Axillary Dissection Versus No Axillary Dissection in Older Patients With T1N0 Breast Cancer

15-Year Results of a Randomized Controlled Trial

Gabriele Martelli, MD, Patrizia Boracchi, PhD,‡ Ilaria Ardoino, PhD,‡ Laura Lozza, MD,† Silvia Bohm, MD,* Gaetano Vetrella, MD,§ and Roberto Agresti, MD**

Objective: To assess the role of axillary dissection in older breast cancer patients with a clinically clear axilla.

Background: Axillary dissection, once standard treatment for breast cancer, is associated with considerable morbidity. It has been substituted by sentinel node biopsy with dissection only if the sentinel node is positive. We aimed to determine whether axillary surgery can be omitted in older women, thereby sparing them morbidity, without compromising long-term disease control.

Methods: We carried out a randomized clinical trial on 238 older (65–80 years) breast cancer patients, with clinically N0 disease of radiographic diameter 2 cm or less. Patients were randomized to quadrantectomy with or without axillary dissection. All received radiotherapy to the residual breast but not the axilla; all were prescribed tamoxifen for 5 years. Main outcome measures were overall survival and breast cancer mortality. We also assessed overt axillary disease in those who did not receive axillary dissection.

Results: After 15 years of follow-up, distant metastasis rate, overall survival, and breast cancer mortality in the axillary dissection and no axillary dissection arms were indistinguishable. The 15-year cumulative incidence of overt axillary disease in the no axillary dissection arm was only 6%.

Conclusions: Older patients with early breast cancer and a clinically clear axilla treated by conservative surgery, postoperative radiotherapy, and adjuvant tamoxifen do not benefit from axillary dissection. This study was registered at clinicaltrials.gov (ID NCT00002720).

Keywords: axillary surgery, breast cancer, older patients, randomized trial, tamoxifen

(*Ann Surg* 2012;256: 920–924)

Breast cancer is diagnosed earlier than in the past, mainly due to mammographic screening; and the incidence and the extent of axillary node involvement have consequently declined.[1] Axillary dissection was for many years part of the standard treatment for breast cancer, in line with Halsted's thesis that cancer cells move from the breast primary to the axillary nodes and only later spread to other organs. It was consequently believed that axillary clearance resulted in better locoregional control and survival.[2] Fisher et al[3] were the first to challenge this idea, providing evidence that lymph node involvement was an indicator, not a governor of distant spread, and that the risk of distant spread was mainly determined by the biological characteristics of the primary.

In the early 1990s[4,5] sentinel node biopsy profoundly changed the surgical approach to the axilla for patients with a clinically clear axilla. Randomized studies[6,7] showed that omission of axillary dissection in patients with a negative sentinel node had no effect on overall survival or breast cancer mortality.

Our observations supported this: in fact our recently published prospective nonrandomized study on elderly breast cancer patients recruited from 1987 to 1992 showed no difference in breast cancer mortality, after 15 years of follow-up, between patients (with clinically clear axillary nodes) who did and did not receive axillary dissection.[8] In 1996, we began a prospective randomized trial to address the issue of axillary dissection in older women. We recruited older patients with T1N0 breast cancer treated by breast-conserving surgery, and randomized to immediate axillary dissection versus no axillary dissection. Five-year results of this trial were published in 2005.[9] In this article, we present the 15-year results.

PATIENTS AND METHODS

Study Design and Procedures

This single-center randomized trial recruited women aged 65 to 80 years with primary T1N0 breast cancer of 2 cm or less in mammographic diameter, without palpable axillary nodes, presenting from January 1996 to June 2000. The trial was registered at clinicaltrials.gov (NCT00002720). Patients with bilateral breast carcinoma, distant metastases at diagnosis, or a history of other cancer except basal cell carcinoma of the skin were excluded. The study was approved by the scientific and ethical committees of our institute, and all patients gave written informed consent. After verifying eligibility, the data manager at the study coordination center randomly assigned patients to either breast-conserving surgery plus axillary dissection or to breast-conserving surgery with no axillary dissection. The original trial protocol specified the recruitment of 642 patients with the power of about 94% to exclude an increase of 10% in distant metastasis within the no axillary dissection group; however, recruitment was very slow in these older patients, and we decided to stop after 4.5 years (1.5 years longer than specified in the protocol).

Of the 238 patients randomized, 5 were excluded for ineligibility (they were erroneously recruited) and a further 14 were excluded for protocol violations. The remaining 219 patients (109 in the axillary dissection arm and 110 in the no axillary dissection arm) were analyzed on an intention-to-treat basis.

Treatment

All patients received quadrantectomy. For those randomized to axillary dissection, all 3 Berg levels were removed. In all cases, resection margins were disease free. All patients also received postoperative radiotherapy to the residual breast using a conventional irradiation technique employing 2 opposing tangential fields. The radiation was delivered by ^{60}Co or 6 MV photons: 50 Gy was given in 25

From the *Breast Unit and †Radiotherapy Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan; ‡Department of Clinical science and Community Health, University of Milan; and §Unit of Preventive Gynecology, Melegnano Hospital, Melegnano, Italy.

Disclosure: This study was financed by the Italian Association for Cancer Research (AIRC). The authors declare no conflicts of interest.

Reprint: Gabriele Martelli, MD, Breast Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20131 Milan, Italy. E-mail: gabriele.martelli@istitutotumori.mi.it.

ISSN: 0003-4932/12/25606-0920
DOI: 10.1097/SLA.0b013e31827660a8

fractions. A boost of 10 Gy was administered to the tumor bed. Irradiation aimed to treat the breast only, with no attempt to include axilla, supraclavicular or internal mammary nodes in irradiation fields.

Regardless of hormone-receptor status, all patients were prescribed 20 mg per day tamoxifen for 5 years, as stipulated in the study protocol.

Follow-up

Physical examination was performed every 6 months for the first 5 years and yearly thereafter. Mammography and chest radiography were performed annually. Because tamoxifen was prescribed, gynecological examination with pelvic ultrasound was performed every 6 months for the first 5 years and thereafter annually. Disease status or cause of death was ascertained from clinical records or by contacting the general practitioners of patients no longer in follow-up. Median follow-up was 150 (range: 125–175) months in the axillary dissection arm and 149 (range: 124–174) months in the no axillary dissection arm.

Tumor Grade and Hormone Receptor Status

Tumor grade was assessed according to Elston and Ellis.[10] Hormone receptors were determined by immunoperoxidase phenotyping as described in detail previously.[9] Tumors were considered positive for estrogen (ER) or progesterone (PgR) receptors if more than 10% of tumor cell nuclei were immunostained.

Statistical Analysis

The main endpoints were overall survival and breast cancer mortality. Survival times were calculated from the date of randomization to the date of death (any cause) or to the latest follow-up. Additional endpoints were adverse breast events (ipsilateral breast cancer, contralateral breast cancer, and distant metastases) and overt axillary disease for patients who did not receive axillary dissection. Disease-free survival was calculated from the date of randomization to the date of the first evidence of disease or latest follow-up. Median follow-up was calculated by the reverse Kaplan-Meier method.[11] Overall survival curves were estimated using the Kaplan-Meier method and compared by the log-rank test.

Multivariable Cox regression modeling was used to estimate the hazard ratio with 95% confidence intervals of death (all causes) in the no axillary dissection group compared with the axillary dissection group, adjusting for tumor grade and estrogen receptor status.

Crude cumulative incidences of breast cancer mortality and of adverse breast events, with 95% confidence intervals,[12] were estimated in a competing events framework and compared by the Gray test.[13] When death due to breast cancer was the endpoint, death for other causes was a competing event. When distant metastasis was the endpoint, local recurrence, other primary cancer, and death for nonneoplastic causes were competing events.

Multivariable Fine and Gray models[14] were used to estimate the subdistribution hazard ratio (hazard specific for crude cumulative incidence) with 95% confidence intervals for breast cancer death and distant metastases in the no axillary dissection compared with the axillary dissection arm, adjusting for tumor grade and estrogen-receptor status. Fine and Gray models are an extension of Cox proportional hazards' models in which the risk of competing events is taken into account.

RESULTS

Patient characteristics by treatment group are shown in Table 1. Median age was 70 (range: 65–80) years. Eight patients had pT2 disease, in all cases ≤2.5 cm (consistent with the mammographic selection criterion of ≤2 cm for randomization). ER and PgR receptor status was determined in 218 of 219 patients, 191 of whom (87.6%) were positive for 1 or more receptors (ER+, PgR+, or both), 149 (68.4%) were positive for both receptors, and 25 (11.4%) were ER− and PgR−. Most patients had G1-G2 cancers, 9.3% of patients had G3 tumors. Eleven patients (5%) had a poor prognostic profile (ER−, PgR−, G3); one of these developed liver metastases and died of her disease; another developed contralateral breast cancer and is alive and disease free; 2 others died of a second non–breast cancer; and 1 patient died of causes unrelated to cancer. Of the 109 patients in the axillary dissection group, 23% had involved axillary nodes; in most (72%), only 1 node was involved. Of the 110 patients in the no axillary dissection arm, 4 developed ipsilateral axillary disease 7, 97, 131, and 157 months after surgery; all 4 patients received delayed axillary dissection, and 2 subsequently developed distant metastases and died of breast cancer; the other 2 are alive and disease free.

TABLE 1. Characteristics of Patients in the Axillary Dissection and No Axillary Dissection Arms

	AD	No AD
Median age at diagnosis (yrs)	70	70
Pathological tumor size		
T1a	2 (1.8%)	6 (5.4%)
T1b	30 (27.6%)	44 (40%)
T1c	69 (63.3%)	52 (47.3%)
T2 (≤2.5 cm)	8 (7.3%)	8 (7.3%)
Histological type		
Ductal carcinoma	60 (55%)	61 (55.4%)
Lobular carcinoma	20 (18.3%)	19 (17.3%)
Other infiltrating carcinoma	29 (26.7%)	30 (27.3%)
Grade		
G1	22 (20.2%)	27 (24.5%)
G2	73 (67%)	72 (65.5%)
G3	12 (11%)	8 (7.3%)
Not evaluated	2 (1.8%)	3 (2.7%)
Receptor status		
ER+ PgR+	68 (62.4%)	81 (73.6%)
ER+ PgR−	25 (23%)	17 (15.5%)
ER− PgR+	1 (0.9%)	1 (0.9%)
ER− PgR−	15 (13.7%)	10 (9.1%)
Not evaluated	0	1 (0.9%)

Table 2 shows the distribution of first events and causes of death by treatment group, together with 15-year crude cumulative incidence estimates of first events and death. The 15-year crude cumulative incidence of axillary disease was 6% (95% confidence interval: 0%–12.6%) in the no axillary dissection arm and zero in the axillary dissection arm. Seven patients in the no axillary dissection arm and 4 in the axillary dissection arm had ipsilateral breast tumor recurrence; all were treated by wide resection (not mastectomy). Two ipsilateral breast tumor recurrence patients in the axillary dissection arm developed distant metastases and 1 died of her disease. Three ipsilateral breast tumor recurrence patients in the no axillary dissection arm developed distant metastases and died of their disease; another ipsilateral breast tumor recurrence patient in this arm developed colon cancer and died of that disease. The crude 15-year crude cumulative incidence of ipsilateral breast tumor recurrence was 4% (95% confidence interval: 0.1%–7.8%) in the axillary dissection arm and 8.3% (95% confidence interval: 2.1%–14.5%) in the no axillary dissection arm.

Nine patients in each arm developed distant metastases as first event. The 15-year crude cumulative incidence of distant metastases was 8.6% (95% confidence interval: 3.2%–13.9%) in the axillary dissection arm and 9.6% (95% confidence interval: 3.3%–15.9%) in

TABLE 2. Fifteen-Year Crude Cumulative Incidences of First Unfavorable Events and Death in the Axillary Dissection and No Axillary Dissection Arms

	AD		No AD		Total	
	N	CCI% (95% CI)	N	CCI% (95% CI)	N	CCI% (95% CI)
First event						
IBTR*	4	4 (0.1–7.8)	7	8.3 (2.1–14.5)	11	8.4 (4.7–12.1)
Axillary relapse		No cases	4	6 (0–12.6)		
Contralateral breast cancer	2	1.9 (0–4.4)	8	8.9 (2.6–15.1)	10	5.3 (2–8.6)
Distant metastasis	9	8.6 (3.2–13.9)	9	9.6 (3.3–15.9)	19	9.1 (5–13.2)
Non–breast malignancy	8	7.7 (2.5–12.9)	9	8.8 (3.3–14.3)	15	7.8 (4.1–11.5)
Cause of death						
Breast cancer	8	7.6 (2.5–12.7)	10	9.2 (3.7–14.6)	18	8.4 (4.7–12.1)
Non–breast malignancy	6	5.5 (1.2–9.8)	7	6.4 (1.8–10.9)	13	5.9 (2.8–9.1)
Not due to cancer	17	24.7 (7.6–41.8)	18	18.1 (10.3–26)	35	21.4 (11.9–31)

CCI indicates 15-year crude cumulative incidence; CI, confidence interval
*IBTR ipsilateral breast tumor recurrence.

the no axillary dissection arm. Seventeen patients with distant metastases as first events died of breast cancer. All patients who developed distant metastases received second-line hormone treatment.

Eight axillary dissection arm patients had a second primary cancer as first event (2 lung cancers, 2 colon cancers, 1 each of liver, kidney, lymphoblastic leukemia, and endometrial cancer). Nine patients in the no axillary dissection group developed a second primary (2 stomach cancers, and 1 each of small cell lung, sarcoma, bladder, ovarian, colon, renal, and endometrial cancer). Mortality for non–breast cancer was similar in the 2 groups (crude cumulative incidence 5.5% in the axillary dissection arm; 6.4% in the no axillary dissection arm), as was mortality not due to cancer (crude cumulative incidence 24.7% vs 18.1%). No patient died of thromboembolic complications.

The 15-year crude cumulative incidence of breast cancer death was 7.6% (confidence interval: 2.5%–12.7%) in the axillary dissection arm and 9.2% (confidence interval: 3.7%–14.6%) in the no axillary dissection arm. Crude cumulative incidence curves for breast cancer mortality and distant metastases did not differ significantly between the 2 groups (Gray 2-sided test; $P = 0.64$ for breast cancer mortality and $P = 0.95$ for distant metastases) (Figs. 1, 2).

The results of the multivariable Fine and Gray modeling of influence of putative prognostic factors on breast cancer mortality and distant metastases are shown in Table 3. Neither axillary dissection nor tumor grade had a significant effect on the 2 endpoints. By contrast, estrogen-negative tumors were associated with significantly greater risk of breast cancer death and distant metastases than estrogen-positive disease, with subdistribution hazard ratios for estrogen-negative disease almost 5 times and more than 3 times greater, respectively, than estrogen-positive disease. Kaplan-Meier curves for overall survival in the 2 treatment groups are shown in Figure 3 and indicate no difference in survival. Cox modeling, adjusting for tumor grade and estrogen-receptor status also indicated that the hazard of death (all causes) did not differ significantly between the 2 study arms (hazard ratio = 1.18, 95% confidence interval: 0.73–1.92).

DISCUSSION

The findings of this randomized controlled study provide further strong evidence that older patients with early breast cancer, treated with conservative surgery, postoperative radiotherapy, and adjuvant tamoxifen, do not benefit from axillary dissection. Specifically, after 15 years of follow-up, distant metastasis rate, overall survival, and breast cancer mortality in the axillary dissection and no axillary dissection arms were indistinguishable. Furthermore, although 23% of the 109 patients who received axillary dissection had positive lymph nodes, only 4 of the 110 patients (15-year crude cumulative incidence, 6%) who did not receive axillary dissection developed overt axillary disease in 15 years of follow-up and required delayed

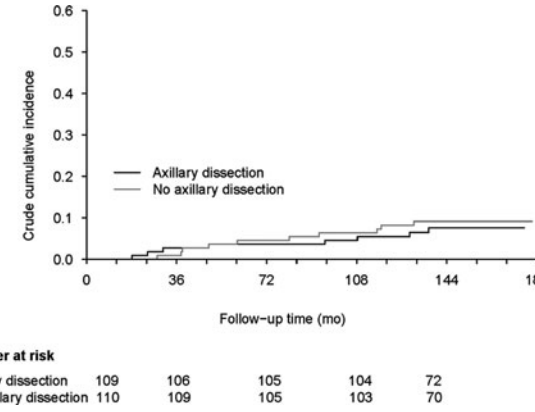

FIGURE 1. Crude cumulative incidence curves of breast cancer mortality in the 2 treatment arms.

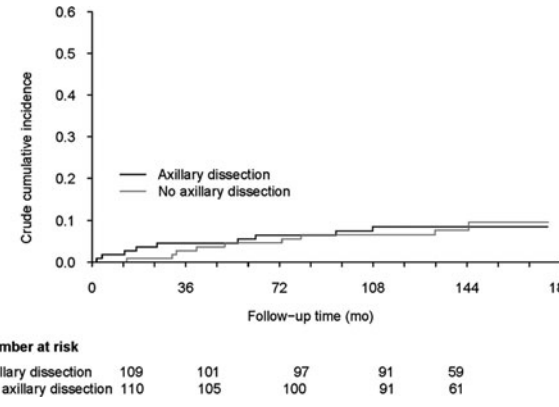

FIGURE 2. Crude cumulative incidence curves of distant metastases in the 2 treatment arms.

TABLE 3. Fine and Gray Model Estimates of Subdistribution Hazard Ratios, With 95% Confidence Intervals for Breast Cancer Death and Distant Metastasis According to Treatment Arm (Axillary Dissection and No Axillary Dissection); Tumor Grade and Estrogen Receptor Status

	Breast Cancer Death Subdistribution Hazard Ratios (95% Confidence Interval)	Distant Metastasis Subdistribution Hazard Ratios (95% Confidence Interval)
Treatment arm (axillary dissection vs no axillary dissection)	0.721 (0.27–1.89)	1.572 (0.70–3.50)
	$P = 0.51$	$P = 0.27$
Tumor grade (G3 vs G1/G2)	0.234 (0.03–2.02)	0.243 (0.04–1.43)
	$P = 0.19$	$P = 0.12$
Estrogen receptor status (ER− vs ER+)	4.868 (1.65–14.38)	3.019 (1.25–7.27)
	($P = 0.004$)	($P = 0.015$)

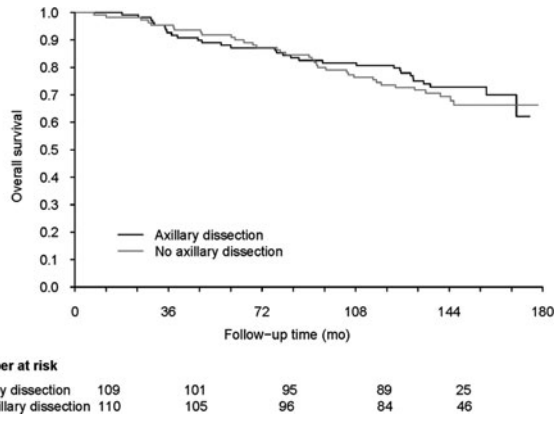

FIGURE 3. Overall survival curves in the 2 treatment arms.

axillary dissection. One may assume a similar 23% rate of occult axillary involvement in the no axillary arm; yet, this manifested as overt disease in only 4 cases and had no effect on overall outcomes.

Our findings are identical to those of Fisher's NSABP B-O4 trial,[15] which, after 25 years, found no difference in distant metastasis-free survival or overall survival between patients (with a clinically clear axilla) randomized to radical mastectomy versus simple mastectomy without axillary dissection. Furthermore, only 18% of the simple mastectomy arm patients subsequently developed overt axillary disease, even though 40% of patients in the radical mastectomy arm had involved axillary nodes.

Support for the nonuse of axillary dissection in elderly patients comes from other studies. We have mentioned our recently published prospective nonrandomized study[8] on elderly patients where, after 15 years of follow-up, there was no difference in breast cancer mortality between the axillary dissection and no axillary dissection groups. There is also the International Breast Cancer Study Group trial,[16] which randomized patients older than 60 years to axillary dissection versus observation. Tamoxifen was prescribed to all patients for 5 years. After 6.6 years of follow-up, there was no difference in overall or disease-free survival between the 2 arms. Moreover, 28% of patients in the axillary dissection arm had metastatic axillary nodes, whereas only 3% of observation arm patients developed overt axillary disease, and breast cancer mortality was unaffected.

The results of the recently published American College of Surgeons Oncology Group Z0011 trial[17] are also relevant even though it was not confined to elderly women. This study randomized women with T1-T2N0 breast cancer and an involved sentinel node to axillary dissection versus no further axillary treatment. After a median follow-up of 6.3 years, there was no significant difference in disease-free survival or overall survival between the 2 groups, despite the fact that 27% of axillary dissection patients had additional metastatic lymph nodes.

Given that axillary dissection is mainly a staging procedure, the information provided from resected axillary nodes rarely influences postoperative therapy options, which are now mainly determined by the biological profile of the primary.[18]

A possible explanation for the low rate of overt axillary disease in patients who did not receive axillary dissection in this trial (and other studies) is that postoperative radiotherapy administered to whole breast incidentally irradiates the lower part of axilla. That this may not be the principal explanation is suggested by the results of another prospective study we carried out[19]: the 15-year crude cumulative incidence of axillary relapse among 354 elderly breast cancer patients who received quadrantectomy without axillary dissection and also without postoperative radiotherapy followed by adjuvant tamoxifen was only 4.2%. A study that assessed doses to levels I and II of the axilla during conventional irradiation found that they were unlikely to have been sufficiently high to reliably eliminate axillary disease.[20] If conventional whole breast irradiation offers little benefit to elderly women with early breast cancer not receiving axillary dissection,[19] then partial irradiation techniques that limit the dose to the tumor bed are also likely to be of little use.

Another possible explanation for the low rate of overt axillary disease is that only cancer stem cells within involved lymph nodes can give rise to progressive disease within the axilla and may be relatively rare within lymph node metastases.[21,22] It is also likely that immunological surveillance by intact axillary nodes together with tamoxifen or other hormonal therapies can prevent residual cancer cells from dividing for many years, if not indefinitely.

As in our previous studies on elderly breast cancer patients, we found that estrogen-negative status was a major predictor of distant metastases and breast cancer death. In this study, the hazard ratio of death was nearly 5 times greater in women with estrogen-negative tumors than in those with estrogen-positive tumors, and these patients present a treatment dilemma because hormonal therapy is not indicated: however, we would not be in favor of cytoxic chemotherapy in elderly patients with estrogen receptor-negative disease unless they were in good physical condition with no major concomitant illnesses. Elderly patients are likely to die of other causes before dying of breast cancer, and quality of life is paramount in this age group.

By contrast, the multivariable analysis found that tumor grade had no influence on the crude cumulative incidence of breast cancer death or distant metastases (Table 3). In fact, most patients who developed distant metastases had G2 cancers (16/145 G2 cases) whereas one patient had G1 disease (1/49 G1 cases) and another had G3 disease (1/20 G3 cases).

A limitation of our study is that it did not recruit the required number of patients, which makes it underpowered to demonstrate noninferiority between the 2 arms. However, the 95% confidence limits of the difference between the estimated metastasis incidence at 15 years in the no axillary dissection and the axillary dissection arm were −0.07 and 0.09, respectively. Because the upper limit is less than 0.10, we may conclude that the trial has demonstrated noninferiority of the no axillary dissection treatment.[17]

To conclude, the long-term results of this prospective randomized trial confirm that older patients with early breast cancer and no palpable axillary nodes can be safety treated with conservative surgery without axillary dissection, but with adjuvant tamoxifen, because breast cancer mortality and overall survival are indistinguishable from those who receive axillary dissection. Even sentinel node biopsy can be avoided because the 15-year crude cumulative incidence of overt axillary metastases was very low, and information from removed lymph nodes is unlikely to modify postoperative therapeutic choices because hormonal therapy in early receptor-positive breast cancer is standard treatment for this age group.[23]

ACKNOWLEDGMENTS

The authors thank Don Ward for help with the English and acknowledge Professor G. De Palo who died recently, without whose help and encouragement the trial would never have been implemented.

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