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The Impact of Prophylactic Axillary Node Dissection on Breast Cancer Survival—A Bayesian Meta-Analysis

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Background: Because of the general acceptance of the NSABP B-04 study, prophylactic axillary node dissection for women with clinically negative axillae is considered diagnostic, but not therapeutic, by many oncologists. Nevertheless, several authors have shown that B-04 did not include enough patients to exclude a small survival advantage.

Methods: A Bayesian meta-analysis of the available literature was performed comparing standard treatment to standard treatment without axillary node dissection. Six randomized controlled trials were identified, consisting of nearly 3000 patients and spanning four decades.

Results: All six trials showed that prophylactic axillary node dissection improved survival, ranging from 4% to 16%, corresponding to a risk reduction of 7%-46%. Combining the six trials showed an average survival benefit of 5.4% (95% CI = 2.7-8.0%, probability of survival benefit > 99.5%). Adjusting for biases in the individual studies did not alter the conclusions, nor did subset analysis of Stage I patients.

Conclusions: Axillary node dissection improves survival in women with operable breast cancer. Nevertheless, two important limitations of this analysis are noteworthy. Few of the patients in the six trials had T1a tumors, so extrapolation of these results to this subset (and those with nonpalpable tumors) may be inappropriate. Essentially no patients in the six trials were treated with adjuvant therapy, as contrasted to current clinical practice. It is possible that the risk reduction seen in this meta-analysis may be diminished in patients receiving adjuvant chemotherapy. Despite these limitations, this study suggests that axillary dissection should be performed in most women with palpable tumors for diagnostic, as well as therapeutic, purposes.

Key Words: Breast neoplasms—Axillary lymphadenectomy.

Most authorities recommend axillary lymphadenectomy (ALND) for the treatment of breast cancer.[1–4] Because the presence of metastatic cancer in axillary lymph nodes is the best predictor of long-term survival, and physical examination of the axilla may be inaccurate,[5] ALND offers the opportunity for accurate staging and prognostication, and benefits patients when adjuvant treatment planning will be based on the results of the procedure.[6] In patients with clinically positive nodes, ALND clearly minimizes axillary recurrences;[7] however, the necessity of routine ALND for women with clinically negative axillae (N0, N1a) is being questioned.[8–11] Patients undergoing lumpectomy without ALND may be operated upon using local anesthesia and do not require hospitalization. ALND adds morbidity and expense to breast conservation treatment, because patients require general anesthesia and, often, overnight hospitalization. Although major postoperative disability from ALND is rare,[12, 13] minor degrees of long-term disability (e.g., lymphedema, neuranesthesia, pain, and breast edema) are relatively common.[14–17] Additionally, the results of ALND may not be required for effective treatment planning; patients often receive adjuvant therapy regardless of nodal status, based on other parameters.[18]

Since the publication of NSABP B-04 (B-04),[19] many surgical oncologists have felt that prophylactic ALND does not confer a survival benefit for women with clinically negative axillae. Gardner,[20] however, argues that B-04 and other studies lack sufficient statistical power to confirm or deny a survival advantage from ALND. Furthermore, Harris and Osteen[21] note that 35% of the

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patients in the control arm of B-04 actually had a limited axillary dissection, which might have hidden a small survival advantage. Several randomized trials have analyzed relative survival after ALND (Table 1). Although these trials have been reviewed in a qualitative fashion,[2,18,22] no publications have combined these individual trial results in a detailed mathematical analysis. The current study was undertaken to address possible survival benefit for prophylactic ALND in breast cancer patients with clinically negative axillae, using a meta-analytic framework.

MATERIALS AND METHODS

Selection of trials for inclusion in the meta-analysis

This study identified randomized trials comparing standard treatment (mastectomy/ALND or segmentectomy/ALND plus breast irradiation) to standard treatment without ALND. Trials were identified by references in review articles, the meta-analysis from the Early Breast Cancer Trialists' Collaborative Group[23] (henceforth referred to as *Trialists*), an adjuvant radiotherapy meta-analysis,[24, 25] and by MEDLINE search. We excluded those trials that referred to Stage II patients only,[26] but included trials with mixtures of Stage I and II patients. Trials were included only if one randomized arm included axillary clearance; thus, we did not analyze those studies comparing axillary irradiation to no axillary treatment. Trials were included if they were published in the literature or if sufficient information was included in the Trialists'[27] publications to permit appropriate analysis of the study. Data recorded for each study included years of patient entry, methods of randomization, patient characteristics (age, tumor size, exclusion criteria, prevalence of positive nodes in the treated arm), follow-up, and survival.

More than 30 trials were considered; of these, six met the inclusion criteria and are included in the meta-analysis. B-04 is considered a "classic study," comparing radical mastectomy with total mastectomy in patients with clinically negative axillae. A third arm of this trial, which compared total mastectomy with total mastectomy and irradiation, is beyond the scope of the current study and is not included in the baseline analysis. The remaining five trials, although similar from a meta-analytic viewpoint, vary from B-04 in terms of patient selection criteria or addition of postoperative adjuvant therapy, or in the surgical treatment of the breast itself. An older trial from Copenhagen (henceforth referred to as *Copenhagen*)[28, 29] included all stages of breast cancer, randomized between extended radical mastectomy and total mastectomy plus irradiation. The South-East Scotland trial (SES)[30–32] compared radical mastectomy to total mastectomy with axillary irradiation. Two trials from Guy's Hospital, London, England (Guy's I and Guy's II)[7,33–35] compared radical mastectomy to breast wide local excision (without axillary dissection). Although patients in the wide excision arm of the study received postoperative irradiation, the dosage is considered inadequate by modern standards. The Institut Curie trial (henceforth referred to as *Curie*)[36] compared lumpectomy and axillary dissection to lumpectomy and postoperative irradiation. Some patients in the treated arm received postoperative chemotherapy. Details of the individual trials are included in Table 1.

Most of the trials that were excluded from this analysis compared total mastectomy to total mastectomy with irradiation, and did not include an axillary dissection arm.[37,38] Studies in this group include the frequently cited Manchester[39] and King's/Cambridge[40] trials. Although the Manchester trial compared radical mastectomy to axillary irradiation in Stage II patients, Stage I patients received simple mastectomy alone. A number of other trials used axillary biopsy as the control arm, and did not use an untreated control group.[41–43]

Two other trials included in the Trialists' meta-analysis were not included in the main analysis, but are included in a separate analysis. An unpublished study by the West of Scotland Surgical Association (WSSA) randomized patients to modified radical mastectomy versus simple mastectomy and irradiation. Review of the Trial-

TABLE 1. *Baseline characteristics of included trials*

Trial	Years	No. patients	Age (y)	Pre (%)*	Stage I (%)	Size	% T1	% N+
Copenhagen	1951–1957	425	–	–	68	–	–	–
Guy's I	1961–1971	370	61	9	60	3.5	17	54
SES	1964–1971	498	55	69	55	3.7	–	41
B-04	1971–1974	727	56	28	100	3.2	–	39
Guy's II	1971–1975	258	–	–	100	–	38	31
Curie	1982–1987	658	51	60	100	1.5	67	18

* Percentage of premenopausal women in the trial.
N+, node-positive.

ists' data suggests potential problems with this study, and short follow-up. An additional unpublished trial (Mexico National Cancer Center, 1974 [MNCC]) was listed in the Trialists' meta-analysis, but not summarized in their comprehensive work, and thus, is not included in the baseline analysis. The effect of removing these two trials is included in the sensitivity analysis.

Statistical methods

Classical statistical analysis calculates *P* values and uses significance testing to assess survival differences between treatment arms of a trial. Most of the cited trials calculated their own *P* values, which are included in Table 2. Additional *P* values needed for this analysis were calculated using Fisher's exact test. For the meta-analysis, the method of DerSimonian and Laird was used, assuming a random effects model.[44] In essence, a point value (approximating the true survival difference between ALND and no ALND) is calculated, as well as 95% confidence intervals (CI), which estimate the uncertainty of the point estimate. As noted by Brophy and Joseph,[45] classical statistics have several limitations when used to combine studies. For example, sample sizes are critically important when determining *P* values. When using classical significance tests, two trials showing nearly identical treatment differences (e.g., B-04 and Curie) may lead to different statistical conclusions based on slightly different numbers of patients. Additionally, confidence intervals do not give clinically intuitive results. A 95% confidence interval gives no clinically useful probabilistic information, but implies that if a large enough number of 95% confidence intervals were constructed, approximately 95% of them would contain the "true value" for the treatment difference.[46]

Bayesian statistical analysis places probability distributions on the parameters of main interest, for example, 5-year survival probability.[47] A Bayesian analysis starts by summarizing clinical information (available from literature review or other sources) into a prior distribution over the parameters of interest. Then, a likelihood function is created for each trial used in the meta-analysis. These likelihood functions are then combined with the prior information to create a posterior density function that is clinically interpretable. Another advantage of Bayesian analysis is that subfunctions may be created to deal with uncertainty in trial biases. This becomes particularly advantageous when combining studies with dissimilar study designs and methodology. Technical details of Bayesian analyses are explained elsewhere.[48] All statistical calculations in this paper used the software Fast-Pro (Academic Press, Boston, MA),[49] using noninformative prior distributions. The six selected trials were judged to be statistically homogeneous by χ^2 testing and graphical analysis.[50]

Trial biases

Biases may affect the internal validity of a study or may affect comparisons with other studies (external validity). Identification of these biases enables correction with specific statistical methodology (implemented by Fast-Pro and other software packages), and, to a reasonable extent, allows comparisons of somewhat dissimilar trials. The most important internal bias in these trials relates to control patients receiving axillary treatment. For example, 35% of the control patients in B-04 had at least one axillary node excised, and 13% had six or more nodes excised. There were no subsequent axillary failures in the group having six or more nodes removed, and only an 8% failure rate in those patients with one to five nodes removed (compared to a 21% axillary failure rate in those without any axillary nodes removed).[5] In another total mastectomy trial[40] a similar percentage of patients (31%) had axillary node sampling as part of the intended simple mastectomy. The Copenhagen and SES trials do not mention the percentage of simple mastectomy patients having nodes removed.

Another correctable bias relates to the axillary dissection arm not receiving the intended treatment (dilution bias). This problem varied in the cited studies. For example, 24% of the extended radical mastectomy group in

TABLE 2. *Uncorrected survival*

Trial	No. patients	Follow-up (y)	% Survival		% Difference	% Reduction	*P* Value
			Control	Treated			
Copenhagen	425	10	46	50	4	7.4	NS
Guy's I	370	10	43.6	51.6	8	14.2	NS
SES	498	10	51.5	61	9.5	19.6	.04
B-04	727	10	54	58	4	8.7	NS
Guy's II	258	10	57	73	16	37.2	.01
Curie	658	5	92.6	96.6	4	45.9	.03

NS, not significant.

the Copenhagen study did not undergo the proposed surgery, and 4% of those undergoing extended radical mastectomy had no nodes removed.[28] The SES study randomized patients before biopsy, and therefore withdrew almost half when the mass was discovered to be benign. Because their analysis includes only those patients actually receiving the randomized treatments, bias related to dilution should be nonexistent. Dilution bias in B-04 is minimal, because only 0.8% of patients received a lesser operation than proposed. Dilution bias is easily corrected mathematically.

Biases to external validity are more subtle and require more assumptions to correct in the final analysis. An obvious problem with a meta-analysis spanning four decades relates to the diminishing size of tumors over this time span and the variation in staging systems. The earliest study (Copenhagen) included all breast cancer patients, whereas the latest study (Curie) included only patients with tumors smaller than 3 cm, without clinically involved nodes, and suitable for breast preservation. Subset analysis may correct some of these disparities when the appropriate information is available. Thus, the Copenhagen study divides patients into "operable" and "inoperable," making possible the usage of the "operable" subset in the current analysis. Other ways of correcting size and stage biases include using relative survival differences, instead of absolute survival. Additionally, a separate analysis is performed for those studies that specifically breakdown their results as to clinical stage.

Treatment intensity and adjuvant therapy are important confounding variables. The Copenhagen trial used extended radical mastectomy (with internal mammary node excision) as the treatment arm. Because there are no data supporting a survival advantage to extended radical over radical or modified radical mastectomy, no correction was required. Likewise, lumpectomy series (Guy's I/II and Curie) were included with mastectomy series. No corrections were made for the adjuvant radiotherapy given in several of the trials, which is unlikely to improve survival. The usage of chemotherapy in node-positive patients in the Curie series is more problematic. Fortunately, only 11 of 60 patients with positive nodes [18.3% of the 60 Curie patients with positive nodes; 3.3% of all Curie patients (326) receiving ALND] received chemotherapy. For analysis, I assumed that these 11 patients received an 11% percent survival benefit[51] from the addition of chemotherapy. Length of follow-up also may influence bias. Five of the cited studies reported 10-year follow-up data, whereas the Curie study reported 5-year follow-up data. Examination of eligible patients (Table 1) shows differences in patient mix by age and menopausal status. Although it is possible that age and menopausal status may exert an effect modification, it is unlikely that these differences would substantially affect the current analysis, and no correction was made.

RESULTS

Baseline analysis

A survival advantage from axillary dissection was seen in all six trials, ranging from 4% to 16% (Table 2; Fig. 1). This absolute improvement in survival was equivalent to a relative reduction in deaths ranging from 7%-46%. In half of the trials, the improvement in survival was statistically significant. Although the other three trials failed to reach statistical significance, Bayesian analysis shows that a survival benefit was still quite likely. Thus, the Copenhagen study had a 78% probability of a survival benefit, compared with 85% probability for B-04, and a 93% probability for Guy's I. Combining the six trials by standard methodology (DerSimonian and Laird) showed a 5.4% survival improvement (95% CI overall; mean, 2.6%-8.1%). Analysis with Bayesian methodology showed nearly identical results (5.4% survival improvement; 95% CI = 2.7%-8.0%) (Fig. 2). This equates with a $>$ 99.5% probability of survival benefit from axillary dissection.

Corrected analysis

Correction of biases in individual trials leads to minor changes in estimated survival benefit. For example, the calculated survival benefit in B-04 increases from 4%-5.7%, but is accompanied by more uncertainty, and a widened confidence interval (−4.3-15.5). Correction for the adjuvant chemotherapy given to some patients in the Curie study had minimal affect on survival benefit. All

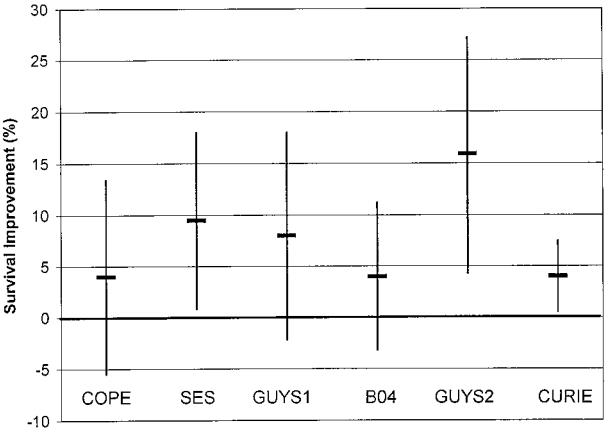

FIG. 1. Comparison of six randomized trials. Vertical bars are 95% confidence intervals, and the horizontal line through each bar represents the estimated survival benefit for each study. COPE, Copenhagen study; SES, SouthEast Scotland Study.

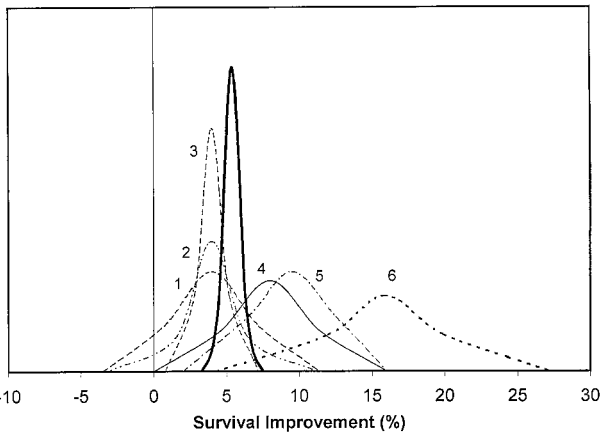

FIG. 2. Bayesian analysis of survival benefit. Black line: results of meta-analysis. Numbers 1-6, individual studies. *1*, Copenhagen; *2*, B-04; *3*, Curie; *4*, Guy's I; *5*, SouthEast Scotland; *6*, Guy's 2.

six studies continue to show a survival advantage, although several have 95% confidence intervals that include 0, and, therefore, are not statistically significant. The Bayesian combination of the six trials shows that axillary dissection confers a survival advantage of 5.4% (95% CI = 2.8-8.1), with a probability of benefit > 99.5%.

Trials of Stage I patients

Three of the trials (B-04, Guy's II, and Copenhagen) included only Stage I patients in their design. Sufficient data are given in the other three trials to permit analysis of this subgroup. All three of these trials demonstrated an improved survival when the analysis was limited to Stage I patients (Table 3). In the Copenhagen trial, survival improved by 5.0% (95% CI = −6.3-16.3); in the SES trial, survival improved by 17.9% (95% CI = 6.5-28.9); and in the Guy's I trial, survival improved by 5.9%(95% CI = −7.1-18.9). Because of the limited numbers of Stage I patients in the earlier trials, the confidence intervals are wide, and only the SES study is statistically significant. Combining the six groups of Stage I patients demonstrates a definite survival advantage of 5.6% (95% CI = 2.9-8.4, $P < .01$). Although this absolute improvement in survival is similar to that seen when Stage II patients are included, the relative reduction in cancer deaths is increased (to 25%), because of the lower baseline risk Stage I patients.

Sensitivity analyses

Addition of rejected trials

As noted earlier, two unpublished trials were included in the Trialists' meta-analysis but were rejected from the main analysis. In the WSSA trial the survival rate was better for the 94 patients in the control arm (47.9%) than for the 118 axillary dissection patients (41.5%, P = NS). Similar findings were observed in the MNCC study. Survival was 62.3% in the control arm (130 patients), versus 55.5% in the axillary dissection arm (126 patients, P = NS). Addition of these two studies made little difference in the results of the meta-analysis. A significant survival advantage was still observed (4.4%, 95% CI = 1.9-6.9).

Longer follow-up time

As noted earlier, five of the included trials were analyzed with 10-year follow-up, whereas the Curie trial had only 5-year follow-up. The Trialists' meta-analysis used longer follow-up times, with data from individual trials available until 1992. Using the Trialists' figures,[23] a separate analysis, which showed similar results to the baseline analysis, was performed. All trials continued to show a survival benefit ranging from 2.7%-7.9% for axillary dissection. Although only the Curie and Guy's series were statistically significant, the other three studies showed a probability of benefit ranging from 86%-91%.

Effect of individual trials

Re-analysis by removing one trial at a time was used to assess for the influence of each trial. In general, the only trial that appears to exert a significant effect is the Curie

TABLE 3. *Stage I patients*

Trial	No. patients	% Survival		% Difference	% Reduction	P Value
		Control	Treated			
Copenhagen	290	54	59	5	10.9	NS
Guy's I	220	52	58	6	12.5	NS
SES	275	53	71	18	38.3	<.01
B-04	727	54	58	4	8.7	NS
Guy's II	258	57	73	16	37.2	.01
Curie	658	92.6	96.6	4	45.9	.03

NS, not significant.

trial. Removing this trial increases the overall survival benefit to 7.3% (95% CI = 3.2-11.3), probably because of the relatively large number of patients (658) in this trial, and the relatively small (4%) survival benefit.

DISCUSSION

The existence of a survival benefit from axillary node dissection for breast cancer patients with clinically negative axillae is controversial. NSABP B-04, perhaps the most influential clinical trial to address this question, clearly states that axillary dissection "is therapeutic only in that it reduces the possibility of subsequent regional recurrences"[19] and that it does not alter patient survival. Despite the general acceptance of the B-04 conclusions, several surgical oncologists have noted that B-04 has limitations that may have hidden a modest survival advantage.[20, 21] Because it is unlikely that a large enough randomized controlled trial will be performed to answer this question specifically, other approaches to interpreting the available literature are required. Meta-analysis can be defined as a "quantitative synthesis of data across several different but related studies."[52] Recent examples of breast cancer meta-analyses include those of the Early Breast Cancer Trialists' Group[23] comparing various adjuvant treatments, and two meta-analyses analyzing postoperative radiotherapy.[24, 25, 53]

This study, a meta-analysis of the available literature, demonstrates a 5.4% survival advantage for clinically node-negative breast cancer patients treated with prophylactic axillary dissection. This survival benefit was noted in six separate randomized clinical trials, including almost 3000 patients and spanning nearly four decades of patient accrual. Despite differences in trial design and patient populations, the six trials showed similar results, with survival benefit ranging from 4% to 16%. This survival benefit was not limited to the few Stage II patients included in the earliest trials. In fact, the largest benefit was noted in the Guy's II trial, which was limited to patients with clinically negative axillae. Hayward[7] stated that the majority of the survival benefit in the Guy's trials was gained by those patients with T1 tumors. Because other trials did not report their data on the basis of tumor size, the current study is unable to specifically evaluate Hayward's conclusion.

The results of this study seem to be in opposition to B-04 and the Trialists' meta-analysis. In actuality, B-04 does show a survival benefit for the axillary dissection arm (1% at 5-year follow-up, 4% at 10-year follow-up, and 4% with the data set reported to the Trialists, circa 1992). Because of inadequate numbers of patients to avoid a possible Type II error, the lack of a significant *P* value for this study may be misleading. By using Bayesian techniques (which can assign a posterior probability), the probability that B-04 shows a survival advantage is 86% for the 10-year data and the long-term data. This high probability is clinically relevant and suggests that an alternative explanation of the B-04 data may be appropriate. Careful analysis of the Trialists' paper[23] shows that multiple surgical techniques and radiotherapy regimens were lumped together for their particular analysis. When only the six trials that are truly relevant to the subject of axillary node dissection are analyzed, the Trialists' data become quite similar to the analysis reported here.

Like all meta-analyses, this study has limitations. Although attempts were made to collect the complete literature on randomized trials of axillary dissection, there is a possibility of unpublished and unavailable trials causing bias in the analysis. Because of the importance of breast cancer globally, it is unlikely that many large scale trials exist that were not published. We included two unpublished trials, located by the Trialists, in the sensitivity analysis and noted no change in the overall conclusions. The six trials included in the meta-analysis used several different types of surgical management, as appropriate during each era of patient accrual. Although the differences in surgical management may have altered the results of the meta-analysis, it is unlikely. Including the Copenhagen trial is somewhat controversial. The extended radical mastectomy of the Copenhagen study has never been shown to be superior to standard radical mastectomy, so no bias correction was made. Removing this trial from the meta-analysis had no effect on the conclusions, nor the estimated benefit of node dissection. Likewise, the SES control patients received axillary irradiation. If anything, this would have improved the survival in the control arm, and would further strengthen the conclusions of the meta-analysis. Although the Guy's trials used inadequate local treatment to the breast in their control arms, it is very unlikely that the local treatment would be responsible for the observed survival difference.[54]

Analysis of trials spanning nearly four decades leads to problems that may limit extrapolation to contemporary breast cancer treatment. The tumors observed in the six trials were much larger than those seen in current practice and were associated with a higher proportion of involved lymph nodes. The mean size of the tumors in three of the included trials was more than 3 cm, and it is likely that the mean size in the Copenhagen trial, although not reported, was even larger. The percentage of positive lymph nodes in the early series was high, ranging from 39% to 54% for B-04, SES, and Guy's I. It is

unlikely that any of the patients in the six trials had mammographically detected breast cancers, because screening was unavailable during the earlier trial years and in its infancy during the later trial years. In contrast, recent series note median tumor sizes of 1.5 cm, accompanied by nodal positivity in only 31% of patients, and a significant trend toward mammographic detection.[55] Almost all patients in the six trials were treated without chemotherapy or tamoxifen, as contrasted to current clinical practice, where most patients receive adjuvant therapy. Because adjuvant therapy may have cytotoxic effects on axillary metastases, it is possible that the risk reduction seen in this meta-analysis may be diminished in patients receiving adjuvant chemotherapy. This hypothesis could not be directly tested, due to the limitations of available trials.

The 5.4% survival advantage seen in this meta-analysis is similar to that predicted by Harris and Osteen.[21] As noted by Gardner,[20] the subset of patients who may be "cured" by prophylactic axillary dissection is likely to be relatively small. Those patients with disease confined to the breast do not need axillary dissection, and those patients with distant metastases will not be helped by the procedure. Furthermore, B-04 suggests that there is a subset of patients with relatively indolent axillary metastases who are still cured by delayed axillary dissection,[19] and more recent NSABP data suggest that preoperative chemotherapy (which is often used in current practice) may successfully eradicate some axillary metastases.[56] The 5.4% survival advantage noted by the meta-analysis is equivalent to a 16% risk reduction, which is practically, as well as statistically, significant. However, the survival benefits to contemporary women with small, nonpalpable tumors cannot be assessed by this study, and are likely to be much less than those noted here. This potential survival benefit should be discussed with patients as a potential reason for including axillary dissection in their treatment plan. Although certain patient subgroups may not require axillary dissection because of the low likelihood of metastases,[57] this study supports consideration of axillary node dissection in most women with operable breast cancer.

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