Increased Mortality Risk Associated With Medial Breast Tumors May Be Due to Untreated Internal Mammary Node Metastases

Caroline Lohrisch, MD

ABSTRACT

Recent reports suggest that medial breast tumors are independently associated with decreased disease-free and overall survival compared with lateral breast tumors. Surgical evidence indicates that medial tumors with positive axillary nodes have an increased rate of internal mammary node (IMN) metastases. It is hypothesized that IMN disease that does not receive local therapy (surgery or radiotherapy) may be a reservoir for eventual systemic spread, and may account for the increased recurrence and death rates associated with medial tumors. Although early trials are divided as to the benefit of local IMN therapy, they were conducted largely in the absence of adjuvant systemic therapy. Are there reliable methods to assess IMN status, and does IMN irradiation significantly reduce the excess risk of medial tumors in women who receive today's "standard" adjuvant systemic therapy?

Oncology Spectrums *2001;2(1):37-43*

TABLE 1. RECENT STUDIES COMPARING OUTCOME FOLLOWING EARLY BREAST CANCER ACCORDING TO PRIMARY TUMOR LOCATION

Author, year	N (medial/ lateral)	Inclusion Years	Median f/u (mo)	Population	Systemic Treatment (ST)	Outcomes			
						LR	DFS	DSS	OS
Zucali[8] 1998	2,396 (777*/1,619)	1973–89	147	T<2.5 cm N0-1 M0	N0: None N1: CMF from 1976	N/A	Medial<lateral Hz ratio 1.3	N/A	Medial<lateral Hz ratio 0.8
Lohrisch[9] 2000	5,365 (1,511/3,848)	1989–95	47	T1-3 N0-1 M0	N0: 61% None N1: 95% Yes	No ST: NS ST: NS	Medial<lateral No ST: *P*=0.16 High risk *P*=0.43 Low risk *P*=0.19 ST: *P*=0.001 High risk *P*=0.003 Low risk *P*=0.60	Medial<lateral No ST: *P*=0.79 High risk *P*=0.66 Low risk *P*=0.87 ST: *P*=0.002 High risk *P*=0.03 Low risk *P*=0.69	NA
Kroman[10] 2000	35,319†	1977–present	?	Primary breast cancer	Not specified	N/A	N/A	N/A	Medial<other 15-21% ↓
Hammer[11] 2000	644 (220†/429)	1984–95	77	T1-2 N0-1 M0	N0: not specified N1: 6 CMF, Tam	*P*=0.08	Medial<lateral *P*=0.001	Medial<lateral *P*=0.009	Medial<lateral *P*=0.0009

* Includes central tumors (Kroman, n=55; Zucali, n=not specified);
† Population-based study, outcome comparisons made for upper outer quadrant versus other locations.

f/u =follow-up; Hz=hazard ratio; LR=locoregional recurrence; DFS=disease-free survival; DSS=disease-specific survival; NS=difference not significant; OS=overall survival; T=tumor stage; N0=axillary nodes negative; N1=axillary nodes positive; T1=tumor<2 cm; T2=tumor 2–5 cm; T3=tumor>5 cm; M0=no metastatic disease; N/A=not available; CMF=cyclophosphamide/methotrexate/5-fluorouracil; Tam=tamoxifen.

Lohrisch C. *Oncology Spectrums.* Vol 2, No 1. 2001.

TALKING POINTS Physicians Pharmacy Formulary Cancer Nurses

Given the almost universal systemic therapy use in women with node-negative and –positive breast cancer, inadequately treated regional disease is reemerging as an important consideration.

Adjuvant chemotherapy has been shown to be of benefit in all but the lowest risk of node-negative disease, and anthracyclines may be preferable to cyclophosphamide/methotrexate/fluorouracil.

Local therapy issues that need prospective evaluatoin include whether there are reliable noninvasive or minimally invasive ways of identifying occult internal mammary node (IMN) spread, and whether IMN treatment reduces the adverse prognosis associated with medially located tumors and IMN metastases.

Randomized trials suggest that regional radiation in women with high-risk disease who have had a mastectomy and systemic chemotherapy offers a survival advantage.

Dr. Lohrisch is a research fellow at the Investigational Drug Branch for Breast Cancer at the Institute Jules Bordet in Brussels, Belgium.

TABLE 2. FREQUENCY OF IMN METASTASES IN OPERABLE BREAST CANCER

Author	Data Type	Year	Population	N	Positive IMN			
					*P*N0		*P*N1	
					N	%	N	%
Handley[13]	Retrospective	1975	Operable, IMN biopsy	1,000	26	8.0	187	35
Urban[14]	Retrospective	1977	cN+ and/or inner location	455	34	13.7	99	48
Lacour[15]	RCT	1983	T <7 cm, N0-1, M0	703	33	10.0	105	28
Veronesi[16]	Retrospective	1985	Outer >2 cm or cN+, inner<70 years old	1,119	51	9.0	162	29

IMN=internal mammary node; NO=axillary nodes negative; N1=axillary nodes positive; cN+=clinically axillary node positive; pN=pathologic axillary node status; RCT=randomized controlled trial; T=tumor stage; M0=no metastatic disease.

Lohrisch C. *Oncology Spectrums.* Vol 2, No 1. 2001.

INTRODUCTION

The presence of systemic micrometastases is the dominant risk for recurrence of early breast cancer. However, these are difficult to detect routinely, and characteristics of the local tumor, including nodal status, size, hormone receptor status, and grade, as well as the patient's age, are used to form adjuvant systemic therapy recommendations.[1] As a result of the clear independent survival benefits associated with systemic adjuvant polychemotherapy and hormone therapy in young and old women with both node-negative and -positive disease, systemic therapy is recommended for the majority of women with early breast cancer today.[1-3] Given the almost universal systemic therapy use, inadequately treated regional disease is reemerging as an important consideration. In women who receive adjuvant systemic therapy, optimal local control has been shown to play an important role in reducing both locoregional recurrences and disease-specific death.[4-7]

PROGNOSIS OF MEDIAL TUMORS

Several recent reports have identified increased recurrence and mortality risk for tumors located in the medial compared with lateral breast quadrants (Table 1).[8-11] These retrospective series incorporated patients largely treated with modern surgical techniques, ie, without biopsy or removal of the internal mammary nodes (IMNs), and with chemotherapy and/or hormone therapy in cases of node-positive and high-risk node-negative disease. The adverse prognostic impact of medial tumor location observed in these series is posited to be due to IMN spread that remains undetected and inadequately treated. Using multivariate analysis, three of these series reported a significantly higher mortality risk for medial vs lateral tumors, despite a lower incidence of axillary lymph node metastases in the former group.[8-10] The lower axillary node-positive rate and lower survival in medial tumors are more likely due to preferential spread to and undertreatment of IMN than to differences in tumor behavior linked to anatomic location in the breast.

"The lower axillary node-positive rate and lower survival in medial tumors are more likely due to preferential spread to and undertreatment of IMN than to differences in tumor behavior linked to anatomic location in the breast."

THE HISTORICAL CONTRIBUTION OF IMN TREATMENT TO EARLY BREAST CANCER SURVIVAL

Spread of breast cancer to the axillary nodes is recognized as the most important prognostic factor.[12] It is logical to conclude that it is the ability of these tumors to spread regionally at an early stage, rather than axillary location itself, that imparts this poorer prognosis. By analogy, tumors that spread to other areas of lymph drainage of the breast would also be expected to have an increased relapse risk. Although the axilla is the predominant lymph drainage basin for the lateral half of the breast, where the majority of breast cancers arise, early surgical studies demonstrated that a significant proportion of tumors also spread to the IMN basin.[13-16] Overall, 8% to 14% of axillary node-negative and 28% to 48% of axillary node-positive breast cancers had positive IMNs, depending on the series. Moreover, for axillary node-positive tumors, the rate of IMN spread was higher for medial than for lateral tumors, 32% to 34%, and 17% to 21%, respectively. There was no difference between medial and lateral tumors that were axillary node negative (Table 2).[13-16]

Series that compared survival in the era preceding routine adjuvant systemic therapy reported that only one third of women with both axillary node and IMN spread were alive after 10 years vs up to two thirds of women with only axillary node spread. This suggests that IMN involvement significantly impacts the probability of disease recurrence.[16,17] Among

195 patients, most of whom had medial tumors and underwent extended radical mastectomy, the presence of IMN metastases (24% overall, 18% and 36% of axillary node-negative and -positive tumors, respectively) was a highly significant prognostic factor for reduced survival (p=0.004), after axillary node status (p<0.0005). Tumor size was less significant (p=0.077) than IMN status.[18]

Estimates of the increased mortality risk associated with medial location in recent series range from 1.2- to 2-fold.[8-11] This range of increased risk arises from differences in the systemic therapy received and from inclusion of central tumors, thought to have a worse prognosis themselves, with medial tumors in some series. Estimates of recurrence and death risks would also be lower when low- and high-risk tumors (or axillary node-negative and -positive tumors) were analyzed together, such as in the reports by Zucali and Hammer, than when they were considered separately.

The incidence of locoregional recurrence does not appear to be increased for women with medially located tumors. One reason for this may be that IMN recurrences are generally inoperable, and therefore may be classified as systemic rather than regional recurrences. Additionally, untreated IMN deposits presumably act as a reservoir for future systemic dissemination, analogous to axillary node-positive tumors that tend to recur systemically rather than locally. If this were true, direct treatment of the IMN would be expected to decrease the incidence of distant metastases and death. However, early randomized and retrospective series comparing no treatment with treatment of the IMN—by either extended radical mastectomy or irradiation after radical mastectomy—show mixed results (Table 3).[14,19-26]

The patient population in these studies included women with axillary node-negative and -positive disease, and tumors in medial, central, and lateral locations. Thus, the risk of IMN spread would be variable, and therefore the power of these trials to show a benefit from IMN treatment may have been significantly

TABLE 3. TRIALS OF IMN THERAPY VS NO IMN THERAPY IN OPERABLE BREAST CANCER

Author, Year	Study Type	Years of Study	N	Population	Intervention	Overall Survival
Lacour[19] 1976	RCT	1963–68	1580	T1-3a, (<7 cm) N0-1 M0	RM vs ERM	Equivalent overall Medial N1 tumors(n=190): ERM>RM
Veronesi[16] 1981	RCT	1964–68	737	T1-3a, (<7 cm) N0-1 M0	RM vs ERM	At 10 years: RM=60.7%; ERM=57.0%; NS
Deemarski[20] 1984	unspecified	?–1984	997	T1-2 N0-1 M0 Medial, central	RM vs ERM	ERM>RM by 10% for N0, 16% for N1 tumors
Arriagada[21] 1988	Retrospective	1958–78	1195	N1, RM or ERM	RM vs ERM or RM+RT*	Medial tumors: ERM/RM+RT >RM ERM=RM+RT RT ↓ local recurrences, all subgroups
Meier[22] 1989	RCT	1973–82	123	T1-2 N0-1 M0 (60% medial)	RM vs ERM	At 10 years: RM ERM P All tumors 60% 74% 0.13 Medial tumors 60% 86% 0.025
Meier[22] 1989	Retrospective	1973–82	390	T1-2 N0-1 M0	RM vs ERM	ERM>RM (NS) for medial tumors
Horino[23] 1991	Retrospective	1967–87	671	Operable breast cancer	RM vs ERM	Similar at 10 years in pts with IMN+ERM and N1 disease (67%) (80% of medial and 39% of lateral tumors had ERM)
Shiba[24] 1992	Retrospective	1965–80	183	Medial/central	RM vs RM+RT* vs ERM	RM RM+RT ERM P 5 years 91% 82% 82% NS 10 years 79% 67% 70% NS RM+RT and ERM >RM if >4 axillary nodes +
Kaija[25] 1995	RCT	1989–91	270	T1–3 N0–1 M0	IMN RT yes vs no	No efficacy results Pneumonitis 18% vs 14% (NS) More pulmonary fibrosis in IMN RT group
Obedian[26] 1999	Retrospective	1970–90	984	T1–3 N0–1 M0	IMN RT yes vs no	At 10 years IMN yes 72% IMN no 84% NS Yes group: more medial, T2, N1, indeterminate margins. 94% of N1 had systemic therapy

*RT inclusive of IMN.

RCT=randomized controlled trial; T1=tumor<2cm; T2=tumor 3–5 cm; T3=tumor>5 cm; RM=radical mastectomy; ERM=extended radical mastectomy; N0=axillary nodes negative; N1=axillary nodes negative; RT=radiotherapy; IMN=internal mammary node; NS=difference not significant.

Lohrisch C. *Oncology Spectrums.* Vol 2, No 1. 2001.

reduced by lack of selection. Many of these studies were also conducted prior to the routine use of systemic adjuvant therapy, which would have substantially reduced the incidence of recurrence and death associated with already disseminated systemic micrometastases. It may be that, in the absence of systemic therapy, the risk of recurrence is directly related to the presence of untreated systemic micrometastases. Thus, treatment of the IMNs, irrespective of their status, would not significantly influence disease course. Both the absence of systemic adjuvant therapy and the unselected patient population may have diluted any impact of IMN therapy on overall survival. In fact, subgroup analyses of some of the overall negative studies suggested that, even in the absence of systemic therapy, there was a significant survival benefit for the subset of women with axillary node-positive medial tumors, presumably because this is the subgroup with the highest incidence of IMN disease.[19,22,23]

"Available data support the hypothesis that women with tumors in the medial hemisphere of the breast are at highest risk for IMN spread, particularly with axillary node involvement. Unfortunately, there is currently no noninvasive way to assess IMN status."

Historically, the treatment of breast cancer has focused on radical surgery, including removal of the entire breast, pectoralis major, axillary nodes, IMNs, and various endocrine organs, most notably the ovaries.[27] Progressively conservative surgical techniques developed in parallel with recognition of the benefits of radiotherapy to achieve local control and of systemic therapy to prevent distant metastases.[4,28] Removal of the fascia, chest wall muscles, and IMNs has been largely replaced with breast-conserving surgery followed by radiotherapy or simple mastectomy. Axillary clearance, particularly in women with positive sentinel nodes, is still used more or less routinely as part of primary breast cancer surgery. The AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery) trial, which is sponsored by the European Organization for the Research and Treatment of Cancer (EORTC), is comparing the outcomes of patients with positive sentinel nodes treated either by axillary dissection or axillary radiotherapy.[29] Surgical IMN dissection was largely forsaken, being technically difficult, disfiguring, and of equivocal survival benefit in early randomized surgical studies.

This absence of a clear survival improvement with IMN dissection, coupled with increased risk of pulmonary and cardiac injury with irradiation of the mediastinal region, is probably why radiotherapy has not replaced surgical treatment of IMN, as it has replaced mastectomy. Thus, for most women today, local control includes surgical removal of the tumor, exploration of the axilla, and radiotherapy of the breast plus or minus the axilla and supraclavicular areas. Most centers do not have a standard radiotherapy policy for IMN treatment, although some irradiate this region in women with medial or otherwise high-risk tumors.

DETECTION OF IMN METASTASES

Available data support the hypothesis that women with tumors in the medial hemisphere of the breast are at highest risk for IMN spread, particularly those with axillary node involvement. Unfortunately, there is currently no noninvasive way to assess IMN status. Radiologic imaging techniques, such as computerized tomography and magnetic resonance imaging, are not adequate to exclude microscopic disease in nodes. Even routine hematoxylin and eosin (H&E) histologic examination of axillary nodes may miss a substantial proportion of microscopic metastatic foci, and there is conflicting data about whether the recurrence risk of tumors with such micrometastases more closely resembles that of node-positive rather than node-negative disease.[30-35] By analogy, the proportion of tumors with IMN spread reported in early surgical series for high-risk medial and lateral tumors may be underestimated, if microscopic deposits were missed.

Presumably, techniques for identifying the sentinel axillary node, including radioactive tracers and dyes injected preoperatively into the primary tumor region, could be used to identify tumors whose primary lymphatic drainage is medial, and which have a theoretically increased risk of IMN spread. However, these techniques are operator-dependent and sentinel node sampling techniques are still considered experimental, despite their growing use.[36] It is current practice to perform a formal axillary dissection when a sentinel axillary node is found to be positive; however, no such tenet exists for positive internal mammary sentinel nodes. At least one report suggests that the reliability of these methods for identifying IMN sentinel nodes may be quite low,[37] while another says that it may be reasonably high.[38]

There is mounting interest in the use of positron emission tomography (PET) to identify occult disease in both the high-risk adjuvant and metastatic settings. This technique uses 18-fluorodeoxyglucose, a radiolabelled glucose tracer, to identify areas of increased

metabolic activity, such as those found in infective, inflammatory, and neoplastic processes. It is being used increasingly when other imaging techniques prove unhelpful. Several studies evaluating the utility of PET scans in breast cancer have been reported over the last 2 years; however, there is little data on its accuracy.[39-42]

A pilot study of preoperative PET scanning in eight women with medial tumors of at least 2 cm correctly identified occult liver metastases in one patient (confirmed by biopsy), axillary spread in two (confirmed by axillary dissection), and IMN disease in one (confirmed by biopsy). PET scanning in another patient also suggested IMN disease; however, this remained unconfirmed because she received neoadjuvant chemotherapy. In no case of pathologically confirmed axillary node-negative disease was the PET scan falsely positive.[43] These promising results have led to initiation of formal pet scan studies to determine its sensitivity and specificity investigations to identify occult foci of disease. Results of these investigations, particularly with respect to IMN disease, are pending.

Yet PET scans are not a diagnostic panacea. PET imaging is not widely available, and it would be costly to set up facilities for routine PET scans. In addition, they are more expensive than the traditional radiologic work-up used to exclude metastatic disease prior to primary surgery.[44] In centers where CT scans of the chest and abdomen are used routinely instead of the simpler imaging techniques such as chest x-rays and abdominal ultrasound, PET scanning may be more cost effective. Inability to detect micrometastases may be another limitation. If its specificity and sensitivity were confirmed, PET scanning could be a noninvasive way to accurately assess IMN status in patients with medial tumors, and the results could guide IMN therapy recommendations.

NEW STRATEGIES FOR TREATMENT OF IMNS

It is unlikely that routine surgical dissection of the IMN will come back into vogue, despite the potential therapeutic value in selected cases. There are no prospective studies comparing IMN surgical excision with irradiation, although one retrospective series suggests they are equivalent in terms of overall survival.[22] Irradiation of this region has traditionally been technically difficult, particularly in patients who have had a lumpectomy or immediate reconstruction, and damage to cardiac and pulmonary tissue is a risk with older techniques of mediastinal irradiation. There are, however, new mapping strategies using CAT scanning and radiotherapy techniques that can reduce scatter to mediastinal organs and decrease toxicity.[45,46] Randomized trials suggest that regional radiation (including the IMN region) in women with high-risk disease who have had a mastectomy and systemic chemotherapy offers a survival advantage.[6,7] The extent to which the IMN radiotherapy contributed to this advantage is unknown because the studies were too small to analyze the subset of women with axillary node-positive medially located tumors. It is possible that irradiation of IMNs in women at high risk for IMN disease provides benefits independent of systemic therapy.

"The value of IMN treatment must be reassessed prospectively in women with high risk of IMN disease who have been treated with systemic therapy according to today's standards."

In the series by Lohrisch et al, women with medial tumors who received 4-field irradiation (exclusive of the IMN region) had inferior disease-free and disease-specific survival compared with the combined group of women with medial tumors treated with 5-field irradiation (inclusive of the IMNs) and women with lateral tumors treated with either 4- or 5-field irradiation.[9] However these data are not reliable, given that there was no standard institutional policy for who should receive 4- or 5-field radiotherapy volumes. Other retrospective series have failed to demonstrate such a difference in outcome.[47,48]

The value of IMN treatment must be reassessed prospectively in women with high risk of IMN disease who have been treated with systemic therapy according to today's standards. Two large multicenter studies are prospectively exploring the impact of adding an IMN field to standard radiotherapy volumes in patients with early breast cancer. The National Cancer Institute of Canada (NCIC) trial MA.20, open to women with high-risk axillary node-negative and -positive disease, will compare tangential fields to a modified 4-field technique that includes the upper ipsilateral IMNs. Recruitment began in December 1999 with less than 100 patients randomized to date.[49] An EORTC trial (EORTC 22922/10925) is enrolling women with node-negative central or medial tumors, and node-positive tumors of any quadrant. About half of the accrual target of 3,780 women has been reached after 4 years.[50] The study is powered to show a 5% increase in 10-year overall survival.[51]

Clearly both of these trials are several years away from having reportable results. Because the majority of breast tumors are located in the upper outer quadrant, and the incidence of IMN metastases in these patients is relatively low, the individual trials may not be able to demonstrate a benefit of more extensive radiotherapy, if one exists. Pooling of patients with medial tumors from both studies, however, may conclusively demonstrate whether irradiation of the IMNs has a clinically meaningful benefit for all medial tumors or for medial tumors with axillary node involvement, which appear to be at greatest risk for IMN spread.

"Local therapy issues that need prospective evaluation include whether there are reliable noninvasive or minimally invasive ways of identifying occult IMN spread, and whether IMN treatment reduces the adverse prognosis associated with medially located tumors and IMN metastases."

CONCLUSIONS

Clinicians and researchers treating patients with early breast cancer are grappling with the dilemma of how much adjuvant therapy is enough. Adjuvant chemotherapy has been shown to be of benefit in all but the lowest risk node-negative disease, and anthracyclines may be preferable to cyclophosphamide/methotrexate/fluorouracil.[1,2,52,53] Systemic therapy overviews have confirmed that the benefits of hormone therapy and chemotherapy are independent of each other and they are therefore complimentary.[2,3] Women with multiple node-positive disease appear to benefit from the addition of radiotherapy to mastectomy.[6,7] On the other hand, there does not seem to be an added benefit to chemotherapy outside the conventional cumulative dose and dose intensity ranges[54-56] or to myeloablative doses with stem cell support.[57-60]

Clearly, the absolute benefit of adjuvant therapy is greater in women with higher baseline risk.[2,3] Recent series support a poorer prognosis for medial compared with lateral breast tumors, independent of adjuvant systemic therapy and other tumor and patient characteristics. Whether this is due to undertreated metastases in IMNs is unconfirmed, although surgical evidence suggests both an increased incidence of such spread in medial tumors and decreased survival in patients with tumors with IMN spread. Local therapy issues that need prospective evaluation include whether there are reliable noninvasive or minimally invasive ways of identifying occult IMN spread, and whether IMN treatment reduces the adverse prognosis associated with medially located tumors and IMN metastases. Older randomized studies are of limited value in addressing this last question, given that most did not give adjuvant systemic therapy, which has an independent impact on survival. It is hoped that the large ongoing NCIC and EORTC radiotherapy trials, which incorporate such adjuvant systemic therapy, will satisfactorily address this important issue of optimal local control.

REFERENCES

1. Goldhirsch A, Glick JH, Gelber RD, Senn HJ. Highlights: international consensus panel on treatment of primary breast cancer. *J Natl Cancer Inst.* 1998;90:1601-1608.
2. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet.* 1998;352:930-942.
3. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomized trials. *Lancet.* 1998;351:1451-1467.
4. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med.* 1989;320:822-828.
5. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet.* 2000;355:1757-1770.
6. Overgaard H, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med.* 1997;337:949-955.
7. Ragaz J, Jackson SM, Le N, et al. Adjuvant radiotherapy and chemotherapy in node positive premenopausal women with breast cancer. *N Engl J Med.* 1997;337:956-962.
8. Zucali R, Mariani L, Marubini E, et al. Early breast cancer: evaluation of the prognostic role of the site of the primary tumor. *J Clin Oncol.* 1998;16:1363-1366.
9. Lohrisch C, Jackson J, Jones A, Mates D, Olivotto IA. Relationship between tumor location and relapse in 6,781 women with early invasive breast cancer. *J Clin Oncol.* 2000;18:2828-2835.
10. Kroman N, Wohlfahrt J, Mouridsen HT, Melbye M. Influence of tumor location on axillary nodal status and breast cancer prognosis [abstract 243]. *Eur J Cancer.* 2000;36(suppl 5):S91.
11. Hammer J, Track C, Seewald DH, Zoidl JP. Breast cancer: the medial tumor location-an unfavorable disease! Results from 644 patients (1984-1995) [abstract 313]. *Eur J Cancer.* 2000;36(suppl 5):S104.
12. Dent DM. Axillary lymphadenectomy for breast cancer. *Arch Surg.* 1996; 131:1125-1127.
13. Handley R: Natural history of breast cancer. In: Harris J, Lippman ME, Morrow M, Hellman S, eds. *Diseases of the Breast.* 1996: 384
14. Urban J. Is there a rationale for an extended radical procedure? *Int J Radiat Oncol Biol Phys.* 1977;2:985-988.
15. Lacour J, Mle M, Caceres E, et al. Radical mastectomy versus radical mastectomy plus internal mammary dissection. *Cancer.* 1983;51:1941-1943.
16. Veronesi U, Valagussa P. Inefficacy of internal mammary nodes dissection in breast cancer surgery. *Cancer.* 1981;47:170-175.
17. Veronesi U, Cascinelli N, Greco M, et al. Prognosis of breast cancer patients after mastectomy and dissection of internal mammary nodes. *Ann Surg.* 1985;202:702-707.
18. Cody HS III, Urban JA. Internal mammary node status: a major prognosticator in axillary node-negative breast cancer. *Ann Surg Oncol.* 1995;2:32-37.

19. Lacour J, Bucalossi P, Cagers E, et al. Radical mastectomy versus radical mastectomy plus internal mammary dissection. Five year results of an international cooperative study. *Cancer.* 1976;37:206-214.
20. Deemarski L, Seleznev IK. Extended radical operations on breast cancer of medial or central location. *Surgery.* 1984;96(1):73-77.
21. Arriagada R, Le MG, Mouriesse H, et al. Long-term effect of internal mammary chain treatment. Results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. *Radiother Oncol.* 1988;11:213-222.
22. Meier P, Ferguson DJ, Karrison T. A controlled trial of extended radical versus radical mastectomy. Ten-year results. *Cancer.* 1989;63:188-195.
23. Horino T, Fujita M, Ueda N, et al. Efficacy of internal mammary node dissection in the treatment of breast cancer. *Jpn J Clin Oncol.* 1991;21:422-427.
24. Shiba E, Miyauchi K, Kobayashi T, Takai S, Mori T. Radical mastectomy with parasternal node dissection or radiation to the parasternal region for breast cancer of medial or central location. *Surg Today.* 1992;22:124-127.
25. Kaija H, Maunu P. Tangential breast irradiation with or without internal mammary chain irradiation: results of a randomized trial. *Radiother Oncol.* 1995;36:172-176.
26. Obedian E, Haffty BG. Internal mammary nodal irradiation in conservatively-managed breast cancer patients: is there a benefit? *Int J Radiat Oncol Biol Phys.* 1999;44:997-1003.
27. Bland KI, O'Leary JP, Woodward ER, Dragstedt LR. Immediate oophorectomy and adrenalectomy in the treatment of stage III breast carcinoma. A ten year follow-up study. *Am J Surg.* 1975;129:277-285.
28. Bonadonna G, Brusamolino E, Valagussa P, et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med.* 1976;294:405-410.
29. Bourez RLJH, Rutgers EJTh, Distante V, Van de Velde CJH. Quality control in the EORTC-AMAROS (=after mapping of the axilla: radiotherapy or surgery) trial no. 10981 [abstract 269]. *Eur J Cancer.* 2000;36(suppl 5):S97.
30. Meyer JS, Fahrner M, Daniel FC. Pathology and behavior of small breast carcinomas. *Semin Diagn Pathol.* 1999;16:257-268.
31. Maibenco DC, Weiss LK, White JJ, et al. Impact of micrometastases on the survival of women with T1 breast cancer [abstract 10]. *Breast Cancer Res Treat.* 1999;57:27.
32. Reitsamer R, Menzel R, Prokop E, et al. The histopathologic examination of the sentinel lymph node- identification of micrometastases [abstract 305A]. *Proc Am Soc Clin Oncol.* 2000;19:79a.
33. Dowlatshahi K, Witt TR, Bloom KT, Fan M, Spitz DJ, Oleske D. Detection of occult micrometastases by 0.25mm sectioning and cytokeratin staining of sentinel nodes in early breast cancer [abstract 305]. *Proc Am Soc Clin Oncol.* 2000;19:79a.
34. Cote RJ, Peterson HF, Chaiwun B, et al. Role of immunohistochemical detection of lymph-node metastases in management of breast cancer. *Lancet.* 1999;354:896-900.
35. Hanna WM, Kahn HJ, Chapman JA, Trudeau M, Murray D. The clinical significance of micrometastases in node negative breast cancer patients: a retrospective study [abstract 486]. *Eur J Cancer.* 2000;36(suppl 5):S139.
36. Ng PC, Chua AC, Lannin DP, Van Eyk JJ, Swanson MS, Tafra L. Age and surgeon experience: the only significant factors contributing to sentinel node mapping failure in breast cancer , [abstract 12]. *Breast Cancer Res Treat.* 1999;57:27.
37. Noguchi M, Tsugawa K, Miwa K. Internal mammary chain sentinel lymph node identification in breast cancer. *J Surg Oncol.* 2000;73:75-80.
38. Abreu de Sousa J, Fougo JL, Cunha D, et al. Internal mammary chain sentinel node biopsy in patients with breast cancer [abstract 272]. *Eur J Cancer.* 2000;36(suppl 5):S97.
39. Ohta M, Tokuda Y, Saito Y, et al. Whole-body positron emission tomography for evaluation of bone metastases in patients with breast cancer: comparison with Tc99m MDP bone scintigraphy [abstract 385]. *Proc Am Soc Clin Oncol.* 2000;19:100a.
40. Flanagan FL, Dehdashti F, Siegel BA. PET in breast cancer. *Semin Nucl Med.* 1998;4:290-302.
41. Hoh CK, Schiepers C. 18-FDG imaging in breast cancer. *Semin Nucl Med.* 1999;1:49-56.
42. Mortimer JE, Dehdashti F, Welch MJ, Katzenellenbogen JA, Trinkaus K, Siegel BA. Prediction of response to hormonal therapy by serial positron emission tomography [abstract 311]. *Proc Am Soc Clin Oncol.* 2000;19:81a.
43. Bernstein V, Jones A, Mankoff D, Davis N, Kuusk U. Preoperative assessment of internal mammary nodes (IMN) in medial hemisphere breast cancer (MHBC) by fluorodeoxyglucose (FDG) positron emission tomography (PET) [abstract 487]. *Proc Am Soc Clin Oncol.* 2000;19:125a.
44. Health Economics Research Group, Brunel University, UK. Positron emission tomography: establishing priorities for health technology assessment. *Health Technol Assess.* 1999;3(16):1-54.
45. Marks L B, Hebert ME, Bentel G, et al. To treat or not to treat the internal mammary nodes: a possible compromise. *Int J Radiat Oncol Biol Phys.* 1994;29:903-909.
46. Nixon A, Manola J, Gelman R, et al. No long-term increase in cardiac-related mortality after breast-conserving surgery and radiation therapy using modern techniques. *J Clin Oncol.* 1998;16:1374-1379.
47. Fowble B, Hanlon A, Freedman G. Internal mammary node irradiation neither decreases distant metastases nor improves survival in stage I and II breast cancer. *Int J Radiat Oncol Biol Phys.* 2000;47:883-894.
48. Freedman GM, Fowble BL, Nicolaou N. Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist? *Int J Radiat Oncol Biol Phys.* 2000;46:805-814.
49. MA.20: A phase III study of regional radiation therapy in early breast cancer. National Cancer Institutes of Canada Clinical Trials Group. Available at: http://www.ctg.queensu.ca/PUBLIC_site/Clinical_Trials/ph3_trial_summ.htm
50. EORTC 22922/10925. Radiotherapy group trials. European Organisation for the Research and Treatment of Cancer. Available at: http://www.eortc.be
51. Poortmans PH, Van den Bogaert W, Venselaar J, et al. The hypothetical influence of dose variation on survival in EORTC trial 22922/10925 investigating the role of internal mammary chain (IMC) irradiation: a quality assurance report [abstract 295]. *Eur J Cancer.* 2000;36(suppl 5):S101.
52. Fisher B, Dignam J, DeCillis DL, et al. The worth of chemotherapy and tamoxifen (TAM) over TAM alone in node-negative patients with estrogen-receptor (ER) positive invasive breast cancer (BC): first results from NSABP B-20 [abstract 1]. *Proc Am Soc Clin Oncol.* 1997;16:1a.
53. Hutchins L, Green S, Ravdin P, et al. CMF versus CAF with and without tamoxifen in high-risk node-negative breast cancer patients and a natural history follow-up study in low-risk node-negative patients: first results of Intergroup trial INT 0102 [abstract 2]. *Proc Am Soc Clin Oncol.* 1998;17:1a.
54. Fisher B, Anderson S, Wickerham DL, et al. Increased intensification and total dose of cyclophosphamide in a doxorubicin-cyclophosphamide regimen for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-22. *J Clin Oncol.* 1997;15:1858-1869.
55. Fisher B, Anderson S, DeCillis A, et al. Further evaluation of intensified and increased total dose of cyclophosphamide for the treatment of primary breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-25. *J Clin Oncol.* 1999;17:3374-3388.
56. Henderson IC, Berry D, Demetri G, et al. Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (pts) with node-positive primary breast cancer (BC) [abstract 390A]. *Proc. Am Soc Clin Oncol.* 1998;17:101a.
57. Rodenhuis S, Richel DJ, van der Wall E, et al. Randomised trial of high-dose chemotherapy and haemopoietic progenitor-cell support in operable breast cancer with extensive axillary lymph-node involvement. *Lancet.* 1998;352:515-521.
58. The Scandinavian Breast Cancer Study Group 9401. Results from a randomized adjuvant breast cancer study with high dose chemotherapy with CTCb supported by autologous bone marrow stem cells versus dose escalated and tailored FEC therapy [abstract 3]. *Proc Am Soc Clin Oncol.* 1998;18:2a.
59. Peters W, Rosner G, Vredenburgh J, et al. A prospective, randomized comparison of two doses of combination alkylating agents as consolidation after AC in high-risk primary breast cancer involving ten or more axillary lymph nodes: preliminary results of CALGB 9082/SWOG 9114/NCIC MA-13 [abstract 2]. *Proc Am Soc Clin Oncol.* 1999;18:1a.
60. Hortobagyi GN, Buzdar AU, Theriault RL, et al. Randomized trial of high-dose chemotherapy and blood cell autografts for high-risk primary breast carcinoma. *J Natl Cancer Inst.* 2000;92:225-233