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Opinion Open Access

Controversies in Axillary Treatment of Breast Cancer Patients and Metastatic Sentinel Lymph Node

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Opinion

In the last two decades the treatment of breast cancer has undergone multiple modifications, evolving from aggressive surgical interventions focused on the regional control, to the multidisciplinary treatment that allows local and systemic control of the disease. An example of this was the beginning of breast conserving surgery in the eighties [1], based on adjuvant breast radiotherapy. Some studies have shown that this association of treatments is an alternative to the mastectomy [2-4] in early stage breast cancer, offering similar local recurrences rates and overall survival.

Another example of change in breast cancer treatment is the management of regional lymph nodes. Historically, axillary lymph node dissection (ALND) played a key role in breast cancer. On one hand, axillary lymph node removal allowed locoregional control and offered a staging and prognostic tool. On the other hand, pathologic lymph node information contributed to the decision of adjuvant chemotherapy and radiotherapy. However, two developments have helped to reduce the number of ALND. First, the description of sentinel lymph node biopsy (SLNB) in patients with clinically node-negative axilla, that is able to identify the node status through a simple and reproducible procedure with high sensitivity and specificity, and lower morbidity than ALND [5-11]. Second, the description of different tumor subtypes, in which the decision of systemic therapy (chemotherapy, hormone therapy and radiation therapy) is based.

Despite this change in the indication of ALND, there are still women with ALND without axillary fat, infiltration, generating controversy about the need to treat the axilla in selected women with sentinel lymph node involvement. Several clinical trials have examined the impact of axillary treatment in women with early stage breast cancer (Table 1) [12-23]. From these studies, two main conclusions are generated. The first, axillary relapse is a rare event in patients without lymph node involvement (N0) or limited involvement in the axilla (N1) and its incidence varies between 0% and 3.6% [14,16]. These results are opposite to those obtained from clinical trials with patients with axillary mass involment (N2-N3), where adjuvant axillary radiotherapy allows a decrease of local relapses from 26% to 12.5% [13,15]. The second conclusion is that residual axillary disease does not necessarily progress to an axillary recurrence. Two facts show this circumstance. The first fact is that SLNB false negative rates do not match to the expected incidence of axillary relapse. Example of this are Milan trial [16], the NSABP32 trial [17] and GIVOM trial [18] that reflect axillary relapse of 0.2% despite false negative rates of 4.6%, 9.8% and 7.3%, respectively. The second fact relates to the low relapse incidence in women with positive sentinel lymph node (SLN) whithout ALND. This data comes from three recent publications questioning the value of regional treatment in positive SLN early stage breast cancer patients.

The first of these trials, Z0011 [14], from the American College of Surgeons Oncology Group, includes patients with T1-T2 tumors and clinically node-negative axilla with 1 or 2 positive sentinel nodes, undergoing breast conserving surgery. Patients were randomized to observation or ALND, and a median follow-up of 6.3 years showed less than 1% nodal relapse and similar overall and disease-free survival in both groups. Many criticisms have received this trial, including the lack of information on the radiation fields used and early closure for low number of events, which determined a lack of power to determine differences between groups. In any case, the criteria used in the Z0011 [14] are applied in clinical practice guidelines, raising doubts about positive SLN patients without ALND, who receive breast irradiation with tangential fields, including axillary level I, in whom the need for axillary radiotherapy is discussed.

In the same field, the European Organization for Research and Treatment published AMAROS clinical trial [21]. These compare axillary radiotherapy with ALND in women with invasive breast cancer and SLN involvement. 6.1 years follow up showed no significant difference in local recurrence incidence (0.43% vs 1.19%; ALND vs axillary radiotherapy, respectively) and overall and disease-free survival. Additionally, patients treated with axillary radiotherapy had lower lymphedema incidence. Like Z0011 [14] this trial is underpowered because the low number of axillary relapse.

Finally, the publication of the Canadian clinical trial MA.20 [22], that includes women with breast conserving surgery and ALND with moderate or high risk of regional recurrence and compared a control group with breast radiotherapy alone and a study group with lymph node radiotherapy. Mean follow-up was 9.5 years and a statistically significant reduction in locoregional recurrence has been showed (2.5% vs 0.5%), with no increase in overall survival. However, radiotherapy group presented an increase in acute (dermatitis and pneumonitis) and chronic (lymphedema and subcutaneous fibrosis) adverse event.

Like the ACOSOG Z0011 [14] and AMAROS [21], the AATRM 048 studies [19] and IBCSG 23.1 [20] have shown an axillary relapse lower than 2.5% despite 27%, 13% and 13% residual disease rates respectively. So we can conclude that ALND and/or axillary radiotherapy did not influence overall survival in women with breast cancer. Thus in patients N0 or N1mic an ALND does not improve overall survival regarding a SLNB [17,19] and even ALND or axillary radiotherapy does not improves overall survival in N1 patients [14,22].

In summary, axillary treatment in breast cancer women is planned depending on clinical stage and histological findings in the primary

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Clinical Trial	Year	Clinical Stage	Lymph Node Stage	Evaluated Treatment	Axillary Relapse	Residual axillary disease	Overall Survivall
NSABP 04 (12)	1977	I	cN0	LA	19%	40%	No benefit
Ragaz Trial (13)	1997	II, III	N1, N2, N3	RTP	22% vs 12%	-	0.05
DBCG 82 (15)	1997	II, III	N1, N2, N3	RTP	26% vs 5%	-	Benefit
Milan Trial (16)	2003	I	N0	LA	0%	4.6%	No benefit
NSABP 32 (17)	2007	I	N0	LA	0.2%	9.8%	No benefit
GIVOM Trial (18)	2008	I	N0	LA	0.2%	7.3%	-
ACOSOG Z0011 (14)	2010	I	N1	LA	1.8% vs 3.6%	27.3%	No benefit
AATRM 048/13/2000 (19)	2013	IB	N1mic	LA	2.5% vs 1%	13%	No benefit
IBCSG 23-01 (20)	2013	IB	N1mic	LA	1% vs 0.2%	13%	No benefit
AMAROS (21)	2014	II	N1	LA vs RTP	0.5% vs 0.1	33%	No benefit
MA20 (22)	2015	I, II, III	N0, N1, N2	LA vs RTP	2.5% vs 0.5%	-	No benefit
EORTC 22922 (23)	2015	I, II, III	N0, N1, N2, N3	RTP	1.9% vs 1.3%	-	No benefit

Table 1: Results of clinical trials that have examined axillary treatment impact on global and disease-free survival.

tumor and axillary lymph node. Guidelines accept the N0 patients do not require additional treatment in the armpit and have a very low incidence of axillary relapse, despite the 7% false negative rate for SLNB. Meanwhile, patients with positive lymph node (N2-N3) require an ALND and axillary radiotherapy to achieve adequate loco regional control. Finally, women with limited axillary metastatic diseases (N1) are the group of discussion. Three alternatives are proposed for these patients with positive SLN: monitoring, ALND or axillary radiotherapy. The first option is for patients with micro metastatic sentinel node (N1mic) since the Spanish trial AATRM048 [19] and Italian IBCSG 23.1 [20] have shown a similar regional recurrence incidence with no impact on overall survival and less morbidities rates.

Meanwhile, in macrometastases sentinel node patients the ACOSOG Z0011 trial [14] propose observation for those patients treated with conservative surgery, based on tangential breast fields that include the axillary level I and provide adequate control of the process, circumstance that does not occur in women with a mastectomy. However, the review of the radiotherapy planning of patients enrolled in this clinical trial [24] discloses that at least 17% of the patients received an additional field in supraclavicular/axillary region, possibly by risk factors related to tumor and patient. For its part, the MA.20 [22] study showed an improvement in regional control after axillary radiotherapy in women with risk factors for relapse, but showed no improvement in overall survival.

Several studies [25,26] identify mastectomy, axillary radiotherapy and ALND as risk factors for lymphedema, reaching an incidence about 40% when radiotherapy and ALND [27] are associated. In contrast, lymphedema rates in SLNB are 3-12%. AMAROS [21] study showed similar local control diseases with a lower rate of lymphedema in patients with axillary radiotherapy without ALND. So, in our opinion the axillary radiotherapy is appropriate in women with positive SLN and risk factors without ALND, as the MA.20 [22] and the AMAROS [21] support, demonstrating local control and lower rate of lymphedema compared to ALND.

In coming years we will obtain information from various studies that will help to clarify the need for axillary treatment. For example, in 2023 the POSNOC [28,29] trial will report the value of the ALND and axillary radiotherapy in women with axillary involvement. Dutch group also designed BOOG 2013-07 trial to assess the need of ALND for patients with a mastectomy and sentinel lymph node involvement.

In conclusion, women with early stage breast cancer and lymph node involvement N1 have a low incidence of axillary relapse. In this group of patients, axillary irradiation and/or ALND does not improve overall survival. However, the regional radiation contributes to regional control in those patients with risk factors and limited involvement of the axillary lymph nodes, with less morbidity than an ALND, so we consider essential to use selective criteria for women who should receive axillary radiotherapy

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