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Is sentinel lymph node biopsy enough for axillary macrometastasis?

Aksilla makrometastazlarında sentinel lenf nodu biyopsisi yeterli mi?

Merdan Fayda[1], Makbule Tambaş[1], Hasan Karanlık[2]

Dear Editor,

Although the omission of further treatment of the axilla in early stage clinical N0 breast cancer patients with conserved breast and one or two positive micrometastatic sentinel lymph node(s) is relatively well established, the optimal management of the axilla in macrometastatic disease is still controversial. There are three randomized studies, which shed light on this issue (Table 1). The very first trial is Z0011, which includes patients with both micro and macrometastasis in sentinel lymph node(s). Early stage breast cancer patients with clinical N0 disease and one or two positive sentinel lymph node(s) are randomized to axillary lymph node dissection (ALND) vs. sentinel lymph node dissection (SLND) alone. At a median follow-up of 6.3 years, both 5-year overall survival (91.8% vs. 92.5%; ALND vs. SLND) and 5-year disease-free survival (82.2% vs. 83.9%; ALND vs. SLND) are not significantly different between the arms (1, 2). Arguably, Z0011 study is one of the most important practice changing or at least practice questioning randomized study in recent years. The second trial is the International Breast Cancer Study Group (IBCSG) 23-01 study, which has the same patient population of Z0011 but with only one or 2 sentinel micrometastatic lymph node(s) and also the same randomization. In IBCSG 23-01 trial, the 5-year disease-free survival is also not significantly different between the groups (84.4% vs. 87.8%; ALND vs. SLND) (3). IBCSG 23-01 trial not only further strengthens the results of the Z0011 for the omittance of axillary dissection in patients with sentinel micrometastatic lymph node breast cancer but also shows that the quality of life (QOL) of patients could be improved with sentinel biopsy alone in terms of sensory motor neuropathy and lymphedema (3, 4). In the consensus report of Saint Gallen 2013, the policy of avoiding full axillary clearance after one or two positive sentinel nodes is endorsed in situations of conservative surgery and radiotherapy (73%, YES; 21%, NO), including several opinions that the inclusion criteria of the available trial results should be considered (5).

Although the Z0011 trial provokes us to omit axillary dissection in patients with cT1-2cN0 disease finally staged at pT1-2pN1(sn), it creates more problems than it solves in terms of radiotherapy fields (1). The radiotherapy directed to axillary basins (i.e., third field nodal radiotherapy) is not allowed in the protocol of the Z0011 trial. However, the details of radiotherapy fields could not be clearly understood from the original report (1). Many radiation oncologists try to irradiate at least some part of the axillary level 1-2 (i.e., high-tangential fields) and even think of using third field (i.e., supraclavicular level 3), particularly for patients with no reasonable systemic treatment option (i.e., triple negative case). Recently, the detail of radiotherapy fields at least for some part of the patients in the Z0011 trial is presented at the San Antonio Breast Cancer Symposium 2013 (6). Detailed radiotherapy records were received for 228 patients only: 104/389 (26.7%) ALND vs. 124/404 (30.7%) SLND. Sixty-one of 104 (59%) patients in ALND arm also received some form of lymphatic radiotherapy [supraclavicular, n=22 (21%), posterior axillary boost n=6 (6%), and high tangents n=33 (32%)]. In the SLND arm, some form of lymphatic radiotherapy was also used for 73 of 124 (59%) patients [supraclavicular n=21 (17%), posterior axillary boost n=12 (10%), and high tangents n=40 (32%)] (6). Although the data of the central radiotherapy review of the entire Z0011 population could not be available currently, approximately 60% of the patients have received some form of lymphatic radiotherapy and 18.9% of them have major protocol violation (i.e., third field nodal radiotherapy is not allowed in the protocol). Thus, regional radiotherapy may contribute to the results that have been obtained from both arms of the Z0011 trial.

The third trial is the AMAROS study, which included almost the same population of Z0011 but with different randomization. Patients with cT1-2cN0 disease and with positive sentinel lymph node are randomized to axillary radiotherapy (level I+II+III and medial supraclavicular) vs. ALND. Five-year axillary recurrence rates (1.03% vs. 0.54%; Axillary RT vs. ALND) are not significantly different between the arms (7). There are no significant differences between treatment arms regarding overall survival (5-year estimates:

[1]Department of Radiation Oncology, İstanbul University Oncology Institute, İstanbul, Turkey

[2]Department of General Surgery, İstanbul University Oncology Institute, İstanbul, Turkey

Address for Correspondence
Yazışma Adresi
Merdan Fayda
e-mail:
merdanfayda@yahoo.com

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Table 1. Randomized trials of patients with early stage breast cancer having clinical N0 disease and one or two positive sentinel lymph node(s)

	cT1-2cN0 pT1-2pN1(sn)						
Trial	**Micromet, SN**	**Macromet, SN**	**Extracapsular extension**	**Randomization**	**Radiotherapy**	**Results (regional control)**	**Comment**
Z0011 (1, 6)	≈40% [ITC included]	≈60%	Gross ECE not included	ALND vs. SLND	Mastectomy (0%) Breast only RT. But at least 70% of both arms received some form of lymphatic RT	ALND≅SLND	Regional radiotherapy may contribute to both arms
IBCSG 23-01 (3)	Yes [ITC included]	None	Not included	ALND vs. SLND	Mastectomy (9%). Breast only RT. PMRT details were not clear.	ALND≅SLND	Less sensory-motor neuropathy and lymphedema with SLND
AMAROS (7)	29% micromet; 12% ITC	59%	Not evaluated	ALND vs. Axillary RT	Mastectomy (17%). Breast only RT or PMRT [34 of 127 (26%) in ALND arm and 51 of 121 (42%) patients in axillary RT arm received CWRT].	ALND≅Axillary RT	Less lymphedema with axillary RT

RT: radiotherapy; ALND: axillary lymph node dissection; SLND: sentinel lymph node dissection; SN: sentinel node; PMRT: postmastectomy radiotherapy; CWRT: chest wall radiotherapy; ITC: isolated tumor cells

92.5% Axillary RT vs. 93.3% ALND; p=0.3386) and disease-free survival (5-year estimates: 82.7% Axillary RT vs. 86.9% ALND; p=0.1788). Lymphedema was found significantly more often after ALND (1-year: 22% Axillary RT, 40% ALND; p<0.0001 and 5-year: 14% Axillary RT, 28% ALND; p<0.0001). There is a non-significant trend toward more early shoulder movement impairment after Axillary RT. These findings are compatible with a trend in the following two QOL items in the arm symptom scale: swelling (Axillary RT better) and movement (ALND better). There are no other differences in QOL. Both axillary RT and ALND are equally effective in terms of local control but have lesser lymphedema with axillary RT (7).

Another matter of debate is whether these results could be applicable to the patients treated with mastectomy and SLNB. Only IBCSG 23-01 and AMAROS study included patients with mastectomy (9% and 17% of the patients, respectively). Because radiotherapy details of patients treated with mastectomy in IBCSG 23-01 is not clear, the authors of the trial stated that despite the numbers being small, subgroup analysis suggested that no axillary dissection is acceptable for patients undergoing mastectomy, provided the invasive component of the breast lesion is small (3). Seventeen percent of the patients in the AMAROS study were treated with mastectomy. The chest wall radiotherapy was applied to 34 of 127 (26%) patients in the ALND arm and to 51 of 121 (42%) patients in the axillary RT arm. It is still not clear whether the results of both IBCSG 23-01 and AMAROS trials could be applicable to the patients treated with mastectomy. The decisions should be made individually.

According to the recently published results of a single-center prospective study in patients meeting the Z0011 clinicopathologic criteria (pT1–2; cN0 with <3 positive sentinel lymph nodes), presence of extracapsular extension (ECE) was associated with greater axillary disease burden (8). Twenty percent and 3% of the patients with and without ECE, respectively, had ≥4 additional positive nodes at the completion of ALND (p<0.0001); 33% of patients with >2 mm ECE had ≥4 additional positive nodes at the completion of ALND when compared with 9% in the <2 mm group (p<0.0001). On multivariate analysis, the strongest predictor of ≥4 positive nodes at the completion of ALND was >2 mm of ECE (odds ratio, 14.2) (8). Gross extranodal extension was excluded from the Z0011 trial and unfortunately was not reported in the AMAROS trial (1, 7). Even gross ECE (i.e., >2 mm of ECE) was not reported, axillary radiotherapy may still be considered as an alternative treatment option to the axillary dissection according to the results of AMAROS.

In conclusion, the omission of further treatment to axilla after positive micrometastatic sentinel lymph node in patients with conserved breast cT1-2cN0 disease is relatively well established. However, the optimal management of the axilla in macrometastatic disease is still controversial. Z0011 is the only trial that suggests that radiotherapy of the breast alone is enough for axillary macrometastatic sentinel lymph node. However, we have learned from the central radiotherapy review of Z0011, approximately 60% of the patients received some form of lymphatic radiotherapy and 26% of them had major protocol violation (i.e., third field nodal radiotherapy is not allowed in the protocol). Hence, the omission of further treatment to axilla in patients with macrometastatic sentinel lymph node is not appropriate according to the available data. In this case, the best evidence that we have is the AMAROS trial, and it shows us that either ALND or axillary radiotherapy can be an effective option to treat patients with lesser lymphedema in the axillary RT arm. It is still not clear whether these suggestions could be applicable to the patients treated with mastectomy.

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