PAPER

T1a Breast Carcinoma and the Role of Axillary Dissection

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Hypothesis: Axillary dissection (AD) does not affect recurrence or survival in T1a breast cancer.

Design: Cohort study comparing patients who underwent AD and those who did not.

Setting: Provincial cancer agency.

Patients: Six hundred ninety-one women with pathologically diagnosed T1a tumors.

Main Outcome Measures: Rates of axillary metastases stratified according to grade and lymphovascular and/or neural invasion, rates of relapse, and disease-specific survival.

Results: Grade 1, 2, and 3 tumors without lymphovascular and/or neural invasion had axillary nodal involvement rates of 0.7%, 7%, and 7.8% of patients, respectively; with lymphovascular and/or neural invasion, axillary nodes were involved in 9.1%, 39.3%, and 44.4%, respectively. No statistically significant differences were found between the cohorts in relapse rates ($P=.70$) or survival ($P=.84$).

Conclusion: Higher tumor grade and lymphovascular and/or neural invasion increased the rate of nodal metastases in T1a tumors, but AD did not improve relapse rates or breast cancer–specific survival.

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AXILLARY DISSECTION (AD) provides prognostic information and directs adjuvant therapy in patients with breast carcinoma.[1] Its role in the management of small T1a lesions (tumor size ≤5 mm) is questioned owing to the suggestion that the rates of axillary metastases in pathologically staged T1a (pT1a) lesions are low. Studies that contain both pathologically and clinically staged tumors quote rates between 10% and 20%.[2,3] More recent reports are lower at 0% to 12%. These later series were pathologically staged but include few patients. This study examined the rates of axillary metastases among 552 women who had T1a breast cancer. Stratification by grade and lymphovascular and/or neural invasion (LVNI) status was used to identify a subgroup for whom AD would have a very low probability of finding nodal involvement.

An equally important question to the rate of nodal involvement is whether AD is independently associated with improved locoregional control and survival. Many studies have examined this question but controversy remains. To clarify the role of AD on outcomes for patients with pT1a breast cancer, relapse and breast cancer–specific survival were compared between 691 women who did and did not undergo AD.

METHODS

Subjects were selected from the Breast Cancer Outcomes Unit Database of the British Columbia Cancer Agency. This database contains detailed demographic, staging, treatment, and outcome information for patients diagnosed as having pT1a breast cancer and referred to the British Columbia Cancer Agency since January 1, 1989. During the period between January 1, 1989, and December 31, 1998, six hundred ninety-one women who had pT1a invasive breast cancer were identified. Exclusion criteria included males, tumors larger than 5 mm, locally advanced tumors, metastatic tumors, and any patient with synchronous invasive or in situ disease of the contralateral breast.

To examine the predictive value of AD, patients having AD were stratified according to the tumor's Nottingham grade, presence of an LVNI, and nodal status at surgery. To examine the effect of AD on outcome in T1a breast cancer, patients who underwent AD and those

Table 1. Axillary Nodal Status Stratified by Grade and LVNI Status of the Primary Tumor

Grade	LVNI Status	Total No. of Tumors	Nodal Involvement, No. (%)
1	LVNI–	151	1 (0.7)
	LVNI+	11	1 (9.1)
2	LVNI–	215	15 (7.0)
	LVNI+	28	11 (39.3)
3	LVNI–	129	10 (7.8)
	LVNI+	18	8 (44.4)

Abbreviation: LVNI, lymphovascular and/or neural invasion.

who did not were compared for age at diagnosis using a *t* test and the proportions receiving radiotherapy, hormonal therapy, or chemotherapy using χ^2 tests and the Fisher exact test, where appropriate. Logistic regression and the Cox proportional hazards model were used to explore the association between axillary node dissection and end points of regional or distant relapse and breast cancer–specific death rates at 2 and 5 years, adjusting for age, grade, and LVNI status. Unadjusted differences in times to relapse and death were illustrated with Kaplan-Meier plots and compared using log rank tests. Data were analyzed using the statistical software package SPSS for Windows, Version 10 (SPSS Institute Inc, Chicago, Ill). *P* values were all 2-tailed and those less than .05 were considered statistically significant.

RESULTS

There were 691 patients aged 26 to 90 years (mean age, 59.8 years) eligible for analysis. A total of 581 patients (84.0%) underwent AD. Of those who underwent AD, the grade and LVNI status of the primary tumor was known in 552 (79.9%). The proportions of histologic subtypes among these 552 patients were as follows: invasive ductal carcinoma in 69.7% of the patients, comedocarcinoma in 11.4%, tubular carcinoma in 10.0%, lobular carcinoma in 4.9%, and other subtypes in 4.0%.

Table 1 gives the tumor characteristics and nodal status after AD for the 552 patients with known grade and LVNI status. Patients with higher than grade 1 tumors had an increased chance of axillary metastases (grade 1 vs grade 2, $P=.004$; grade 1 vs grade 3, $P=.002$), but the presence of LVNI had a more profound effect on the rate of axillary metastases (LVNI positive vs LVNI negative, $P=.001$).

Patients who underwent AD and those who did not were analyzed to identify significant demographic and treatment differences between cohorts. Patients who underwent AD had a mean age of 58.8 years (median age, 59.0 years) at diagnosis compared with 64.8 years (median age, 66.5 years) for those who did not undergo AD ($P<.001$). Histologic tumor type was independent of AD ($P=.17$-$.78$). Patients who underwent AD were significantly more likely to receive chemotherapy than those who did not, 6.9% and 0.9%, respectively ($P=.02$). Adjuvant radiotherapy ($P=.04$) and hormonal therapy ($P=.04$) use was similar between both groups.

Patients who underwent AD and those who did not were analyzed using logistic regression to detect differences in regional and/or distant relapse rates and time to first relapse. Because of the few events, both regional and distant relapse rates were combined. The overall relapse rates at 2 and 5 years were 2.5% and 6.2%, respectively. There were no differences in 2-year relapse rates between cohorts ($P=.40$) even after adjustments for age, grade, and LVNI status ($P=.70$). Five-year relapse rates were similar between cohorts who underwent AD and those who did not ($P=.70$) even when adjusted for age, grade, and LVNI status ($P=.90$).

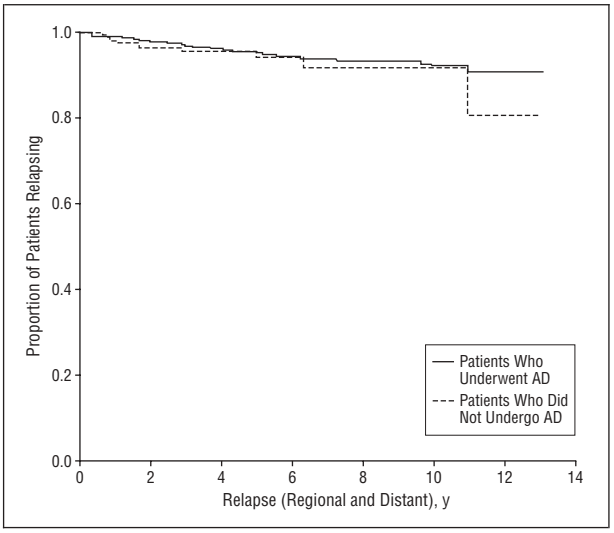

Figure 1. There was no statistically significant difference in time to regional or distant relapse between the 2 cohorts by the log rank test ($P=.50$). AD indicates axillary dissection.

Time to regional or distant relapse is shown in **Figure 1**. The relapse rate was independent of AD ($P=.50$). The Cox proportional hazards model was used to examine time to regional or distant relapse while adjusting for age, grade, and LVNI status; there was no statistically significant difference by AD ($P=.70$).

Time to cancer-specific death is shown in **Figure 2**. There was no significant association between death rates and AD ($P=.70$) even when adjusted for age, grade, and LVNI status ($P=.60$). The Cox proportional hazards model was used to examine time to death from breast cancer while adjusting for age, grade, and LVNI status; no statistically significant difference by AD use was identified ($P=.80$).

COMMENT

Many recent articles have examined the rates of axillary metastases in patients with pT1a breast cancer. **Table 2** summarizes the recent literature.[4-12] In these articles, the incidence of nodal metastases varied from 0% to 12.2%, with the discrepancy likely related to the small sample sizes of these studies. These studies, like others before them, have highlighted the fact that primary tumor characteristics affect the rate of nodal metastases. It may be that the studies showing higher rates of nodal metastases had women with more aggressive primary tumors.

To develop a simple model to predict the likelihood of nodal involvement at AD, we chose the primary tumor Nottingham grade and LVNI status to stratify patients. These 2 primary tumor characteristics are universally available on light microscopic examination of primary tumor via open or core biopsy specimens. Both have

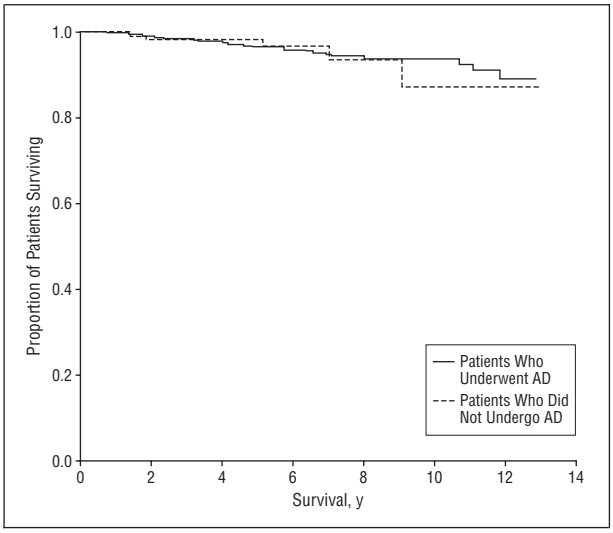

Figure 2. There was no statistically significant difference in time from diagnosis to cancer-specific death between the 2 cohorts by the log rank test (P=.90). AD indicates axillary dissection.

Table 2. Literature Review of the Rates of Nodal Metastases in Patients With Pathologically Staged T1a Tumors

Source	Total No. of Nodal Metastases	Incidence, %
Silverstein et al[4]	101	5.0
Whitten et al[5]	82	4.0
McGee et al[6]	74	12.2
White et al[7]	123	9.8
Visser et al[8]	141	6.9
Fein et al[9]	?	8.8
Pandelidis et al[10]	54	3.7
Madan et al[11]	5	0
Mincey et al[12]	39	0

been shown to be strong predictors of nodal metastases.[13] Estrogen receptor (ER) status was not used in the analysis since this information was unknown in 41% of our patients and since ER status provides less prognostic information compared with other primary tumor characteristics.[14] We stratified the 552 patients who underwent AD in whom the grade and LVNI status of the primary tumor were known, to identify a subgroup for whom nodal involvement would approximate 0%. Patients with grade 1 tumors that were LVNI negative only had a 0.7% incidence of axillary metastases. If one was to recommend omission of AD based on low rates of nodal involvement alone, as opposed to whether AD improves survival, a less than 1% incidence of nodal positivity would be acceptable to most women and is unlikely to adversely affect survival. In patients with clinically negative axillae and primary tumors 5 mm or smaller that are LVNI negative, omission of an AD has been estimated to decrease 5-year disease-free survival by less than 1%.[15]

The role of AD must evolve as adjuvant therapies are increasingly chosen based on primary tumor characteristics.[16] This is illustrated by a recent report of a randomized trial examining axillary radiotherapy instead of AD. Women with tumors smaller than 1.2 cm who underwent partial mastectomy were randomized to receive either no axillary treatment or axillary radiotherapy alone. Patients received either tamoxifen citrate therapy for 5 years for ER-positive tumors, or combined cyclophosphamide, methotrexate, and fluorouracil chemotherapy for 6 months if they had ER-negative tumors that were grade 3 and displayed a high proliferative index. No difference was found between cohorts for axillary metastases. In addition, distant metastases were rare in this series, with actuarial survival at 5 years estimated at 99%.[17] One would presume these good results are partially owing to the adjuvant hormonal therapy or chemotherapy received, as only 84 of the 435 subjects received none. The trend toward giving adjuvant therapy based on primary tumor characteristics should affect the decision to proceed with AD, especially if AD does not independently improve locoregional control or survival.

Many studies have looked at the ability of AD to improve control and survival; however, controversy remains owing to the administration of adjuvant therapy and small sample sizes. One randomized trial showed that AD for tumors smaller than 3 cm was associated with improved survival, but patients who underwent AD were more likely treated with chemotherapy and it was, therefore, unclear if the survival advantage was because of undergoing AD or receiving the adjuvant treatment.[18] Data prior to the era of adjuvant systemic therapy suggest that AD provides excellent regional control and may also improve survival.[19] In contrast, a prospective randomized trial that compared mastectomy plus axillary clearance vs mastectomy alone with no adjuvant therapy was terminated early because there were significantly more axillary recurrences in those who did not undergo AD (P=.06). However, at 10 years there were no differences in time to recurrence or survival rates among the 95 women involved in the study.[20] In the lack of consistent evidence from large randomized trials, the controversy regarding the effect of AD on survival remains.

Many studies have shown no survival benefit for elderly women who have early breast cancer and these may be another group of patients who would not benefit from AD irrespective of grade and LVNI status. Martelli et al[21] performed a retrospective review of 321 patients over the age of 70 years with T1-3 and T4b breast carcinoma with clinically nonpalpable nodes. These patients all underwent partial mastectomy and subsequently received tamoxifen therapy. The cumulative probabilities of developing a local, axillary, or distant recurrence at 72 months were 5.4%, 4.3%, and 6.2%, respectively. The 72-month relapse-free survival rate was 76% with a 25.8% incidence of death from intercurrent disease. Because about 70% of the women in this study had T1 tumors, the researchers concluded that their data were in agreement with other reported literature, in that patients aged older than 70 years with T1 tumors and clinically negative axillae may be treated with partial mastectomy and tamoxifen therapy alone. High response rates to hormonal therapy and increased death rates due to concomitant diseases among elderly women were hypothesized to account for these results. Similarly, Feigelson et al[22] concluded that AD does not decrease recur-

rence or improve survival in women older than 70 years with T1 breast carcinoma. None of the 78 women in their cohort received chemotherapy and 14 women did not undergo AD.

Wazer et al[23] reported a prospective study with 73 women aged older than 65 years with stage I/II breast cancer treated with partial mastectomy without AD and locoregional radiotherapy. Tamoxifen therapy was used in 66 of these patients. At 8 years, the rates of locoregional control were 92.5% and 100%, respectively. At 8 years, rates of local and regional lymph node control were 92.5% and 100%, respectively. Breast cancer–specific survival was high at 93.8%, although overall survival was only 52.5% owing to comorbid disease. These authors suggested that limiting aggressive regional and systemic therapies resulted in good outcomes in these patients.[23] Truong et al[24] reviewed 8038 women stratified according to 3 age-specific cohorts of 50 to 64, 65 to 74, and 75 years and older. Axillary dissection was omitted in 4%, 8%, and 22% of these patients, respectively. In the cohort aged 75 years and older, no statistically significant differences in systemic therapy use, regional relapse, or breast cancer–specific survival were demonstrated between women who did and did not undergo AD. This was not the case in the younger cohorts and, as such, they concluded that AD could only be omitted for this older cohort. In the current study, patients were not stratified by age as the numbers involved would have been too small to draw any meaningful conclusion.

In this study, patients were divided into 2 cohorts, those who underwent AD (n=581) and those who did not (n=110). Consistent with the findings from prior studies, the age of the cohort that did not undergo AD was significantly older,[25] by almost 6 years. Significantly fewer patients in the older cohort who did not undergo AD received chemotherapy. However, there were no statistically significant differences in relapse or survival outcome between patients who underwent AD and those who did not in relation to histologic type, adjuvant radiotherapy, or hormonal therapy. Of 110 patients who did not undergo AD, only 1 received chemotherapy, 1 received irradiation to the axillary nodes, and 17 received hormonal treatment.

Even with significantly more chemotherapy received in the AD group, we did not show any significant advantage for AD among women with T1a breast cancer. Regional and/or distant relapse rates at 2 and 5 years as well as time to relapse were similar between groups as defined by AD use, even when adjusted for age, grade, and LVNI status. The combined total regional and distant relapse rates were 6.4% (37/581) in those who underwent AD and 7% (8/110) in those who did not. Similarly there was no difference between these groups for time to death even when adjusted for age, grade, and LVNI status.

A limitation of this study is the retrospective cohort design and the fact that patients who did not undergo AD were significantly older. As discussed, older patients tend to have better outcomes than their younger counterparts. In addition, the number of regional and distant relapse events were small in the group that did not undergo AD (only 8 of 100), therefore limiting the power needed to discern small differences.

CONCLUSIONS

Axillary dissection may be omitted for patients with pT1a tumors that are grade 1 and are LVNI negative without compromising adjuvant therapy choices or patient outcome. Patients with higher-grade primary tumors and LVNI-positive disease may benefit from AD owing to higher rates of axillary metastases; however, we were unable to show a survival advantage even after adjusting for age, grade, and LVNI status. Because of the small sample size and that patients who did not undergo AD were significantly older in this study, we cannot recommend that AD be abandoned in patients with a high-grade and/or LVNI-positive T1a tumors.

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All statistical analysis was done by Mr Mackinnon, a statistician employed by the British Columbia Cancer Agency.

The paper reports data from the Breast Cancer Outcomes Unit which records information on all patients registered at the British Columbia Cancer Agency. The British Columbia Cancer Agency is a referral-based provincial organization that provides oncologic care and research for patients diagnosed as having cancer.

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DISCUSSION

John T. Vetto, MD, Portland, Ore: Recent trends toward a downward shift in the mean size of tumors, smaller operations, and more systemic therapy for patients with node-negative breast cancer have led to a heated debate over the need for routine axillary staging. The authors are to be congratulated for presenting data that provides important information, rather than just adding more fuel to the fire.

Instead of taking one side or another, I would like to take the tack of the Harvard Negotiation Project in their book "Getting to Yes" (like many surgeons, I am excited that I read something that has nothing to do with surgery and so I want to tell you about it) and propose a solution to achieve a mutual goal, which I believe all of us who treat breast cancer have—to provide our patients with the highest cure rate with the least morbidity.

Let us look at the value of AD from the standpoint of its 2 reported benefits. First, regarding its effect on local control and survival, it is recognized that earlier studies showing a survival benefit for AD were relevant mostly to a time gone by when tumors were larger and adjuvant therapy was less used. The authors' finding of no effect of AD on relapse of T1a cancers is no surprise given that relapse was so uncommon in their study that they had to combine local and distant relapse in the analysis. Their finding is supported by 3 prospective randomized trials, including one which was limited to T1a cancer, which all showed low rates of axillary recurrence and no effect on survival when the axilla was undissected.

Regarding the effect of nodes on decision making, there is increasing support in the literature for the idea of giving adjuvant therapy based only on tumor rather than nodal factors, particularly the tumor factors that we have just heard mentioned: LVNI status. Conversely, the large database from Nottingham continues to support the inclusion of nodal status in the popular Nottingham prognostic index.

I think the answer may lie in the idea, supported by the data just presented, of T1a cancer as a heterogeneous entity. This idea is demonstrated by the authors' finding (on subgroup analysis, which their large sample size allowed for) that node positivity rates in T1a cancer vary tremendously, between 0.7% and 44.0%, depending on grade and LVNI status. The sixth edition of the *American Joint Committee on Cancer Manual* will recognize this heterogeneity by subdividing T1a cancer further into macroinvasive and microinvasive types. Based on the concept of heterogeneity, I believe that most of us recommend axillary staging for small breast cancers selectively based on factors such as these: Whether the node information will change the treatment plan; the patient's age, or more correctly, their performance status; tumor factors, particularly the ones we have mentioned: grade and LVNI status; and finally, the patient's concerns of recurrence vs the morbidity of the dissection.

I have 4 questions for the authors: First, did the authors find a relationship between node status and survival? If so, this argues that node status is, indeed, important in at least selected patients.

Second, do the authors think that ER status is also a factor in selecting for nodal staging? I know that they did not look at this because it was unknown in 42% of the patients, but a recent National Surgical Adjuvant Breast Project meta-analysis of T1a-b cancers found improved survival from tamoxifen therapy and/or chemotherapy in ER-positive, node-negative patients, suggesting that ER status should not be a factor in helping us decide to do or not to do AD.

Third, how would less invasive or noninvasive methods of nodal staging effect the author's recommendations? Specifically, what about sentinel node biopsy? In a 2000 study by DiFonzo, sentinel node biopsy for T1a-b cancers in women ages 70 through 90 years changed the treatment plan in 14% of cases. What about PET scanning? In a 2001 study by Greco, PET scanning had an axillary staging accuracy of up to 94%, approaching that of sentinel node biopsy, and offering the additional advantages of identifying multicentric and extra-axillary disease.

Fourth, for an undissected axilla, do the authors recommend axillary radiotherapy, as advocated by a recent European trial?

Samuel E. Wilson, MD, Orange, Calif: Could the authors comment on whether there is any subjective or sampling error possible in the histologic determination of lymphoneural invasion?

Fred Dirbas, MD, Stanford, Calif: I was wondering if a subset analysis was done regarding the number of lymph nodes that were involved with metastatic carcinoma and whether that correlated with LVNI status. And, specifically, would it be possible to do a sentinel node biopsy alone in any of these patients and then stop at that point even if it were involved because of a low risk of additional nodal involvement?

Dr Davis: I would like to thank our discussant for very insightful comments, and I would also like to thank Dr Schneidereit and coinvestigators for helping develop this very interesting cohort of patients.

This is one of the largest series of T1a cancer reported, and I believe this cohort is well studied. In fact, 80% of patients have pathologic review at point of entry into the cancer system and, therefore, LVNI status is well reported. Follow-up is through standardized questionnaires to providers, either within the clinic itself or sent to family practitioners and surgeons through the province.

With respect to Dr Vetto's question, no, we did not look at survival based on node status. I assume that there would be poorer survival in women who are node positive than has been shown in every other study. Estrogen receptor status was not measured in 42% of patients, and I believe this is because the surgery was done throughout the Province of British Columbia [BC] in more than 50 separate hospitals in which many do not have the capacity to complete ER status.

The issue of other techniques of axillary staging is certainly interesting. Yes, there are new techniques such as PET or MRI scanning which are still investigational. We have not found that using PET in the axilla achieves as high an accu-

racy as a surgical approach. With respect to sentinel lymph node dissection, this technique has not been as widely introduced as yet in BC, and accuracy standards are difficult to meet. We still see it as a surrogate for axillary lymph node dissection, and this is because of a high false-negative rate. The false-negative rate calculated as false negative over all true-positive nodes is at least 5% in most of the literature. Krag's false-negative rate was reported at 11% in the *New England Journal of Medicine*.

We describe 2 groups of patients with pTla cancer; those with a higher risk have grade 3 disease and LVNI. And, yes, these patients should have sentinel lymph node mapping done if a high accuracy can be achieved. I think we all should have a high index of suspicion that these patients will harbor positive nodes and, therefore, there is a good chance that they will require full nodal dissection. With respect to the low-risk patients, however, I am not convinced that it is even necessary to do sentinel lymph node mapping when the positivity rate is less than 1%.

With respect to axillary radiotherpay, again, this is an interesting topic. When we do sentinel lymph node mapping, we usually find the sentinel nodes are very low in the axilla and most standard radiation fields will cover the level I lymph node basin. Most of our patients are having these low nodes radiated as part of standard treatment. We should not be adding radiotherapy to the level II to III nodal basins routinely due to high morbidity.

Littré's Hernia

In 1700, the French surgeon Alexis Littré (1658-1726) described a new form of hernia and 2 unrecognized examples of a Meckel diverticulum in a hernia sac.[1] Littré thought that the diverticulum was acquired following formation of the hernias. It was not until 1809 that Johann Friedrich Meckel (1781-1833) described his diverticulum and postulated its congenital origin.[2] Since then, many examples of herniation of the diverticulum, both strangulated and incarcerated, have been recorded, thus the name Littré hernia. The hernia was described 109 years before Meckel's report.

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