLN biopsy becomes accepted into surgical practice, accurate intraoperative histologic analysis of nodal status could be very useful. While SLN biopsy can be done as an outpatient procedure using local anesthesia with monitored sedation, it also might be desirable to be able to identify a positive SLN during surgery so that the completion axillary dissection could be performed using the same anesthetic. Frozen section analysis of lymph nodes is technically difficult since there is often a fatty component of nodes that limits the capacity to snap-freeze the node. Innovative techniques must be developed to immediately evaluate the node at multiple histologic levels. The use of “touch preparation” cytology and the development of rapid immunocytochemical stains are likely to prove invaluable in this setting.

In patients undergoing a modified radical mastectomy with or without immediate reconstruction, the finding of a positive node on permanent nodal evaluation several days after surgery has major practical implications. The need to complete a formal nodal dissection in these patients would require re-entering a large operative site and could jeopardize the blood supply of a recent myocutaneous flap reconstruction or could increase the risk of wound infection in patients with recently placed tissue expanders.

In general, the finding of a positive SNL by sentinel dissection will lead to a complete level I and II axillary dissection in the majority of patients (Fig 3), since the number of positive nodes frequently influences recommendations for adjuvant chemotherapy and RT. However, there may be a subset of patients in whom SLN biopsy may be the only axillary procedure offered even if that node is found to be positive. Elderly patients in whom axillary lymphadenectomy would otherwise have unacceptable morbidity from complete dissection but in whom the presence of any number of positive nodes would allow decision-making for tamoxifen therapy (T1b tumors) could potentially undergo SLN biopsy and, if positive, could be treated with axillary irradiation rather than formal dissection.

In addition to sorting out the efficacy of SLN biopsy, we will also need to learn which patients should not be selected for the procedure. Patients with very large tumors may have higher rates of false-negative SLN results. Patients with locally advanced cancers are often treated with neoadjuvant chemotherapy to facilitate local control and augment breast conservation rates. No data have yet addressed whether preoperative chemotherapy will depress the accuracy of SLN biopsy results. We may find that patients with large (T3) cancers are not good candidates for postchemotherapy study. We may find a role for SLN biopsy before neoadjuvant chemotherapy in these cases, or we may conclude that all of these patients with locally advanced cancers should undergo ELND since the likelihood of node-positive disease is so high that the false-negative rates of SLN biopsy becomes unacceptably high in this subgroup. Additional studies considering the multimodality therapy of breast cancer is mandatory in the next few years.

References


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