Is Axillary Lymph Node Dissection Indicated for Early Stage Breast Cancer—A Decision Analysis

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Abstract

Purpose. Axillary lymph node dissection (ALND) has been a standard procedure in the management of breast cancer. In a patient with a clinically negative axilla, ALND is performed primarily for staging purposes, to guide adjuvant treatment. Recently, the routine use of ALND has been questioned because the results may not change adjuvant systemic therapy and/or the survival benefit of a change in adjuvant therapy would be small. We constructed a decision model to quantify the survival benefits of ALND for patients eligible for breast conserving therapy.

Methods. Patients were grouped by age, tumor size, and hormone receptor status. The model uses the Oxford overviews and three combined Cancer and Leukemia Group B studies. We assumed that patients not undergoing ALND received axillary radiation therapy and that the two procedures are equally effective. All chemotherapy combinations were assumed equally efficacious.

Results. The largest benefits from ALND are in Estrogen Receptor (ER) positive women with small primary tumors who might not be candidates for adjuvant chemotherapy if lymph nodes are negative. Virtually no benefit results in ER negative women, almost all of whom would receive adjuvant chemotherapy. Adjusting for quality of life (QOL), ALND may have an overall negative impact. In general, benefits of ALND increase with the expected severity of adjuvant therapy on QOL.

Conclusion. Our model quantifies the benefits of ALND and assists decision making by patients and physicians. The results suggest that routine use of ALND in breast cancer patients should be reassessed and may not be necessary in many patients.

Introduction

Axillary lymph node dissection (ALND) has long been an integral part of the management of breast carcinoma. Initially its purpose was to remove the likely first area of tumor spread from the primary lesion in the breast with the thought that a higher cure rate would result than if mastectomy only were performed. Subsequent clinical trials, however, showed that ALND contributed little to overall survival, despite a relatively high frequency of axillary nodal involvement pathologically in clinically node-negative patients [1]. The concept evolved that positive axillary lymph nodes were primarily a marker for a high risk of occult systemic spread rather than the source of systemic metastases. With the advent of adjuvant systemic therapy, ALND came to be viewed primarily as a staging procedure—it conveyed prognostic information and guided decisions regarding adjuvant systemic therapy.

The concept of breast cancer as a systemic disease has led to the increased use of adjuvant therapy in a wide range of patients with demonstration of benefits in node-negative as well as node-positive patients [2, 3]. These results have called into question the rationale for performing ALND. If information derived from ALND is no longer critical in determining adjuvant therapy for some patients, should it now be omitted in those patients? [4, 5, 6, 7, 8]

ALND is of value if it 1) leads to a more effective adjuvant systemic therapy with improved patient survival. 2) provides local control with a possible increase in survival or 3) provides prognostic information of value to the patient. These benefits must be considered in light of the long-term complications associated with ALND as well as the financial cost.

In this paper, we present a quantitative assessment of the impact on survival (both unadjusted and quality-adjusted) of ALND in patients receiving breast conservation therapy (BCT). Our focus is on BCT since ALND is a distinct and separate operation for these patients, as opposed to patients undergoing mastectomy for whom it is more often an integral part of the procedure. Axillary irradiation appears to provide the same local control and survival benefits (if any) of ALND in patients with clinically uninvolved lymph nodes [9]. Therefore, ALND is useful if it results in an alteration in a patient's proposed plan of therapy and if that different plan improves survival or decreases morbidity, compared with the best plan in the absence of ALND. For some patients the information gained from ALND may be valuable separate from the impact it has on therapeutic decisions. However, we do not incorporate the value of this knowledge in our model. Sentinel node biopsy may be an effective alternative to ALND but is not considered in our present model.

Methods

Decision Model

We consider patients undergoing breast conservation therapy, with clinically negative axillae. The decision to perform a node dissection and the selection of appropriate adjuvant therapy are made in the light of patient characteristics, namely age, ER status, and primary tumor size, as benefits are likely to be different for these groups [10]. Because knowing the result of the ALND might lead to a more appropriate choice of adjuvant therapy, we include two decision points: 1. Choice of either ALND or XRT; 2. Choice of adjuvant systemic therapy. The resulting decision tree is shown in Figure .

We considered four options for adjuvant systemic therapy: tamoxifen (T); combination chemotherapy (CT); combination chemotherapy followed by Tamoxifen (CT+T); and no adjuvant systemic therapy. All adjuvant combination chemotherapy are assumed to be equivalent, both in terms of long–term outcome and effects on quality of life. The alternative of not treating the axilla with either ALND or XRT was not modeled. We wished to utilize strategies that provide equivalent high probability of local control of axillary disease as well as any survival benefits that may accrue from direct treatment of the axilla. Our goal was to obtain results that do not depend on any additional assumptions about the estimated efficacies of axillary treatments.

Probability estimates

The probability distribution of the number of positive nodes for given tumor size, age, and ER status is based on Carter et al. [11] with adjustment to incorporate knowledge of a negative outcome of the clinical examination of the axilla. The model uses estimates of the probabilities of true-negative and false-negative physical examinations [12], and performs the adjustment via Bayes' rule.

Survival of patients with positive nodes receiving chemotherapy was estimated using a multivariate Cox regression model with age, ER status, primary tumor size and nodal involvement as prognostic variables, based on the combined CALGB studies 7581, 8082 and 8541 [13, 14, 15]. The maximum followup in the CALGB studies is 19 years. Rates beyond 19 years were extrapolated based on a constant hazard rate (set to the average hazard rate in years 15 to 19). The hazard rate in the first 19 years is not constant, accounting for greater hazard in the first few months following adjuvant treatment. For this reason our model is more general than so-called Markov decision models. If ALND is performed, the survival estimates incorporate the results of the dissection.

CALGB trials involved only node-positive women. To derive a survival curve for node-negative women, the following strategy was followed. a) For node-negative women with primary tumors larger than 1 cm, results from the EBCTCG overview [2] were used to estimate an adjustment ratio between node-positive and node negative patients receiving chemotherapy. This ratio is 0.42 for the first 4 years and 0.61 for the remainder [2]. b) For node-negative women with primary tumor smaller than 1 cm, the results of Rosen *et al.* [16] and Quiet *et al.* [17] were used to derive two separate adjustment ratios for women with ER positive and ER negative tumors. Mortality from causes other than breast cancer was taken from life tables [18].

Survival of women undergoing adjuvant therapy other than chemotherapy were derived from the previous analysis together with the results of recent EBCTCG overviews [2, 19, 3]. The results among node-positive patients receiving chemotherapy were used as the baseline and then adjusted in accordance with the risk ratios reported in Table 1 to generate survival curves for the other treatment options. Effects that were deemed statistically unstable by the Overview investigators [2, 3] were not modeled. Specifically we assumed that 1) Tamoxifen has no effect of in premenopausal ER negative patients; 2) Adjuvant therapy is equally effective (in terms of risk reduction) in node negative as well as node-positive women. Recent evidence from the NSABP

B-14 [20] trial also shows a risk reduction for node-negative patients that is comparable with that of previously observed node-positive patients.

Additional assumptions of our model are: 1) If metastatic disease develops, the time spent with metastatic disease is not adversely affected by the adjuvant therapy. 2) Local control of subclinical axillary disease can be achieved with radiotherapy in 95% of patients (clinically evident axillary disease requires ALND). Axillary radiation will typically include supraclavicular nodes as well. Therefore, any survival benefit that might be anticipated from administering nodal irradiation to node positive patients will be realized in patients not undergoing ALND as well [9, 12, 21].

Quality of life

Decisions about adjuvant therapy depend on survival benefit as well as loss of QOL resulting from the therapy itself. We incorporate QOL using hypothetical utility coefficients to provide a quantitative assessment of the impact of various health states on QOL [22]. A utility of 1 corresponds to full health while 0 corresponds to death. The impact of adjuvant therapy, ALND, and XRT on QOL may vary substantially from patient to patient. We did not elicit utility scores from patients, but instead choose plausible values to represent four different QOL scenarios, based on our experience with patients as well as published estimates [23].

Our primary analysis uses a scenario representing a moderate impact of adjuvant therapies on QOL. This scenario is named Q_{moderate} and is described in Table 2. To investigate the sensitivity of our primary results to QOL adjustments, we compared the results obtained under the Q_{moderate} scenario to the results obtained under three additional scenarios, termed Q_{mild}, Q_{severe} and $Q_{\text{ALND<XRT}}$ (see Table 3). Q_{mild} exemplifies a patient who experiences little impact on her QOL from her adjuvant therapy (less than in Q_{moderate},) and completely recovers from the negative effects of therapy by the end of one year. Q_{severe} reflects a more severe effect of treatment on QOL than Q_{moderate}. All adjustments for adjuvant therapy vary with time since therapy.

There is a quality of life impact of both complications from ALND and complications from XRT. In scenarios Q_{moderate}, Q_{mild} and Q_{severe} we assume the same QOL adjustment for the negative impact of ALND and XRT, namely half of a percent, corresponding to a quality adjustment of .995. This quality adjustment is assumed to be constant over time and is applied over and above any adjustments resulting from adjuvant systemic therapy. In scenario $Q_{\text{ALND}<\text{XRT}}$ we assume the impact on QOL from adjuvant systemic therapy to be the same as Q_{moderate}, and further assume a negative impact on QOL from ALND greater than that from XRT. The quality adjustment for ALND is .995, while that for XRT is .997.

The endpoint of the decision analysis is the gain in expected quality adjusted life years (QALY) resulting from ALND. This effect is evaluated by computing, for all levels of nodal involvement, the survival benefit gained from a change in adjuvant treatment dictated by the result of ALND. The expected gain is then the average of these gains, weighted using the probabilities of different levels of nodal involvement for that particular patient type.

Results

We first consider in detail two examples, patients A and B. Patient A is 60 years old, with a primary tumor size between 0.5 and 1 cm. Patient B is 38 years old, with a primary tumor size between 3 and 4 cm. Both have ER positive tumors and clinically negative axillae. We then examine the sensitivity of the results to QOL adjustments and give summary results for all patient types.

Survival.

Table 4 considers survival for patients A and B. The first column gives the probability of finding the indicated number of positive nodes. For each degree of nodal involvement, the table gives the additional life expectancy in years for different types of adjuvant systemic treatment compared with no treatment (the absolute percent gain in 10-years survival is shown in parenthesis), compared with no treatment. QOL adjustments are not considered. For example, the probability of finding one to three positive nodes after ALND for patient A is 11%. If one to three positive nodes were found, administration of tamoxifen would lead to a life expectancy which is 2.03 years greater than compared to no adjuvant treatment for patient A, or, in terms of survival rates, an absolute gain of 8% at 10 years. If ALND is not performed, the additional life expectancy is computed as a weighted average of the additional life expectancies in the nodal involvement categories. In all cases, life expectancies are computed over the remainder of a woman's lifetime and are not limited to the first 10 years.

Quality of life: moderate scenario.

Table 5 now considers QOL for patients A and B, summarizing the difference in expected QALYs between the three adjuvant therapies and no treatment, for each level of nodal involvement assuming the scenario Q_{moderate}. The boxes highlight the treatment that results in the greatest gains in QALYs. We will refer to this as best option, for conciseness. When none of the values in a row are boxed, not administering adjuvant therapy is the best option.

For patient A, the best option is T if ALND is not performed (nodal status unknown). If ALND is performed, node-negative patients receive T, while node-positive patients receive CT+T. The gain in QALYs from adding C to T ranges from 0.37 to 0.5 years. Thus ALND can lead to a change in the appropriate adjuvant therapy and increase survival.

The magnitude of the resulting benefit is calculated by the difference between the weighted average of the values in the T column and the weighted average of the boxed values. For patient A this is 0.04 QALYs (about 2 weeks).

For patient B, CT+T is the treatment leading to the largest expected survival and QALYs irrespective of nodal status. Therefore, ALND does not lead to a change in adjuvant systemic therapy or result in any survival gain.

Quality of life: sensitivity analysis.

Table 6 and 7 considers QOL for patients A and B under the alternative scenarios Q_{mild} and Q_{severe}. For patient A in scenario Q_{mild} the optimal adjuvant choices are as in Q_{moderate}. In scenario Q_{severe} the best option if ALND is not performed is no adjuvant treatment, because of the more severe impact of adjuvant treatment on QOL. If ALND is performed, node-negative patients receive no adjuvant treatment, while node-positive patients receive CT+T. In all three scenarios ALND can lead to a change in the appropriate adjuvant therapy. The magnitude of the benefits for ALND for both Q_{mild} and Q_{severe} is 0.06 QALYs (about 3 weeks).

In scenario $Q_{\text{ALND}<\text{XRT}}$, the optimal adjuvant therapy choices, are as in Q_{moderate}. The difference between ALND and XRT is -.02 QALYs. The negative value indicates that the decrement in QOL from ALND outweighs the average benefit of CT+T compared to T alone in node-positive patients.

For patient B, in all scenarios CT+T is the treatment maximizing survival and QALYs irrespective of nodal status. In scenarios Q_{mild} and Q_{severe} there is no gain from ALND. In scenario $Q_{\text{ALND}<\text{XRT}}$ there is a loss (-.04) of average QALYs.

As illustrated by the analysis of patients A and B, decisions may vary depending on patient characteristics. Different patients have different probabilities of finding positive nodes. The effectiveness of adjuvant therapies and the importance of the competing causes of death also vary with the patient, the latter increasing with age.

Table 8 summarizes the expected gains in QALYs resulting from ALND for all patient types and QOL scenarios. Patients are grouped by age, ER status, tumor size and the four QOL scenarios. All zero values in the table indicate that adjuvant therapy will be the same regardless of nodal status; hence there can be no gain from ALND. For example, young women with ER- tumors will all have chemotherapy prescribed irrespective of nodal status. All zero values become negative if we assume a decrement in QOL from ALND compared to XRT (scenario $Q_{\text{ALND}<\text{XRT}}$). Even when gains in QALYs are present, they are small.

To further understand the results of Table 8, Figure 2 shows recommended adjuvant therapy choices for all patient types, in the four quality scenarios. The first four letters in each grouping represents the choices of adjuvant therapy by nodal status (0, 1–3, 4–9, >9), given that ALND has been performed. The underlined letters represent choices of adjuvant therapy if ALND is not performed. The color codes correspond to the numbers in Table 8. All zero values are dark blue. All negative values are lighter blue, with darker shades indicating smaller losses. Due to the very small differences in negative values, shades are very similar. All gains are in green with darker shades indicating greater gains.

Discussion

ALND as a part of the operative management of breast carcinoma was introduced by Halsted at the start of this century [24], the rationale being to remove the first area of likely tumor spread and hence to improve the cure. Attempts at less extensive surgery began in the 1930s and 40s, primarily in Europe. Total mastectomy (TM) and radiation to peripheral lymph nodes was shown to be comparable in outcome to radical mastectomy (RM), leading to the conclusion that radiation therapy could successfully control subclinical disease in lymph nodes [25, 26]. The first successful efforts at breast conservation were also reported during this time. The NSABP further confirmed that TM + RT was equivalent to RM. Indeed, TM alone seemed to provide equivalent survival to the other two procedures. With the introduction of adjuvant systemic therapy in the 1970s, a renewed emphasis was placed on ALND as a means to select patients with a worse prognosis for adjuvant systemic treatment.

Major changes have continued in breast cancer management over the last several decades that relate to the issue of whether to perform ALND or not:

1) Breast conservation therapy has become increasingly popular, its equivalence to RM or modified radical mastectomy having been demonstrated in eight randomized trials [27]. Thus, ALND for many patients is now a separate operation rather than a part of a mastectomy.

2) Adjuvant systemic therapy has demonstrated value in many woman with negative lymph nodes as well as those with nodes involved with cancer. Furthermore, the relative benefits of adjuvant therapy are similar in node-negative and node-positive women [2, 3].

3) The extent of disease in newly diagnosed patients with breast carcinoma has shifted as the use of mammography has grown and the public awareness of breast cancer has increased. Many more patients are encountered with mammographically discovered, quite small primary tumors.

These factors have lead a number of authors to reexamine the issue of ALND and to question its routine use [4, 5, 7, 8, 12]. Arguments that have been marshaled against ALND as standard practice include the following:

1) If adjuvant systemic therapy is to be used in all node-negative patients with a primary

tumor >1 cm, why do the ALND? (This argument assumes that there is no substantive difference between various chemotherapy regimens. Even if there are differences between the various regimens, it is unlikely that the relative risk reduction would be affected by nodal status).

2) Very small primary lesions (less than 0.5 cm), now much more common in the mammographic era, have a low probability of nodal involvement [11], and a good prognosis even if a small number of positive nodes are found [28]. Thus the survival benefits from ALND are likely to be extremely small in this group.

3) Elderly patients, particularly those with hormone receptor positive tumors, will often be treated with tamoxifen anyway, irrespective of nodal status, because of the reluctance to use adjuvant chemotherapy in this group.

4) The morbidity of ALND is small but finite with 10–20% of patients exhibiting some decreased range of motion of the shoulder, approximately 80% experiencing numbness in the distribution of the intercostal brachial nerves, 2-30% reporting arm edema, and 15–50% experiencing breast edema [29, 30, 10, 31].

5) There is a financial cost of the procedure.

Our study uses the methods of decision analysis in an attempt to provide a quantitative framework for the above arguments and a realistic guide for practicing oncologists. Our model incorporates quantitative data regarding the frequency of nodal involvement for different primary tumor sizes, survival benefits to be expected from adjuvant systemic therapy for different patient categories, effects on survival to be anticipated from competing causes of death other than breast cancer, and finally quality of life adjustments. An earlier published decision analysis [32] was confined to T1 patients and did not measure the impact of ALND on specific patient subgroup, as done here.

QOL adjustments are somewhat arbitrary and hard to quantify, but nevertheless important. If there was no QOL trade off, all patients with invasive breast cancer would receive chemotherapy and most would also receive tamoxifen. Clearly, physicians and patients presently incorporate QOL considerations in their decision making. Our model is a step toward quantifying this process. The model could be improved by incorporating utilities provided by patients. In the absence of such data we have assumed four different QOL scenarios, similar to a Q-twist analysis [23].

Certain generalizations can be made despite the difficulties with quality adjustments. It is apparent from table 8 that for many women there are no benefits from ALND over a broad range of quality scenarios. This is true when no change in adjuvant systemic therapy would result from knowledge of the lymph node status, or if ALND is assumed to have a greater negative impact on QOL than XRT. When there is any survival benefit to be derived from ALND, it is small in almost all instances. This overall conclusion depends critically on the fact that the relative benefits of adjuvant therapy are similar in node-negative and node-positive women [2, 3]. Whether the small for some patients gain is worth the performance of an ALND is a judgment best left to the individual patient and her physicians.

Our sensitivity analysis demonstrates that there are subsets in which the preferred choice is sensitive to the QOL adjustments and others in which it is not. In those subsets where it is sensitive, the model would suggest that optimizing QALYs can only be achieved by individualizing decisions about node dissection depending on a patient's preferences and the potential impact on her QOL. The subset of women in which the results are most sensitive to attitudes towards QOL are premenopausal women with small primary tumors. In this group, node-negative women may or may not opt for chemotherapy depending on their personal values. If they expect a small QOL reduction from chemotherapy, ALND is of little or no value to them since they will elect to receive chemotherapy anyway. If they expect a greater QOL reduction, ALND becomes more desirable, as node negative women may wish not to receive chemotherapy.

A related issue is the use of ALND in order to categorize patients by nodal status for possible entry into cooperative group trials testing new therapies. While knowledge of nodal status has been required for almost all large adjuvant trials, it is difficult to justify this practice if no benefit will accrue to the patient from performing the ALND. Strong consideration should be given to designing future trials which do not mandate ALND as an eligibility requirement.

Sentinel node biopsy has been proposed as an alternative to ALND [33, 34]. The accuracy of this procedure in predicting nodal status and any potential decrement in quality of life remain to be fully determined, but sentinel node biopsy may have less long term morbidity than ALND. Expected survival gains resulting from the information gathered by sentinel node removal are unlikely to be greater than those derived from traditional ALND. However, if sentinel nodes biopsy proves to offer accurate prognostic information with minimal morbidity it may produce better quality adjusted survival for many patients than either of the two options considered here. Our model provides a basis for exploring these issues in more detail. This will be carried out in future analyses.

An additional issue is the possibility that adjuvant high dose chemotherapy (with stem cell support) may be of benefit to women with large numbers of positive lymph nodes (for example 10 or more). Should future phase III trials demonstrate this, such information could easily be incorporated into the model.

In conclusion, our model suggests that ALND should not be performed as a routine part of the therapy for patients with breast carcinoma who are undergoing conservation surgery and radiation. Instead, physicians should consider precisely how therapy would be changed and what benefits would be derived from the procedure. We hope that this model will help physicians clarify their own thinking about the appropriateness of ALND and facilitate the counseling of individual women facing this decision.

Future studies will explore the use of the model as a counseling tool in a trial aimed at helping physicians and patients make decisions regarding ALND. We recognize that women may choose to have a node dissection to obtain prognostic information; the value of ALND to them may go beyond that of improving decisions about adjuvant systemic therapy. Our model can provide a framework for investigating whether patients value the prognostic information per se provided by ALND, even when the results will not lead to a change in subsequent clinical management.

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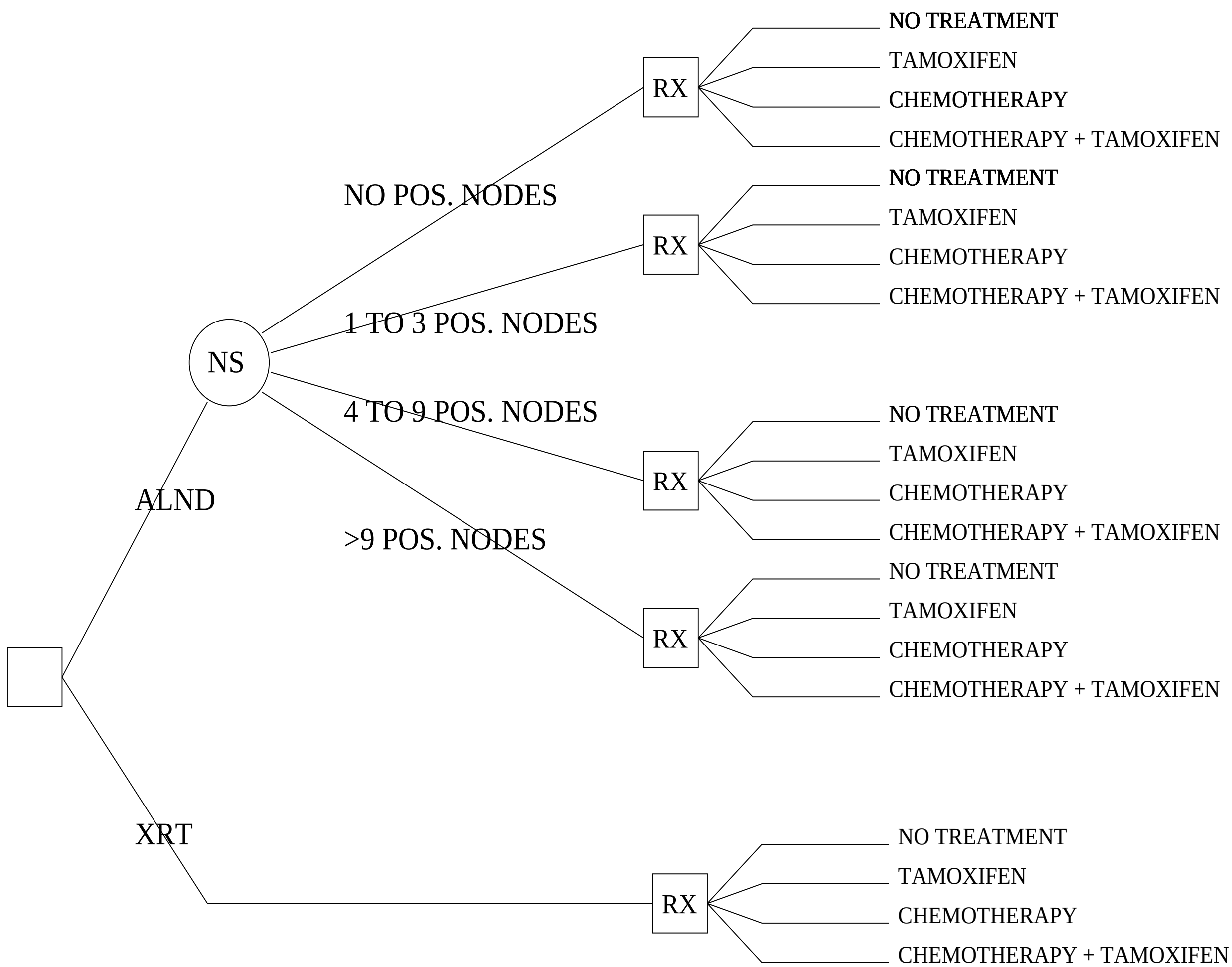
Figure Captions

Figure 1. Decision tree for ALND (dissection) versus XRT (axillary radiation) decision model. The square on the left represents the decision between ALND and XRT. The circle, NS (Nodal status), is an information point, with branches indicating outcomes of the dissection. The RX squares represent decisions about adjuvant therapy.

Figure 2. Summary of recommended adjuvant therapy choices for all patient types, in 4 quality scenarios. At each rectangle, the string of four letters represents the choices of adjuvant therapy by nodal status (0, 1–3, 4–9, >9 from left to right) given that ALND is performed. The underlined letter represents the the choice of adjuvant therapy if ALND is not performed. C–chemotherapy; T—tamoxifen; B—both; N—no adjuvant therapy. The layout is the same as table 8. Color codings represent the gain in QALYs resulting from AND. Blue patient types can expect no benefit (dark blue) or a negative benefit (lighter blue). Green patient types can expect a benefit. Within green, darker colors indicate larger gains from ALND. Within blues, darker colors indicate smaller losses from ALND.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RX

QOL	TS	ER- AGE 30	ER- 40	ER- 50	ER- 60	ER- 70	ER+ 30	ER+ 40	ER+ 50	ER+ 60	ER+ 70
Q_{mild}	<.5	CCCC C	CCCC C	CCCC C	NCCC C	NCCC N	BBBB B	BBBB B	TBBB T	TBBB T	TBBB T
	.5–1	CCCC C	CCCC C	CCCC C	CCCC C	NCCC N	BBBB B	BBBB B	TBBB T	TBBB T	TBBB T
	1–2	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	BBBB B
	2–3	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	BBBB B
	3–4	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	BBBB B
	4–5	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	BBBB B
	>5	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	BBBB B
Q_{moderate}	<.5	CCCC C	CCCC C	NCCC C	NCCC N	NCCC N	BBBB B	BBBB B	TBBB T	TBBB T	TBBB T
	.5–1	CCCC C	CCCC C	CCCC C	NCCC N	NCCC N	BBBB B	BBBB B	TBBB T	TBBB T	TBBB T
	1–2	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	TBBB T
	2–3	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	TBBB T
	3–4	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	TBBB T
	4–5	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	TBBB B
	>5	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	BBBB B
Q_{severe}	<.5	CCCC C	NCCC C	NNNN N	NNNN N	NNNN N	TBBB B	NBBB T	NBBB T	NBBB N	NTBB N
	.5–1	CCCC C	CCCC C	NNNN N	NNNN N	NNNN N	TBBB B	TBBB B	NBBB T	NBBB N	NTBB N
	1–2	CCCC C	CCCC C	NNNN N	NNNN N	NNNN N	BBBB B	BBBB B	TBBB B	TBBB T	NTBB T
	2–3	CCCC C	CCCC C	NNNN N	NNNN N	NNNN N	BBBB B	BBBB B	TBBB B	TBBB T	TBBB T
	3–4	CCCC C	CCCC C	NNNN N	NNNN N	NNNN N	BBBB B	BBBB B	BBBB B	TBBB B	TBBB T
	4–5	CCCC C	CCCC C	NNNN N	NNNN N	NNNN N	BBBB B	BBBB B	BBBB B	TBBB B	TBBB T
	>5	CCCC C	CCCC C	NNNN N	NNNN N	NNNN N	BBBB B	BBBB B	BBBB B	BBBB B	TBBB B
$Q_{\text{ALND<XRT}}$	<.5	CCCC C	CCCC C	NCCC C	NCCC N	NCCC N	BBBB B	BBBB B	TBBB T	TBBB T	TBBB T
	.5–1	CCCC C	CCCC C	CCCC C	NCCC N	NCCC N	BBBB B	BBBB B	TBBB T	TBBB T	TBBB T
	1–2	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	TBBB T
	2–3	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	TBBB T
	3–4	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	TBBB T
	4–5	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	TBBB B
	>5	CCCC C	CCCC C	CCCC C	CCCC C	CCCC C	BBBB B	BBBB B	BBBB B	BBBB B	BBBB B

Proportional mortality reductions for alternative adjuvant therapies.

	Age < 50		Age ≥ 50	
	ER+	ER-	ER+	ER-
Tamoxifen	19 %	0 %	30 %	0 %
Chemotherapy	27 %	27 %	11 %	11 %
Chemotherapy followed by Tamoxifen	41 %	—–	38 %	11 %

Table 1: Mortality reduction for alternative adjuvant therapies, based on the EBCTCG (1998) overviews of breast cancer. Chemotherapy followed by tamoxifen is not considered for ER negative patients <50.

Illustrative quality adjustment factors used in the $Q_{\textbf{moderate}}$ scenario.

		Months 1–6	Months 7–12	Year 2	Years 3–5	Remainder
	No Treatment	1	1	1	1	1
Q_{moderate}	Tamoxifen	0.99	0.99	0.99	0.99	1
	Chemotherapy	0.6	0.9	0.99	0.99	0.99
	ALND	.995	.995	.995	.995	0.995
	XRT	.995	.995	.995	.995	0.995

Table 2: For quality adjustments for Chemotherapy + Tamoxifen (not shown) we use the adjustment factor for Chemotherapy alone for the first six months and both adjustments thereafter. Adjustment for either ALND or XRT is applied for each subsequent year of life over and above any adjustment for adjuvant systemic therapy. We assume here the QOL for ALND and XRT to be the same.

Illustrative quality adjustment factors used in the Q_{mild}, Q_{severe} and $Q_{\text{ALND<XRT}}$ scenarios.

		Months 1–6	Months 7–12	Year 2	Years 3–5	Remainder
	No Treatment	1	1	1	1	1
Q_{mild}	Tamoxifen	1	1	1	1	1
	Chemotherapy	0.8	0.95	1	1	1
	ALND	0.995	0.995	0.995	0.995	0.995
	XRT	0.995	0.995	0.995	0.995	0.995
Q_{severe}	Tamoxifen	0.8	0.8	0.8	0.8	1
	Chemotherapy	0.3	0.6	0.95	0.95	0.95
	ALND	0.995	0.995	0.995	0.995	0.995
	XRT	0.995	0.995	0.995	0.995	0.995
$Q_{\text{ALND<XRT}}$	Tamoxifen	0.99	0.99	0.99	0.99	1
	Chemotherapy	0.6	0.9	0.99	0.99	0.99
	ALND	0.995	0.995	0.995	0.995	0.995
	XRT	0.997	0.997	0.997	0.997	0.997

Table 3: For quality adjustments for Chemotherapy + Tamoxifen (not shown) we use the adjustment factor for Chemotherapy alone for the first six months and both adjustments thereafter. Adjustment for either ALND or XRT is applied over and above any adjustment for adjuvant systemic therapy. In the $Q_{\text{ALND<XRT}}$ quality adjustments for Chemotherapy or Tamoxifen are the same as in the Q_{moderate} scenario.

Additional life expectancy from adjuvant systemic therapy compared to no treatment, by treatment type and nodal group. Quality of life not considered.

Patient A

Nodal Status	Nodal Status Probability	Additional Life Expectancy in years (in parentheses absolute gain in % 10-year survival) T	CT	CT+T
0	0.84	0.5 (2%)	0.18 (1%)	0.63 (2%)
1–3	0.11	2.03 (8%)	0.69 (3%)	2.67 (11%)
4–9	0.03	2.11 (9%)	0.7 (3%)	2.79 (12%)
>9	0.02	2.16 (11%)	0.7 (4%)	2.89 (14%)
Unknown		0.74 (3%)	0.26 (1%)	0.96 (4%)

Patient B

Nodal Status	Nodal Status Probability	Additional Life Expectancy in years (in parentheses absolute gain in % 10-year survival) T	CT	CT+T
0	0.56	2.45 (5%)	3.64 (7%)	6.01 (11%)
1–3	0.23	2.35 (6%)	3.56 (9%)	6.09 (15%)
4–9	0.14	2.21 (7%)	3.37 (10%)	5.84 (16%)
>9	0.07	1.8 (8%)	2.79 (11%)	4.98 (18%)
Unknown		2.35 (6%)	3.52 (8%)	5.93 (13%)

Table 4: The first column indicates nodal status, the second the probability of that nodal state in a clinically node negative patient with the same characteristics as patients A or B. The three columns to the right give, for each adjuvant systemic therapy considered, the additional life expectancy, in years, compared to no adjuvant treatment. In parenthesis is the percent gain in 10-years survival.

Additional QALYs from adjuvant systemic therapy compared to no treatment, by treatment type and nodal group.
Quality of life as in the $Q_{\textbf{moderate}}$ scenario.

Patient A

Nodal Status	Nodal Status Probability	Additional QALYs T	CT	CT+T
0	0.84	$\boxed{0.45}$	-0.26	0.14
1–3	0.11	1.98	0.31	$\boxed{2.23}$
4–9	0.03	2.06	0.34	$\boxed{2.36}$
>9	0.02	2.1	0.36	$\boxed{2.48}$
Unknown		$\boxed{0.69}$	-0.17	0.47
Expected gain from ALND is .04				

Patient B

Nodal Status	Nodal Status Probability	Additional QALYs T	CT	CT+T
0	0.56	2.39	3.15	$\boxed{5.44}$
1–3	0.23	2.3	3.13	$\boxed{5.57}$
4–9	0.14	2.15	2.95	$\boxed{5.34}$
>9	0.07	1.75	2.42	$\boxed{4.53}$
Unknown		2.29	3.07	$\boxed{5.39}$
Expected gain from ALND is 0				

Table 5: This table summarizes the calculations used in solving the decision tree for patients A and B. The layout is as in Table 4. Boxed values indicate the best treatment option for a given nodal status (see text as well).

Additional QALYs from adjuvant systemic therapy compared to no treatment, by treatment type and nodal group.
Quality of life as in the $Q_{\textbf{mild}}$ scenario.

Patient A

Nodal Status	Nodal Status Probability	Additional QALYs T	CT	CT+T
0	0.84	$\boxed{0.45}$	-0.14	0.26
1–3	0.11	1.98	0.44	$\boxed{2.35}$
4–9	0.03	2.06	0.47	$\boxed{2.48}$
>9	0.02	2.1	0.48	$\boxed{2.6}$
Unknown		$\boxed{0.69}$	-0.05	0.6
Expected gain from ALND is .06				

Patient B

Nodal Status	Nodal Status Probability	Additional QALYs T	CT	CT+T
0	0.56	2.39	3.27	$\boxed{5.56}$
1–3	0.23	2.3	3.25	$\boxed{5.7}$
4–9	0.14	2.15	3.08	$\boxed{5.47}$
>9	0.07	1.75	2.54	$\boxed{4.66}$
Unknown		2.29	3.19	$\boxed{5.51}$
Expected gain from ALND is 0				

Table 6: This table summarizes the calculations used in solving the decision tree for patients A and B, Q_{mild} scenario. The layout is as in Tables 4 and 5. Boxed values indicate the best treatment option for a given nodal status.

Additional QALYs from adjuvant systemic therapy by nodal group.
Quality of life as in the Q_{severe}.

Patient A

Nodal Status	Nodal Status Probability	Additional QALYs T	CT	CT+T
0	0.84	-0.46	-1.34	-1.14
1–3	0.11	1.12	-0.47	$\boxed{1.2}$
4–9	0.03	1.21	-0.4	$\boxed{1.37}$
>9	0.02	1.29	-0.3	$\boxed{1.57}$
Unknown		-0.21	-1.2	-0.76
Expected gain from ALND is .06				

Patient B

Nodal Status	Nodal Status Probability	Additional QALYs T	CT	CT+T
0	0.56	1.49	1.96	$\boxed{3.98}$
1–3	0.23	1.45	2.16	$\boxed{4.34}$
4–9	0.14	1.32	2.06	$\boxed{4.19}$
>9	0.07	0.96	1.68	$\boxed{3.55}$
Unknown		1.42	2	$\boxed{4.06}$
Expected gain from ALND is 0				

Table 7: This table summarizes the calculations used in solving the decision tree for patients A and B, Q_{severe} scenario. The layout is as in Tables 4, 5 and 6. Boxed values indicate the best treatment option for a given nodal status. When no value is boxed, no adjuvant treatment is the best option.

Gains in QALYs from ALND by age, ER status, tumor size, and QOL scenario.

QOL	TS	ER-					ER+				
				AGE					AGE		
		30	40	50	60	70	30	40	50	60	70
Q_{mild}	<.5	0	0	0	0.05	0.04	0	0	0.11	0.06	0.02
	.5–1	0	0	0	0	0.04	0	0	0.11	0.06	0.02
	1–2	0	0	0	0	0	0	0	0	0	0
	2–3	0	0	0	0	0	0	0	0	0	0
	3–4	0	0	0	0	0	0	0	0	0	0
	4–5	0	0	0	0	0	0	0	0	0	0
	>5	0	0	0	0	0	0	0	0	0	
Q_{moderate}	<.5	0	0	0.05	0.06	0.02	0	0	0.09	0.04	0
	.5–1	0	0	0	0.06	0.02	0	0	0.09	0.04	0.01
	1–2	0	0	0	0	0	0	0	0	0	0.01
	2–3	0	0	0	0	0	0	0	0	0	0.02
	3–4	0	0	0	0	0	0	0	0	0	0.03
	4–5	0	0	0	0	0	0	0	0	0	0.03
	>5	0	0	0	0	0	0	0	0	0	0
Q_{severe}	<.5	0	0.14	0	0	0	0.5	0.58	0.29	0.19	0.05
	.5–1	0	0	0	0	0	0.12	0.27	0.13	0.2	0.06
	1–2	0	0	0	0	0	0	0	0.06	0.04	0.01
	2–3	0	0	0	0	0	0	0	0.03	0.07	0.02
	3–4	0	0	0	0	0	0	0	0	0.05	0.03
	4–5	0	0	0	0	0.01	0	0	0	0.02	0.05
	>5	0	0	0	0	0.02	0	0	0	0	0
$Q_{\text{ALND<XRT}}$	<.5	-0.11	-0.09	-0.02	0.01	-0.02	-0.12	-0.1	0.01	-0.02	-0.04
	.5–1	-0.1	-0.08	-0.07	0.01	-0.02	-0.12	-0.1	0.01	-0.02	-0.04
	1–2	-0.06	-0.05	-0.05	-0.04	-0.03	-0.08	-0.07	-0.06	-0.05	-0.02
	2–3	-0.05	-0.05	-0.04	-0.03	-0.03	-0.08	-0.07	-0.06	-0.05	-0.01
	3–4	-0.05	-0.05	-0.04	-0.03	-0.03	-0.07	-0.06	-0.06	-0.04	0.01
	4–5	-0.05	-0.04	-0.04	-0.03	-0.02	-0.07	-0.06	-0.05	-0.04	-0.01
	>5	-0.03	-0.03	-0.03	-0.02	-0.02	-0.05	-0.05	-0.04	-0.04	-0.03

Table 8: Expected gains from ALND, in QALYs for all patients groups, in four QOL scenarios. Columns are arranged by age, within ER status; rows are arranged by tumor size, within QOL scenario.