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ORIGINAL REPORT

Prognostic Value of Extracapsular Tumor Spread for Locoregional Control in Premenopausal Patients With Node-Positive Breast Cancer Treated With Classical Cyclophosphamide, Methotrexate, and Fluorouracil: Long-Term Observations From International Breast Cancer Study Group Trial VI

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ABSTRACT

Purpose
We sought to determine retrospectively whether extracapsular spread (ECS) might identify a subgroup that could benefit from radiotherapy after mastectomy, especially patients with 1 to 3 positive lymph nodes (LN1-3+).

Patients and Methods
We randomized 1,475 premenopausal women with node-positive breast cancer to three, six, or nine courses of "classical" CMF (cyclophosphamide, methotrexate, and fluorouracil). After a review of all pathology forms, 933 patients (63%) had information on the presence or absence of ECS. ECS was present in 49.5%. The median follow-up was 10 years.

Results
In univariate analyses, ECS was associated with worse disease-free survival (DFS) and overall survival (OS). In multivariate analyses adjusting for tumor size, vessel invasion, surgery type, and age group, ECS remained significant (DFS: hazard ratio, 1.61; 95% CI, 1.34 to 1.93; $P < .0001$; OS: 1.67; 95% CI, 1.34 to 2.08; $P < .0001$). However, ECS was not significant when the number of positive nodes was added. The locoregional failure rate ± distant failure (LRF ± distant failure) within 10 years was estimated at 19% (± 2%) without ECS, versus 27% (± 2%) with ECS. The difference was statistically significant in univariate analyses, but not after adjusting for the number of positive nodes. No independent effect of ECS on DFS, OS, or LRF could be confirmed within the subgroup of 382 patients with LN1-3+ treated with mastectomy without radiotherapy.

Conclusion
Our results do not support an independent prognostic value of ECS, nor its use as an indication for irradiation in premenopausal patients with LN1-3+ treated with classical CMF. However, we could not examine whether extensive ECS is of prognostic importance.

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INTRODUCTION

Extracapsular spread (ECS) from axillary lymph node metastases has been associated with poorer outcome in breast cancer[1,2] Despite overwhelming data on the impact of the number of involved lymph nodes on prognosis, there are only a few reports that

address the impact of adjuvant systemic therapy[3-5] and irradiation[6,7] in relation to ECS. The British Columbia[8] and the Danish[9,10] trials both reported an overall survival benefit for patients who received postmastectomy radiotherapy (PMRT), especially in the presence of ECS.[11,12]

PMRT is now well accepted for patients with four or more positive axillary lymph nodes or advanced primary tumors, whereas the indication in T1/T2 tumors with one to three positive nodes is less clear.[13,14] An informal survey within participating centers of the International Breast Cancer Study Group (IBCSG; formerly the Ludwig group) showed that in most centers, PMRT was given to patients with one to three positive lymph nodes only in the presence of additional risk factors (Radiation Oncology Task Force, IBCSG, unpublished data, April 2002). One of these risk factors was considered to be ECS.

To investigate whether ECS of axillary lymph node metastases predicts a decreased rate of disease-free survival (DFS) or an increased rate of locoregional recurrence of breast carcinoma,[15] we retrospectively compared patients with ECS with patients without ECS in a large, multicenter clinical trial of premenopausal patients who received classical CMF (cyclophosphamide, methotrexate, and fluorouracil; IBCSG Trial VI).[16] Based on the literature, we developed a hypothesis that the presence of ECS in patients with one to three positive lymph nodes might identify a subgroup that could benefit from PMRT. Our exploration was limited to the assessment of prognosis and not treatment response to radiation therapy because radiation therapy was given exclusively to patients with breast-conserving surgery and not to those with mastectomy. This series represents the largest study of this issue in a premenopausal population.

PATIENTS AND METHODS

From July 1986 to April 1993, 1,554 pre- and perimenopausal women with node-positive breast cancer were randomly assigned to receive three to nine courses of classical CMF in a 2 × 2 factorial design: (A) CMF for six consecutive courses on months 1 to 6; (B) CMF for 6 consecutive courses on months 1 to 6 plus three single courses of reintroduction CMF given on months 9, 12, and 15; (C) CMF for three consecutive courses on months 1 to 3; (D) CMF for three consecutive courses on months 1 to 3 plus three single courses of reintroduction CMF given on months 6, 9, and 12 (IBCSG Trial VI).[16] At 10 years' median follow-up, there were no significant differences in DFS or overall survival (OS) among or between the four treatment groups in the eligible patient population.

All patients had a histologically proven node-positive unilateral breast cancer, classified as T_{1a}, T_{1b}, T_{2a}, T_{2b}, or T_{3a}, pN1 M_0 (International Union Against Cancer [UICC] 1987), with either estrogen receptor (ER) –positive or ER-negative status known. Surgery of the primary tumor was defined in the protocol as either a total mastectomy with axillary clearance and no radiotherapy or a breast-conserving procedure (quadrantectomy or lumpectomy) with axillary lymph node dissection and subsequent local radiotherapy. For women treated with breast-conserving surgery, radiotherapy was postponed until the end of the initial phase of chemotherapy (three or six courses). Details of eligibility, follow-up, patient characteristics, and outcome at the 5-year median follow-up have been previously reported.[16]

Whether ECS was present or not was not asked on the trial case report forms. This information was obtained retrospectively by reviewing the protocol-required pathology reports for the 1,475 eligible cases (G.G., M.L.N.). Determination of the presence or absence of ECS was on the basis of the reported TNM category (UICC 1987) or, if the TNM classification was not provided or not decisive (eg, pN1biv), by a clear statement in the pathology report about the presence or absence of ECS. In case the lymph node capsule was infiltrated but not penetrated, this was rated as ECS being absent. Any penetration of the capsule was rated as ECS present. It was not possible to determine the extent of ECS, as this information was seldom available.

The ECS status could be determined for 933 patients (63%). These patients form the basis for this report. Participating center was the most significant factor associated with whether or not ECS status was available; and the percent of cases included within center varied from 100% to as low as 9%. To explore whether the variability in ECS reporting had an impact on outcome, we also considered data only from the four participating centers with 98% to 100% of patients having known ECS status, which represented 196 of the 198 patients from these centers. Similar to the entire group, 98 (50%) of these patients had ECS. When the outcome analyses were conducted on this subgroup, the results were similar to the results for the entire group.

DFS was defined as the length of time from the date of random assignment to any relapse (including ipsilateral breast tumor recurrence), appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. The Kaplan-Meier estimator[17] was used to estimate survival distributions. Cox proportional hazards regression models[18] were used to estimate the magnitude of differences in DFS and OS rates adjusting for covariates. Locoregional recurrence was defined as a first relapse on the chest wall or the ipsilateral breast, the ipsilateral axilla, ipsilateral supraclavicular or infraclavicular fossa, or the ipsilateral internal mammary region. Categories of sites of failure of interest (as site of first event) were: isolated locoregional failure (LRF; without simultaneous distant relapse); distant failure (DF) alone; LRF with or without simultaneous DF (LRF ± DF). When analyzing the different sites of failure, we considered the other possible first events as competing events. The primary outcome of interest was LRF ± DF. We estimated the cumulative incidence function at 5 and 10 years for the sites of failure, and fitted regression models for the cumulative incidence functions.[19,20] In those multivariate models including the number of positive lymph nodes, that variable was included after transformation by taking its natural logarithm. Distributions of categorical variables were compared using χ^2 tests, or Kruskal-Wallis tests for ordinal scales. The data were analyzed at a median follow-up of 10 years. All *P* values are two sided.

RESULTS

ECS was present in half of the patients overall (462 of 933; 49.5%). The presence of ECS was fairly well balanced among the major patient characteristics, with the exception

of the number of positive lymph nodes ($P < .0001$; Table 1). The proportion of patients with ECS increased as the number of positive lymph nodes increased (one to three positive nodes: 36% ECS present; > three positive nodes: 74% ECS present). The median number of examined axillary lymph nodes was 17 in patients with ECS, and 16 in patients without ECS.

All Patients

In univariate analyses, the presence of ECS had a significant detrimental impact on both DFS and OS when evaluated for all 933 patients. The 10-year DFS ± SE was 40% ± 2% in ECS-positive patients versus 54% ± 2% in ECS-negative patients; the corresponding 10-year OS ± SE was 55% ± 2% *v* 72% ± 2%, respectively.

In multivariate analyses adjusting for tumor size, vessel invasion, surgery type, and age group, but not for the number of positive nodes, presence of ECS maintained its significant effect (DFS: hazard ratio for ECS, 1.61; 95% CI, 1.34 to 1.93); $P < .0001$; OS: hazard ratio for ECS, 1.67; 95% CI, 1.34 to 2.08; $P < .0001$; Table 2). Dividing all patients into the traditional subgroups of one to three and four or more positive lymph nodes, ECS was only borderline or not significant with respect to DFS or OS. Due to the strong association between ECS and number of positive nodes, we further adjusted the Cox proportional hazards models by adding a covariate for the number of positive nodes. No significant impact of ECS was found on DFS or OS based on these models (Table 2). In the four institutions for which

Table 1. Patient-, Tumor-, and Therapy-Related Parameters in Premenopausal Patients With Node-Positive Breast Cancer With or Without ECS

	Total		ECS		No ECS		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	*P* (ECS *v* no ECS)
Total	933	100	462	100	471	100	
Age, years							.15
< 40	181	19	81	18	100	21	
≥ 40	752	81	381	83	371	79	
Estrogen receptor status							.86
Negative	269	29	132	29	137	29	
Positive	664	71	330	71	334	71	
Nodes, positive							< .0001*
1	303	33	84	18	219	47	
2-3	301	32	135	29	166	35	
4-6	159	17	102	22	57	12	
7-9	84	9	67	15	17	4	
≥ 10	86	9	74	16	12	3	
Nodes examined							.20*
1-4	0	0	0	0	0	0	
5-7	18	2	5	1	13	3	
8-10	113	12	53	12	60	13	
11-15	271	29	146	32	125	27	
16-20	271	29	134	29	137	29	
21-30	204	22	101	22	103	22	
> 30	56	6	23	5	33	7	
Tumor size							.13
≥ 2 cm	405	43	189	41	216	46	
> 2 cm	514	55	266	58	248	53	
Unknown	14	2	7	2	7	2	
Vessel invasion							.08
No	443	48	210	46	233	50	
Yes	302	32	163	35	139	30	
Unknown	188	20	89	19	99	21	
Surgery							.13
Mastectomy	643	69	329	71	314	67	
Breast-conserving	290	31	133	29	157	33	
Chemotherapy							.71
CMF × 6	239	26	125	27	114	24	
CMF × 6 + 3	238	26	113	25	125	27	
CMF × 3	225	24	113	25	112	24	
CMF × 3 + 3	231	25	111	24	120	26	

Abbreviations: ECS, extracapsular spread; CMF, cyclophosphamide, methotrexate, and fluorouracil.
*The *P* values from the Kruskal-Wallis test were very close to those from the χ^2 test.

Table 2. HR Estimates for Extracapsular Spread (present *v* absent) From Multivariate Models

	Patients		DFS			OS		
	No.	%	HR	95% CI	*P*	HR	95% CI	*P*
Without adjustment for No. of positive nodes*								
All patients	933	100	1.61	1.34 to 1.93	< .0001	1.67	1.34 to 2.08	< .0001
N1-3	604	65	1.22	0.94 to 1.57	.14	1.42	1.02 to 1.97	.04
N4+	329	35	1.32	0.98 to 1.79	.07	1.03	0.74 to 1.43	.88
With adjustment for No. of positive nodes†								
All patients	933	100	1.13	0.92 to 1.37	.24	1.02	0.80 to 1.31	.85
Mx	643	69	1.16	0.92 to 1.46	.21	1.00	0.76 to 1.32	.99
BCS	290	31	1.06	0.70 to 1.60	.79	1.12	0.65 to 1.92	.69

Abbreviations: DFS, disease-free survival; OS, overall survival; HR, hazard ratio; Mx, mastectomy; BCS, breast-conserving surgery plus radiotherapy.
*Models adjust for estrogen receptor status, tumor size, vessel invasion, surgery type, and age group.
†Models adjust for number of positive nodes, estrogen receptor status, tumor size, vessel invasion, surgery type, and age group.

almost all of the patients had ECS known (196 of 198), exactly half of the patients were ECS positive. Similar to the whole patient group, ECS was strongly significant for both DFS (hazard ratio, 1.78; $P = .006$) and OS (hazard ratio, 2.19; $P = .004$), but became nonsignificant ($P = .25$ and $P = .24$, respectively) when the number of positive lymph nodes was included in the model.

To determine the effect of ECS on LRF with or without DF, we compared the cumulative incidence (± SE) of LRF (Fig 1A) and LRF ± DF (Fig 1B) in the two ECS groups. At 10 years, 14% (± 2%) of patients without ECS experienced LRF, versus 18% (± 2%) of patients with ECS. The corresponding rates for LRF ± DF are 19% (± 2%) versus 27% (± 2%). Both differences are statistically significant in univariate analyses. However, the differences are no longer statistically significant after adjusting for the number of positive nodes in multivariate analyses of the cumulative incidence functions. The same was true in regard to DF as end point. Table 3 summarizes the estimated cumulative incidence of failures at 5 and 10 years for the various events, and the *P* values for ECS from the univariate and multivariate analyses.

Patients With Mastectomy and One to Three Positive Lymph Nodes

Our goal was to investigate whether ECS defined a group that might benefit from the addition of radiotherapy to mastectomy among patients with one to three positive nodes. We identified 642 patients who received mastectomy and no radiotherapy (one patient who received radiotherapy after mastectomy was excluded from this analysis). Among these patients, 382 had one to three positive lymph nodes. A total of 140 (37%) of these patients had ECS, 242 (63%) did not.

The 10-year DFS (± SE) was 50% (± 4%) in the presence of ECS versus 57% (± 3%) in its absence. The corresponding values for OS were 66% (± 4%) and 76% (± 3%), respectively. The estimated hazard ratios for ECS versus no ECS after adjusting for ER status, tumor size, vessel invasion, and age group were 1.30 (95% CI, 0.95 to 1.78; $P = .10$) for DFS, and 1.37 (95% CI, 0.93 to 2.03; $P = .12$) for OS.

The estimated cumulative incidence functions for LRF and LRF ± DF events in this subgroup of patients are shown in Figure 2. The failure rates for the various events at 5 and 10 years are reported in Table 3, together with *P* values from the univariate analyses and the multivariate analyses after adjusting for the number of positive nodes. At 10 years, 14% (± 2%) of patients without ECS experienced LRF, versus 13% (± 3%) of patients with ECS; the corresponding rates for LRF ± DF are 17% (± 3%) versus 18% (± 3%). We found no statistically significant effect of ECS on the different sites of first recurrence either in univariate or multivariate analyses.

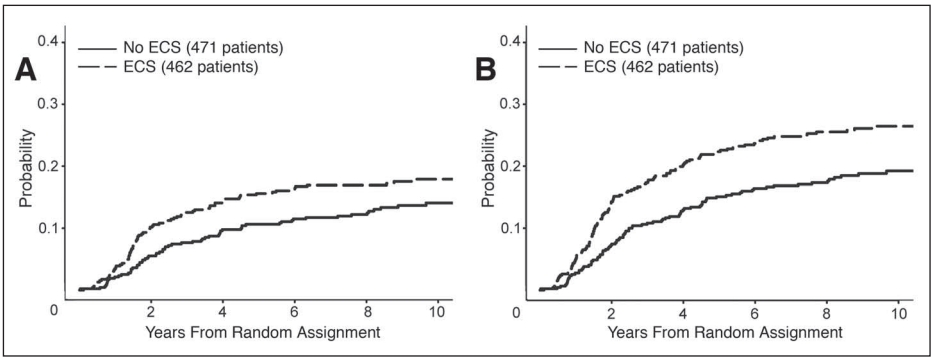

Fig 1. Cumulative incidence functions for 933 premenopausal patients with node-positive breast cancer randomized among four groups that differed according to duration and timing of classical CMF (cyclophosphamide, methotrexate, and fluorouracil) according to presence (dashed line) or absence (solid line) of extracapsular spread (ECS) for (A) local and/or regional failure alone, and (B) local and/or regional failure with or without distant failure.

Table 3. CIF Estimates for Sites of First Failure, With SEs

	ECS				No ECS					
	5-Year CIF (%)		10-Year CIF (%)		5-Year CIF (%)		10-Year CIF (%)			
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE	Univariate P*	Multivariate P†
All patients (n = 933)										
LRF alone	16	2	18	2	11	1	14	2	.034	.45
DF alone	22	2	32	2	18	2	24	2	.004	.51
LRF + DF	7	1	9	1	5	1	5	1	.024	.91
Other	1	1	2	1	2	1	3	1	.366	.55
LRF ± DF	22	2	27	2	15	2	19	2	.001	.55
Patients with Mx, pN+ (1-3) (n = 382)										
LRF alone	12	3	13	3	10	2	14	2	.95	.97
DF alone	18	3	30	4	15	2	23	3	.15	.23
LRF + DF	4	2	5	2	3	1	3	1	.12	.13
Other	0		2	1	2	1	3	1	.49	.51
LRF ± DF	17	3	18	3	14	2	17	3	.44	.47

Abbreviations: CIF, cumulative incidence function; ECS, extracapsular spread; LRF, locoregional failure; DF, distant failure; Mx, mastectomy; pN+, number of positive nodes.
*The P values correspond to the χ^2 distribution with 1 degree of freedom.
†The P values are obtained from fitting regression models to the CIF adjusting for the number of positive nodes (Fine and Gray[20]).

Fitting the regression models for the variables vessel invasion, tumor size, and number of resected lymph nodes in addition to ECS did not alter the results (data not shown).

DISCUSSION

ECS is documented in the range of 24% to 60%[3-5,7,11,15,21-25] in node-positive breast cancer, but it is well known that the number of positive axillary lymph nodes is a strong predictor for ECS: under careful examination, ECS can be found in 41% of patients with one, in 58% of patients with two or three, and in 97% of patients with four or more axillary metastases.[21] Donegan et al[6] reported ECS in 77.5% of patients with four to seven, and in 92% of patients with eight or more positive lymph nodes. Therefore, it was not surprising to find a very strong correlation between ECS and number of positive lymph nodes in our series.

First reports demonstrating decreased survival in patients with ECS[1,2] were confirmed by several studies,[3,4,6,7,12,22,26] all including both pre- and postmenopausal patients, but due to the high association with the number of positive nodes, it is questionable whether ECS is an independent prognostic factor. A few publications have tried to answer this question, but the authors were constrained by the small numbers of patients available for analysis. Pierce et al[22] investigated 45 patients without and 27 patients with ECS, and the probability of death after adjusting for the number of positive nodes was estimated to be three times that of patients without ECS ($P = .06$). Leonard et al[7] showed that both ECS (present in 34 of 81 patients) and the number of positive nodes were independent factors for decreased survival. In a series with 219 patients with ECS in 483 patients with node-positive disease,[4] ECS was significant in multivariate analysis, with a relative risk of 1.6, which is similar to the risk ratio of 1.77 ($P = .1$) in two other studies, with 84 and 50 ECS-positive patients, respectively.[6,26] Recently, Jager et al[25] have identified both ECS (hazard ratio, 1.93; $P = .05$) and pT stage as independent risk factors in 353

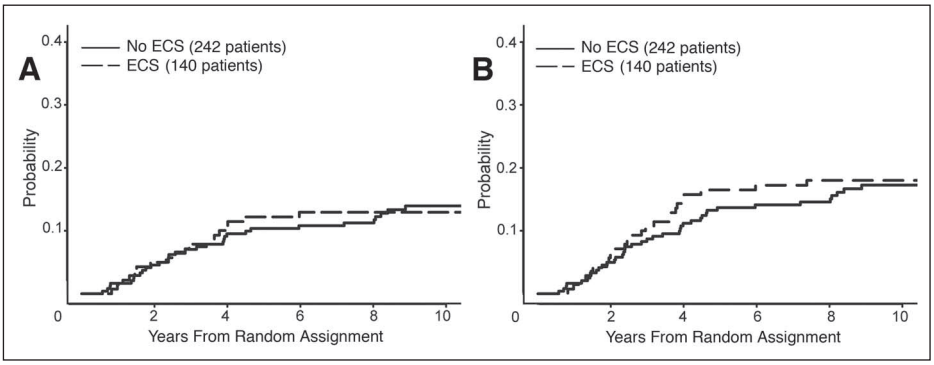

Fig 2. Cumulative incidence functions for 382 patients with one to three positive lymph nodes who received mastectomy without radiotherapy, according to presence (dashed line) or absence (solid line) of extracapsular spread (ECS) for (A) local and/or regional failure alone, and (B) local and/or regional failure alone with or without distant failure.

patients with node-positive disease (49% of them with ECS), but other reports[15,23] (25 and 122 patients with ECS, respectively) could not confirm this finding. The percentages of patients receiving postoperative radiotherapy in the previously mentioned series varied considerably (0%[26]; 10%[25]; 26%[6]; 36%[7]; 100%[15,22,23]). Furthermore, variations in the treatment fields could also potentially account for the difference in the results between series. To our knowledge, the current series reflects by far the largest evaluation of ECS in premenopausal patients prospectively treated in one single randomized trial in which all patients received the same chemotherapeutic agents. We were unable to confirm an independent prognostic significance of ECS on either DFS or OS.

The close relationship between ECS and number of positive nodes should also be considered with respect to locoregional relapse–free survival when we evaluate retrospective data in which LRF rates are doubled in the presence of ECS.[3,25] A recent article from our group demonstrates clearly that patients with four or more positive lymph nodes after mastectomy and an axillary dissection of a required minimum number of examined nodes are at high or very high risk for LRF.[27] This finding is reflected in the treatment recommendations of recent consensus meetings[13,14] and the results of the IBCSG survey (Radiation Oncology Task Force, IBCSG, unpublished data, April 2002), which indicate that further efforts should focus on the identification of risk parameters primarily in the subgroup of patients with one to three positive nodes. Additional risk factors have been widely used in deciding whether to recommend PMRT in this subgroup. ECS was mentioned in the IBCSG survey as one of the leading factors used to offer locoregional irradiation to patients with one to three positive axillary lymph nodes.

The current evaluation did not find an increased locoregional relapse rate in the presence of ECS in premenopausal patients with one to three positive nodes treated with mastectomy and CMF without PMRT. Katz et al[5] have analyzed the effect of ECS in pre- and postmenopausal women with node-positive breast cancer treated with mastectomy and anthracycline-containing systemic therapies without radiotherapy in five randomized trials at The M.D. Anderson Cancer Center between 1975 and 1994. In this single-institution evaluation, the information about the presence or absence of ECS was available in 865 of 890 pathology reports (97% *v* 63% in our series). In that reference, there was no analysis of the value of ECS stratified by menopausal status (menopausal status itself was not significant for locoregional recurrence). ECS with an extent of 2 mm or more was a significant parameter for increased risk of LRF in uni- and multivariate analyses, overall and in the subgroup of T1/T2 tumors with one to three positive nodes. Interestingly, patients with ECS less than 2 mm or ECS not otherwise specified experienced similar LRF rates compared with patients without ECS.[5] In addition, the extent of nodal involvement may be important according to an update of the British Columbia trial.[11] The addition of locoregional radiation therapy to adjuvant intravenous (not classical) CMF resulted in an absolute OS benefit in ECS-positive patients of 20% (51% *v* 31%), with a risk ratio of 0.55, which was highly significant ($P = .004$). This positive effect was especially seen in the (all premenopausal) patients with one to three axillary metastases and ECS.[11] However, only extensive nodal involvement predicted a positive effect of PMRT in all patients (risk ratio, 0.36; $P = .002$) as well as in patients with one to three nodes (risk ratio, 0.30; $P = .01$), and ECS without extensive nodal involvement did not.[28]

In our study, it was not possible to quantify the amount of nodal or extranodal tumor extension, as a central pathology review was not performed. A limitation of the current report is that the extent of ECS—microscopic versus macroscopic—was not reliably available in the pathology reports. It is possible that differences could be detected if analyses were restricted to macroscopic ECS.

In conclusion, this large retrospective analysis does not support an independent prognostic value of the presence of ECS in general in premenopausal patients with node-positive disease treated with classical CMF. In the subgroup of patients with one to three involved axillary lymph nodes, there was no difference in LRF rates with or without ECS. This is in contrast to recent reports in the literature and also contrary to the current opinion as recorded in a survey of radiation oncologists, many of whom would favor postmastectomy radiation therapy in the presence of ECS.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Appendix. International Breast Cancer Study Group (IBCSG): Participants and Authors Trials VI

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(continued on following page)

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REFERENCES

1. Fisher ER, Palekar AS, Gregorio RM, et al: Pathologic findings from the National Surgical Adjuvant Breast Project (protocol No. 4), III: The significance of extranodal extension of axillary metastases. Am J Clin Pathol 65:439-444, 1976

2. Mambo NC, Gallager S: Carcinoma of the breast: The prognostic significance of extranodal extension of axillary disease. Cancer 39:2280-2285, 1977

3. Fisher BJ, Perera FE, Cooke AL, et al: Extracapsular axillary node extension in patients receiving adjuvant systemic therapy: An indication for radiotherapy? Int J Radiat Oncol Biol Phys 38:551-559, 1997

4. Kahlert S, Boettcher B, Lebeau A, et al: Prognostic impact of extended extracapsular component in involved lymph nodes in primary breast cancer. Eur J Cancer 35:S89, 1999 (suppl 4, abstr 292)

5. Katz A, Strom EA, Buchholz TA, et al: Locoregional recurrence patterns after mastectomy and doxorubicin-based chemotherapy: Implications for postoperative irradiation. J Clin Oncol 18:2817-2827, 2000

6. Donegan WL, Stine SB, Samter TG: Implications of extracapsular nodal metastases for treatment and prognosis of breast cancer. Cancer 72:778-782, 1993

7. Leonard C, Corkill M, Tomkin J, et al: Are axillary recurrence and overall survival affected by axillary extranodal tumor extension in breast cancer? Implications for radiation therapy. J Clin Oncol 13:47-53, 1995

8. Ragaz J, Jackson SM, Le N, et al: Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 337:956-962, 1997

9. Overgaard M, 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 337:949-955, 1997

10. Overgaard M, Jensen MB, Overgaard J, et al: Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 353: 1641-1648, 1999

11. Ragaz J, Jackson S, Le N, et al: Postmastectomy radiation outcome in node positive breast cancer patients among N1-3 versus N4+ subset: Impact of extracapsular spread—Update of the British Columbia Randomized Trial. Proc Am Soc Clin Oncol 18:73a, 1999 (abstr 274)

12. Overgaard M: Update of the Danish trials of postoperative radiotherapy in high-risk breast cancer patients given adjuvant systemic therapy, in Kogelnik HD, Lukas P, Sedlmayer F (eds): Progress in Radio-Oncology VII. Bologna, Italy, Monduzzi Editore S.p.A, 2002, pp 483-492

13. Recht A, Edge SB, Solin LJ, et al: Postmastectomy radiotherapy: Clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 19:1539-1569, 2001

14. Goldhirsch A, Glick J, Gelber R, et al: Meeting highlights: International consensus panel on the treatment of primary breast cancer. J Clin Oncol 19:3817-3827, 2001

15. Hetelekidis S, Schnitt SJ, Silver B, et al: The significance of extracapsular extension of axillary lymph node metastases in early-stage breast cancer. Int J Radiat Oncol Biol Phys 46:31-34, 2000

16. The International Breast Cancer Study Group: Duration and reintroduction of adjuvant chemotherapy for node-positive premenopausal breast cancer patients. J Clin Oncol 14:1885-1894, 1996

17. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

18. Cox DR: Regression models and life-tables. J R Stat Soc B, 34:187-220, 1972

19. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988

20. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496-509, 1999

21. Veronesi U, Rilke F, Luini A, et al: Distribution of axillary node metastases by level of invasion: An analysis of 539 cases. Cancer 59: 682-687, 1987

22. Pierce LJ, Oberman HA, Strawderman MH, et al: Microscopic extracapsular extension in the axilla: Is this an indication for axillary radiotherapy? Int J Radiat Oncol Biol Phys 33: 253-259, 1995

23. Vicini FA, Horwitz EM, Lacerna MD, et al: The role of regional nodal irradiation in the management of patients with early-stage breast

cancer treated with breast-conserving therapy. Int J Radiat Oncol Biol Phys 39:1069-1076, 1997

24. Fodor J, Toth J, Major T, et al: Incidence and time of occurrence of regional recurrence in stage I-II breast cancer: Value of adjuvant irradiation. Int J Radiat Oncol Biol Phys 44:281-287, 1999

25. Jager JJ, Volovics L, Schouten LJ, et al: Loco-regional recurrences after mastectomy in breast cancer: Prognostic factors and implications for postoperative irradiation. Radiother Oncol 50:267-275, 1999

26. Mignano JE, Zahurak ML, Chakravarthy A, et al: Significance of axillary lymph node extranodal soft tissue extension and indications for postmastectomy irradiation. Cancer 86:1258-1262, 1999

27. Wallgren A, Bonetti M, Gelber RD, et al: Risk factors for locoregional recurrence among breast cancer patients: Results from International Breast Cancer Study Group trials I through VII. J Clin Oncol 21:1205-1213, 2003

28. Ragaz J, Phillips N, Spinelli J, et al: Extensive nodal involvement or extracapsular spread in predicting the survival impact of loco-regional radiation for stage II breast cancer patients: Long-term observations from the British Columbia randomized trial. Proc Am Soc Clin Oncol 20:12b, 2001 (abstr 1794)