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The effects of ECE on the benefits of PMRT for breast cancer patients with positive axillary nodes

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Background: The purpose of the present study was to retrospectively evaluate the effects of extracapsular extension (ECE) on the benefits of post-mastectomy radiation therapy (PMRT) for groups of patients with varying numbers of positive axillary nodes (1–3, 4–9 and ≥10 positive axillary nodes). Methods: A total of 1220 axillary node-positive patients who had received mastectomy were involved in this study. Patients were grouped as 'Radio + /ECE + ', 'Radio–/ECE + ', 'Radio + /ECE–' or 'Radio–/ECE–' according to status of ECE and whether receiving PMRT or not, and were evaluated in terms of local region relapse (LRR) rate. The 5-year and 10-year Kaplan-Meier disease-free survival and overall survival (OS) rates were analyzed. Results: ECE-positive differed from ECE-negative groups with statistical significance for all comparisons in favor of the ECE-negative group: 5-year locoregional failure-free survival (LRFFS) (82.69% vs 91.83%, $P < 0.001$), 10-year LRFFS (75.39% vs 90.02%, $P < 0.001$); 5-year OS (52.12% vs 74.46%, $P < 0.001$), 10-year OS (35.17% vs 67.63%, $P < 0.001$). There were no significant effects of ECE on the benefits of PMRT for patients with 1–3 ($P = 0.5720$), ≥10($P = 0.0614$) positive axillary nodes. However, for the group of patients with 4–9 positive axillary nodes, ECE status had a significant effect on the benefits of PMRT with respect to 5-year and 10-year LRFFS ($P < 0.05$). Conclusion: In our study, regardless of the ECE status, PMRT didn't significantly improve the LRFFS for patients with 1–3 or ≥10 positive axillary nodes. However, for patients with 4–9 positive axillary nodes, ECE could be an important criterion to consider when deciding whether to receive PMRT.

Keywords: breast neoplasms; ECE; PMRT; prognosis

INTRODUCTION

Extracapsular extension (ECE) of tumor cells is a common finding on histopathological review of axillary nodes in patients with node-positive breast cancer [1]. Fisher *et al*. showed a correlation between ECE of axillary metastases and short-term treatment failure [2]. ECE in axillary node metastases is often associated with locoregional failure (LRF) in breast cancer [3]. The utility of post-mastectomy radiation therapy (PMRT) has been established from evidence including the 1997 Danish clinical trial results and meta-analysis by the Early Breast Cancer Trialists' Collaborative Group in 2005. Multiple trials have shown a significant benefit in locoregional control, disease-free survival (DFS), and overall survival (OS) from the use of PMRT in patients affected by breast cancer [4–6]. However, there is still controversy about the necessity for regional irradiation in general. A few publications have evaluated the prognostic value of ECE, but fewer reports have been made on whether the ECE status can indicate the necessity of PMRT for patients with varying numbers of positive axillary nodes. Therefore, we analyzed the clinical data for breast cancer patients with positive axillary nodes retrospectively, to determine whether ECE could be an indicative factor for PMRT.

MATERIALS AND METHODS

Patient population

We evaluated a total of 1220 breast cancer patients with positive axillary node status who were treated or had their follow-up at Tianjin Cancer Hospital from January

1994 to December 2001. The median age of the patient population was 46 years (range, 18–78 years) (Table 1). Pretreatment workup included diagnostic examinations to exclude metastatic disease. They all underwent modified radical mastectomy and received adjuvant chemotherapy. The schedules applied varied substantially during the observation period. TEC-based (docetaxel, epirubicin, cyclophosphamide) or docetaxel-containing regimens were given to patients receiving chemotherapy. Patients with positive hormone receptors received adjuvant endocrine therapy for 5 years. Axillary dissection was performed in all patients, and the median number of axillary nodes removed was 23.8. There were 473 patients (38.74%) identified as having 1–3 positive axillary nodes, 311 patients (25.47%) having 4–9 positive axillary nodes, and the remaining 436 patients (35.71%) had ≥10 positive axillary nodes. The patients were categorized as having/not having ECE, and 488 (39.97%) were scored as having ECE when on microscopic examination tumor cells were clearly seen to extend beyond the nodal capsule into the tissue. For patients who developed contralateral breast cancer, only the first side treated was considered in the analysis of failure.

Radiation therapy

Of all the patients, 1050 (86.07%) were treated postoperatively with external-beam irradiation (4- or 6-MV photons/60Co) using tangential fields. The dose to the entire chest wall was usually 50 Gy (range, 46–54 Gy) in daily fractions of 1.8–2 Gy, given five times weekly. The mid-axilla received a dose of 50 Gy through an anterior supraclavicular and posterior axillary fields. An additional external boost with electrons (2 Gy/10–14 Gy) was administered in 226 patients with locally advanced disease. The group of patients with ECE who received PMRT was referred to as 'Radio + /ECE + ' , and those who didn't were grouped as 'Radio–/ECE + '. The patients without ECE who received PMRT were grouped as 'Radio + /ECE–', and those who didn't were grouped as 'Radio–/ECE–'.

Follow-up

The median time of follow-up was 156 months (range, 24–176). None of the patients was lost to follow-up. All intervals were calculated from the date of completion of irradiation, and the endpoint was defined as our last follow-up or death. Patients were routinely evaluated for tumor control in 4-month intervals in the first 2 years and in 6-month intervals for the next 3 years. Subsequently, these patients were observed on a yearly basis. Procedures included a careful clinical examination, blood sampling, routine chest radiograph, mammography and ultrasound. Further evaluations were carried out only if clinical findings suggested a progression of the disease. Survival was calculated from the time of surgical resection to the last follow-up. The endpoints of interest included OS and LRFFS. During the period of follow-up, 565 patients died of breast cancer.

Recurrences

LRF was defined as ipsilateral breast and chest wall recurrence and isolated axillary, supraclavicular or internal mammary axillary node recurrence. Simultaneous LRF/DM was scored as DM (distant metastasis). Time-to-recurrence was calculated from the time of surgical resection to the last follow-up.

Statistical analysis

Pearson's chi-square test was used to compare proportions of categorical covariates between groups of patients with and without ECE. Survival analyses were estimated with

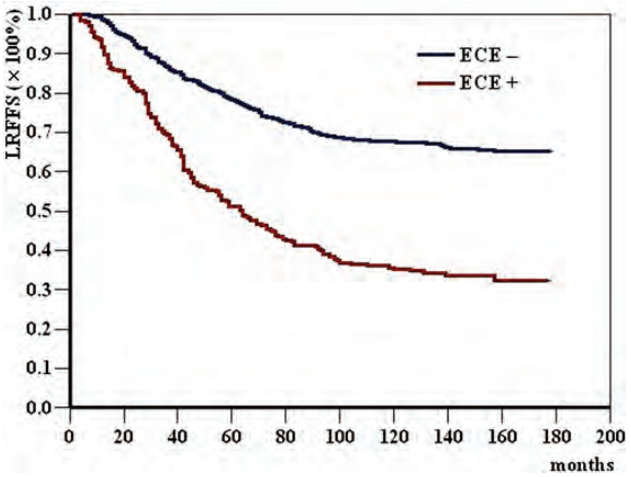

Fig. 1. Kaplan-Meier curve of LRFF survival. (10-year locoregional failure-free survival in ECE-positive group 75.39%, and ECE-negative group 90.02%, $P < 0.001$.)

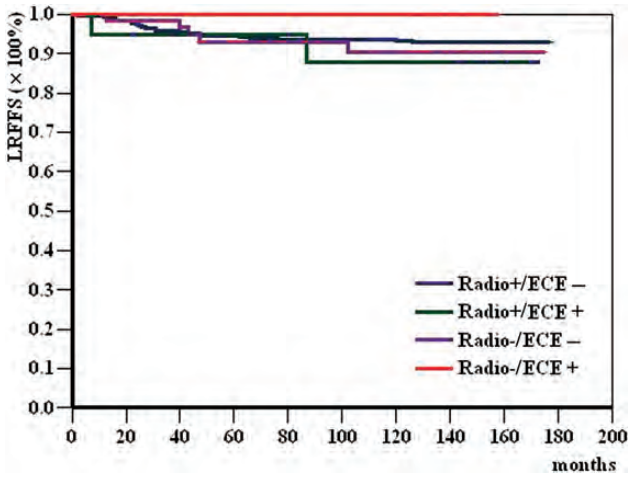

Fig. 2. Kaplan-Meier curve of local failure-free probability. (10-year locoregional failure-free survival in patients with 1–3 positive axillary nodes, $P = 0.5720$.)

the Kaplan-Meier method. Univariate and multivariate Hazard Ratios (HR) and their 95% confidence intervals (CIs) were obtained using Cox's proportional hazard model. Differences were considered statistically significant when the P value was ≤0.05. Statistical analysis was done using an SPSS (version 17.0; SPSS Inc., Chicago, IL).

RESULTS

During our follow-up 565 patients died, 316 (65.02%) of these in the ECE-positive group and 249 (33.51%) in the ECE-negative group. There was a statistical difference in OS between the two groups of patients ($P < 0.001$) (Fig. 1), which indicated that the status of ECE substantially affects the OS of patients. A total of 154 LRF events occurred, most of the relapses being observed during the first 5 years of follow-up. The 10-year cumulative incidence rate was 18.11% for the patients with ECE and 8.88% for ECE-negative patients. ECE tended to be associated with a higher cumulative incidence ($P < 0.001$) (Table 2).

Firstly, we analyzed the clinical features of the breast cancer patients with 1–3 positive axillary nodes (Table 3). During the follow-up, for this group of patients, 73 (93.59%) of the 78 patients with ECE received PMRT. Of the remaining 395 patients without ECE, 361 (91.39%) patients received PMRT. However, there was no significant difference in LRFFS between these four groups ($P = 0.5720$), suggesting that ECE had no dramatic effects on LRFFS for patients with 1–3 positive axillary nodes (Table 6).

Secondly, for patients with 4–9 positive axillary nodes (Table 4), PMRT was performed on 88 of the 114 patients with ECE, of whom 10 (11.36%) suffered LRF. Another 10 (38.46%) of the remaining 26 patients who didn't receive PMRT suffered LRF. For the 197 patients without ECE, 172 patients received PMRT and of these 18 (10.46%) suffered LRF. LRF occurred in 3 (12.00%) of the remaining 25 patients who did not receive PMRT.

The median LRFFS time for the 'Radio–/ECE + ' group was 47.27 months shorter than for the 'Radio–/ECE–' group ($P = 0.0205$), indicating that for patients not receiving PMRT, ECE was a risk factor for LRFFS. Although there was no difference in the median time for LRFFS between the 'Radio + / ECE + ' and 'Radio + /ECE–' groups ($P = 0.3692$), our results indicated that the survival differential between the two groups disappeared after radiotherapy. Thus, PMRT can balance the recurrence risk associated with ECE. No difference was observed in the median time for LRFFS between the 'Radio + /ECE + ' and 'Radio–/ECE–' groups (153.16 vs 157.77, $P = 0.7226$). More importantly, the LRFFS of the 'Radio + /ECE + ' group was significantly different from that of the 'Radio–/ECE + ' group ($P = 0.0009$). These data indicated that if the ECE-positive breast cancer patients didn't receive radiotherapy after surgical treatment, the LRFFS time was shorter. Moreover, in our study the median time for LRFFS in the 'Radio–/ECE + ' group was 49.33 months shorter than that in the 'Radio + /ECE–' group ($P < 0.001$), suggesting that ECE without PMRT could have synergetic effects on increasing the LRF (Table 7).

Finally, in the group of patients with ≥10 positive axillary nodes (Table 5), 300 of the 366 patients with ECE underwent PMRT, and LRF was seen in 56 (18.67%) of these patients. Of the 66 patients with ECE, 8 (12.12%) patients suffered LRF. For the remaining 70 patients without ECE, 56 underwent PMRT and 14 (25.00%) LRF events occurred. Of the 14 patients without ECE who didn't received PMRT, 2 (14.28%) suffered LRF. No significant difference was observed in the LRFFS between these four groups

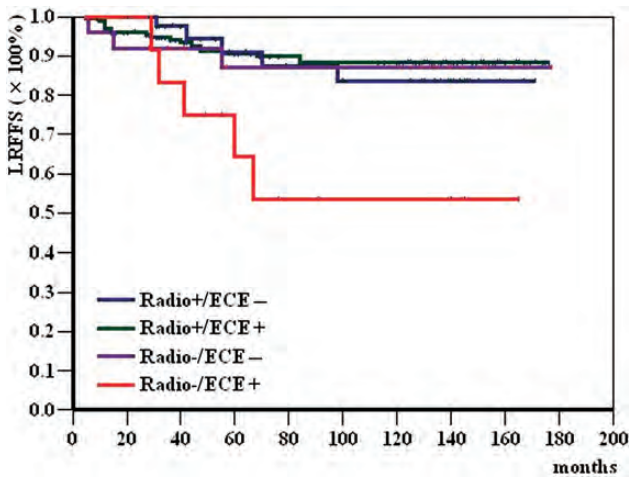

Fig. 3. Kaplan-Meier curve of local failure-free probability. (10-year locoregional failure-free survival in patients with 4–9 positive axillary nodes, comparing 'Radio–/ECE + ', 'Radio + / ECE–', 'Radio–/ECE–', 'Radio + /ECE + ', $P < 0.05$.)

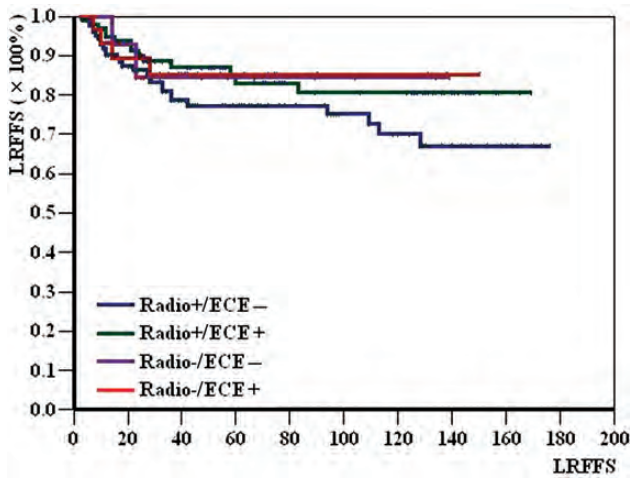

Fig. 4. Kaplan-Meier curve of local failure-free probability. (10-year locoregional failure-free survival in patients with ≥10 positive axillary nodes, $P = 0.0614$.)

(P = 0.0614) (Table 8), which indicated that, regardless of ECE status, PMRT did not improve the LRFFS for patients with ≥10 positive axillary nodes.

Table 1. Clinical characteristics of patients undergoing modified radical mastectomy

	Total number	ECE +	ECE–	*P*
Total	1220	488	732	
Age				
≤50	784	288	496	0.001
>50	436	200	236	
Postmenopausal				
Yes	408	190	218	<0.01
No	812	298	514	
Tumor size				
≤2	154	32	122	<0.001
2–5	713	268	445	
>5	333	188	165	
Histological grade				
I	155	45	110	<0.001
II	798	295	503	
III	267	148	119	
Positive nodes				
1–3	473	78	395	<0.001
4–9	311	114	197	
≥10	436	366	70	
Hormone receptor				
Positive	998	410	588	0.112
Negative	222	48	144	
PMRT				
Yes	1050	461	589	<0.001
No	170	27	143	
Endocrine therapy				
Yes	995	408	587	0.180
No	225	80	145	

DISCUSSION

As Overgaard *et al*. mentioned in their article [7], it is obvious that the number of positive axillary nodes alone is an extremely crude indicator for PMRT. It may be better to consider additional clinicopathologic parameters. In this article, we selected the ECE status as the parameter to investigate the potential benefits of PMRT for patients with different numbers of positive axillary nodes. Despite awareness of extracapsular invasion being a negative prognostic factor, there are, surprisingly, few prospective randomized studies evaluating PMRT in the presence or absence of this parameter. Some publications [8–11] mention patients with extracapsular invasion being treated with local or locoregional RT, but only two retrospective studies [8, 10] compared the results for irradiated vs unirradiated patients with ECE involving positive axillary nodes. The selection criteria for additional irradiation were not specified in either study. Therefore, we presume that the aggressiveness of the tumor as selection bias for PMRT to be comparable to the treatment decisions in our study. Similarly to these previous results, we found a significant difference in the survival curves between these two groups, indicating that ECE could be an important prognostic indicator for patients with positive axillary nodes.

At the St Gallen Breast Cancer Meeting in 2009, the majority of the specialists did not recommend routine adjuvant PMRT, and PMRT was only considered when patients were young or had a poor prognosis. In our study, we evaluate ECE as the risk factor. Our results show that for patients with 1–3 positive nodes, ECE had no significant effects on the benefits of PMRT ($P = 0.5720$), which indicates that independent of ECE status, these patients can get little benefit from PMRT. Thus our studies have demonstrated that for patients with 1–3 positive nodes, PMRT is not recommended (avoiding ipsilateral lymphoedema of the upper extremity [12–14]).

Patients with 4–9 positive nodes are at high risk of locoregional and/or distant relapse and death from cancer [3, 15]. Katz *et al*. found 10-year isolated locoregional relapse rates of 4% in node-negative patients and 10, 21 and 22% in N+ 1–3, N+ 4–9 and N+ ≥10 patients, respectively. The risk of locoregional relapse may be associated not only with T stage and hormone receptor status but also

Table 2. The effects of ECE on the OS and LRFFS of patients with positive axillary nodes

	OS					LRFFS				
	5 yrs %	10 yrs %	Median	95% CI	*P*	5 yrs %	10 yrs %	Median	95% CI	*P*
ECE +	52.12	35.17	88.94	82.91–94.97	<0.001	82.69	75.39	142.64	136.45–148.83	<0.001
ECE–	74.46	67.63	134.98	130.4–139.35		91.83	90.02	163.12	159.90–166.33	

Table 3. Statistical analysis in patients with 1–3 positive lymph nodes

Variable	HR	95% CI	*P*
Univariate analysis			
Tumor size	1.003	0.546–1.843	0.019
ECE	1.345	0.467–3.878	0.001
PMRT	1.076	0.403–2.870	0.028
Multivariate analysis			
Tumor size	1.094	0.592–2.024	0.774
ECE	1.332	0.455–3.901	0.006
PMRT	1.091	0.398–2.996	0.865

Table 4. Statistical analysis in patients with 4–9 positive lymph nodes

Variable	HR	95% CI	*P*
Univariate analysis			
Tumor size	1.109	0.631–1.951	0.017
ECE	2.036	1.117–3.708	0.002
PMRT	2.475	1.290–4.748	0.006
Multivariate analysis			
Tumor size	1.030	0.565–1.878	0.923
ECE	1.958	1.308–3.693	0.038
PMRT	2.307	1.185–4.492	0.014

Table 5. Statistical analysis in patients with ≥10 positive lymph nodes

Variable	HR	95% CI	*P*
Univariate analysis			
Tumor size	1.289	0.871–1.906	0.027
ECE	1.586	0.918–2.740	0.010
PMRT	0.717	0.370–1.390	0.031
Multivariate analysis			
Tumor size	1.246	0.845–1.839	0.267
ECE	1.666	0.948–2.931	0.076
PMRT	0.739	0.378–1.444	0.376

Table 6. The effects of PMRT and ECE on the LRFFS of patients with 1–3 positive axillary nodes

	5 yrs %	10 yrs %	Median	95% CI	*P*
Radio–/ ECE +	100	100	–	–	
Radio–/ ECE–	94.74	87.97	157.56	143.91–171.21	0.5720
Radio + / ECE +	93.00	90.42	163.43	153.68–173.17	
Radio + / ECE–	94.63	93.36	167.49	163.75–171.23	

Table 7. The effects of PMRT and ECE on the LRFFS of patients with 4–9 positive axillary nodes

	5 yrs %	10 yrs %	Median	95% CI	*P*
Radio–/ ECE +	75.00	53.57	110.50	85.23–135.77	
Radio–/ ECE–	87.16	87.16	157.77	137.35–178.19	<0.05
Radio + / ECE +	91.04	83.60	153.16	142.88–163.44	
Radio + / ECE–	90.57	88.28	159.83	152.74–166.91	

Table 8. The effects of PMRT and ECE on the LRFFS of patients with ≥10 positive axillary nodes

	5 yrs %	10 yrs %	Median	95% CI	*P*
Radio–/ ECE +	85.17	85.17	130.06	117.24–142.98	
Radio–/ ECE–	84.42	84.42	120.28	96.34–144.42	0.0614
Radio + / ECE +	77.33	70.08	134.10	124.65–143.54	
Radio + / ECE–	83.01	83.01	149.92	130.38–155.47	

with ECE status [16]. Furthermore, the number of positive axillary nodes is a predictor of supraclavicular fossa relapse [17]. Overall, in patients with > 4 positive nodes who undergo mastectomy, the supraclavicular relapse risk is 15–30% [3, 16–19]. Therefore, in this subgroup, PMRT to the chest wall and supraclavicular fossa is recommended. After PMRT the locoregional relapse rates decline by about two-thirds to 10–15% [18, 20]. Nevertheless, the effect of ECE on benefits of PMRT in this high-risk group of patients is unknown, because there have been few retrospective studies reporting regional relapse rates in the N+ ≥4 subgroup with ECE, and the results have been

discordant. Furthermore, the treatment effect on survival and the best extension of irradiation fields have long remained controversial. In our study, PMRT did not significant improve the LRFFS ($P = 0.8276$) in the subgroup of patients without ECE. However, for patients with ECE, the LRFFS was improved significantly by PMRT, compared to those not receiving PMRT ($P = 0.0009$), suggesting that PMRT was able to counterbalance the risk associated with ECE. Thus, PMRT is recommended for these patients to avoid local recurrence. For patients with ≥10 positive nodes, our results show that regardless of the ECE status, there was no significant benefit from PMRT. Since this group of patients were in the high-risk category and many patients died before local occurrence, the dominant prognostic indicator of the involvement of ≥10 axillary nodes may hide the prognostic indicator effect of ECE, causing our statistics to be misleading for this group.

CONCLUSION

In summary, our results confirm the importance of ECE in predicting OS/LRF and indicating when we should recommend further aggressive treatment for ECE-positive patients. However, in our study only ECE-positive patients with 4–9 positive axillary nodes received significant benefits from PMRT. As a result, we conclude that for patients with other levels of positive nodes, PMRT is not always to be recommended, thus avoiding unwanted side effects. The decision for additional regional radiotherapy should not be based solely on the presence of ECS. In the future, we should take additional pathological factors (such as hormone receptor and HER2) into consideration, in order to identify features that could help to select patients most likely to benefit from the addition of radiotherapy.

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