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RESEARCH ARTICLE/ARAŞTIRMA YAZISI

ISOLATED LOCOREGIONAL RECURRENCE IN PATIENTS WITH POSTMASTECTOMY ADJUVANT THERAPY FOR BREAST CANCER

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ABSTRACT

Objectives: To determine the predictive risk factors for isolated locoregional recurrence (LRR) in breast cancer patients with postmastectomy adjuvant therapy.

Patients and Methods: The impacts of patients' characteristics, tumor stage, and surgery on LRR were evaluated in patients with breast cancer having postmastectomy adjuvant therapy, according to their risk factors using univariate analysis. Factors influencing LRR-free survival were assessed by Cox regression analysis.

Results: Of 368 patients, 28 (7.6%) had isolated LRR. Patients' characteristics such as age, menopause, surgery, tumor size, stage and differentiation, and hormone receptor status were not attributable to LRR. Upper outer quadrant localization was significantly associated with lower LRR occurrence (p=0.048). Among 245 patients whose surgical margin could be assessed, LRR was detected in 6 (20%) of 30 patients with a close surgical margin, while of 215 patients with normal surgical margin, 13 (6%) developed LRR (p=0.007). Kaplan-Meier analysis revealed that larger tumor (p=0.04), presence of LRR (p=0.00001), closer surgical margin (p=0.0085), stage (p=0.0001), and presence of lymph node metastases (p=0.00001) have significantly negative impacts on patients' survival. Tumor size, lymph node status, and closer surgical margin were found to be the independent factors influencing LRR-free overall survival.

Conclusion: Postmastectomy LRR seemed to have a close relationship with the surgical margin status despite standard adjuvant treatments.

Keywords: breast cancer, locoregional recurrence, surgical margin, adjuvant therapy, tumor localization.

MASTEKTOMİDEN SONRA ADJUVAN TEDAVİ ALAN HASTALARDA İZOLE LOKOREJYONEL NÜKS

ÖZET

Giriş: Mastektomili hastalarda, adjuvan tedaviye rağmen lokorejyonel nüks (LRN) gelişiminde etkili prediktif risk faktörlerini belirlemek

Yöntem ve Gereçler: Meme kanseri nedeniyle mastektomi uygulanan ve adjuvan tedavi alan hastalarda, yaş, menopoz durumu, tümörün çapı, evresi, cerrahi şekli, pozitif lenf nodu sayısı, cerrahi sınır uzaklığı, histolojik grade gibi faktörlerin izole LRN'e etkileri tek değişkenli testle, lokal nükssüz sağkalıma etkili faktörler ise Cox regresyon analizi ile incelendi.

Bulgular:368 hastanın 28'inde (%7,6) izole LRN gelişti. Hastaların yaş ve menopoz gibi özellikleri, uygulanan mastektominin cinsi, hastalığın evresi, tümör çapı, aksiller lenf nodu durumu ile tümörün diferansiyasyonu, hormon reseptör durumu LRN üzerine etkili değildi. Tümörün üst dış kadranda yerleşiminde LRN daha az görülmekteydi (p=0,048). Cerrahi sınır uzaklığı kaydedilmiş 245 hastanın 30'unda cerrahi sınır yakındı ve bunların altısında (%20) LRN saptanırken, cerrahi sınırı normal olan 215 hastanın 13'ünde (%6) LRN gelişti (p=0,007). Kaplan-Meier analizinde, sağkalımı olumsuz etkileyen faktörler tümör çapının büyük olması (p=0,04), LRN gelişimi (p=0,00001), cerrahi sınır yakınlığı (p=0,0085), evre (p=0,0001) lenf nodu metastazı varlığıydı (p=0,00001). Tümör boyutu, lenf nodu durumu ile cerrahi sınır yakınlığı, lokal nükssüz sağkalımı etkileyen bağımsız faktörlerdendi.

Tartışma: Cerrahi sınır yakınlığı, mastektomi sonrası LRN gelişiminde, adjuvan tedavilerden etkilenmeyen tek faktördür.

Anahtar sözcükler: meme kanseri, lokorejyonel nüks, cerrahi sınır, adjuvan tedavi, tümör yerleşimi

Introduction

Breast cancer is the most common female cancer in our country as well as in other countries (1,2). Surgery is the essential therapy in stage I, II, and IIIA patients whereas later stages require a multidisciplinary approach. Recent randomized prospective studies on surgical treatment modalities showed that survival analyses of mastectomy vs. breast conserving surgery (BCS) plus radiotherapy were not statistically significant (3-10). Patients' age and choice, tumor localization, the tumor/ breast size ratio, pathological features such as the degree of nuclear atypia, and proliferation activity are major determinants for type of surgery (11-14). Hence mastectomy still continues to be the common surgery in surgical treatment of breast cancer.

External beam radiotherapy is considered for patients at high risk for local recurrence, as an adjunct to mastectomy. Four or more pos-

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Table 1. Adjuvant therapies according to the patients' stage. (HT: Hormonotherapy, ChT: Chemotherapy. RT: Radiotherapy)

	HT	ChT	RT	HT+ChT	HT+RT	ChT+RT	ChT+RT+HT
Stage I	8	2	5	0	2	1	5
Stage IIA	3	5	29	4	19	31	32
Stage IIB	0	0	11	5	17	55	78
Stage IIIA	0	1	2	9	2	27	15

itive axillary lymph nodes, extracapsular invasion, greater primary tumor, and close or positive surgical margins are associated with the high risk of locoregional recurrence (LRR)(15-18). A meta-analysis of Whelan et al. revealed the advantage of postoperative radiotherapy on survival of these patients (19). Similarly, the National Surgical Breast and Bowel Project (NSABP) – 13 study showed the efficacy of adjuvant chemotherapy on patients' survival (20).

Although proven efficacy of postmastectomy adjuvant therapies, local recurrences are still seen. Almost detected just before or with the occurrence of distant metastases, LRR is appraised to be a precursor of metastatic disease. There are many studies for the effect of certain adjuvant or neoadjuvant therapies on LRR after mastectomy (21-24). This study aimed to identify the risk factors affecting the local or regional recurrence of the breast cancer in postmastectomy patients with isolated LRR having an appropriate and evidence-based adjuvant therapy.

Patients and Methods

In a 12 year period, 458 patients underwent surgical therapy for breast cancer in Gülhane Military Medical Academy, Department of General Surgery. All records were reviewed retrospectively. Patients suffering from early or locally advanced breast cancer with undetectable supraclavicular lymph nodes were included in the study provided that they had only a unilateral radical or modified radical mastectomy with removal of all breast tissue as surgical approach. Other inclusion criteria were the presence of at least 10 axillary lymph nodes in surgical specimen, no evidence of any systemic metastasis in physical and biochemical examination, chest radiogram, abdominal ultrasonography, whole body bone scintigraphy, and fitness for regular control.

Thus, 36 patients with initially metastatic disease, and 21 with insufficient number of lymph nodes were excluded. Subsequently, 17 additional patients having non-standardized chemotherapy or radiotherapy after an interval longer than 6 months following surgery for any reason and 16 other patients with poor compliance to follow-up schedule were out of the study. The remaining 368 were recruited for the study. Of these, 311 had invasive ductal carcinoma (84.5%), while invasive lobular carcinoma in 25 (6.8%), invasive ductal and lobular carcinoma in six (1.6%), invasive carcinoma arising from ductal carcinoma in situ (noninvasive ductal carcinoma?) in six (1.6%) were detected. Other 8 patients had medullary carcinoma while apocrine carcinoma in one, combined invasive ductal and mucinous cancer in one, comedo cancer in three, combined lobular and mucinous cancer in one, lobular and tubular cancer in one, mucinous cancer in three, and tubular cancer in two patients was detected. Histopathology revealed stage I breast cancer in 23, stage IIA breast cancer in 123, stage IIB breast cancer in 166, and stage IIIA breast cancer in 56 patients.

Solely hormonal therapy was given in 8 with stage I and 3 with stage IIA patients were given postoperatively. Other than these, all patients received adjuvant chemotherapy with the combination of cyclophosphamide, 5-fluorouracil, and either epirubicin (CAF) or metotrexate (CMF) if tumor diameter was greater than 2 cm and/or lymph node was involved. Medium or high-risk women with positive hormone receptor (according to their age, tumor size or grade) were managed with tamoxifen. Those with four or more lymph node metastases or tumor size greater than 5 cm, surgical margin closer than 1 cm or positive surgical margin were submitted to adjuvant radiotherapy to chest wall and axilla as well (Table 1).

Patients' characteristics such as age and menopause status were recorded. Then, tumor features such as size, closest surgical margin, histopathological grade (25) if available; numbers of overall and metastatic lymph nodes were assessed. If a re-excision was done due to close surgical margin, the latter was taken into account.

Follow-up was performed after staging procedures according to these features plus physical examination and standard therapies. Isolated locoregional recurrence (LRR) was defined as recurrences detected only at surgical wound, and surrounding breast skin, ipsilateral axillary, supraclavicular or infraclavicular fossa, ipsilateral internal mammarian lymph nodes, or ipsilateral chest wall during follow-up. Tumor recurrences outside these regions were considered as distant metastasis. Patients having synchronous metastases or metastases occurring within three months after the onset of LRR were classified as metastatic disease.

Relationship between patients' and tumor characteristics was analyzed with univariate analysis, and compared with surgical technique. Overall (from first diagnosis until last visit or death) and disease-free survival (from first diagnosis until first LRR or distant metastasis) times were assessed from outpatient charts and online digital hospital records.

Table 2. Comparison of patients' characteristics according to locoregional recurrence *(LRR: Locoregional recurrence, MRM: Modified radical mastectomy, RM: Radical mastectomy)*

Patients	*LRR*	*p*	*Disease-free survival (mean±S.E.) (95% CI)*	*Mean follow-up (range)*	*5-year survival*	*Log rank p*
Age (368)						
< 49 (187)	16 / 187 (9.3%)	0.897	123±7(109;137)	83 (15-205)	64%	0.76
≥ 50 (181)	12 / 196 (7.1 %)	0.486	123±6(112;135)	77 (6-181)	70%	0.38
Menopause status						
Premenopause (202)	15 / 202 (7.4%)	0.884	123±7 (110;137)	82 (15-205)	63%	0.72
Menopause(166)	13 / 166 (7.8 %)		123±6 (111;135)	78 (6-181)	72%	0.39
Surgical technique						
MRM (318)	24 / 318 (7.5 %)	0.782	126±6 (114;138)	81 (10-205)	69%	0.91
RM (50)	4 / 50 (8%)		111±11 (91;132)	85 (6-181)	56%	0.34
Stage						
Early (146)	12 /146 (8.2 %)	0.720	138±6 (127;149)	89 (23-205)	78%	13.49
Locally advanced (222)	16 / 222 (7.2 %)		118±6 (106;130)	72 (6-199)	60%	**0.0002**

Data were given as mean ± standard deviation unless otherwise cited. Student's t test was performed for the comparison of independent variables, and chi-square test was used for significance of difference between groups by univariate analysis of group distributions. Disease-free and overall survival times were defined with Kaplan-Meier analysis, and were compared using log rank test. P value below 5 % was considered statistically significant. SPSS 10.0 for Windows was used for backward Cox regression analysis of significant parameters in prognosis of breast cancer such as greater tumor size, lymph node status, stage, and surgical margin status, and independent factors in recurrence-free survival were evaluated.

Results

Of 368 women recruited for the study, 28 (7.6%) developed LRR. Site of recurrences were at chest wall in 22 (78.5%), at axillary region in 5, at both sites in one patient. Between an interval of 6 months to 8.5 years (median: 18 months), metachronous systemic metastasis developed in 14 of these patients (50%).

Patients' characteristics

Age and menopause status were not related to the LRR occurrence in our study. LRR developed in 9.3 % of patients below 49 years old while this was 7.1 % in older patients. There was no statistical significance between two groups (X^2= 0.48; p=0.49). There was no significant difference in terms of disease free survival between age groups. LRR was not affected by menopause status, and also there was no statistical significance in disease free survival (DFS) between premenauposal and menopausal patients (Table 2). 318 (86.4%) of patients underwent modified radical mastectomy (MRM). Mostly before 1990s, 50 patients (13.6%) have had radical mastectomy (RM). LRR occurred in 24 of MRM patients (7.5%) and four of RM patients (8%) recurred on follow-up. Surgical approach did not seem to affect LRR occurrence and DFS (Fisher's exact test, p=0.782 and log rank: 0.91; p=0.34). In 12 of 146 early stage breast cancer patients (8.2%) developed LRR whereas 16 of 222 locally advanced breast cancer patients (7.2%) had LRR. Differences of LRR between two stages were not statistically significant (X^2=0.128; p=0.720). However, DFS of patients with early breast cancer was significantly higher than that of locally advanced breast cancer patients (5-year survival: 78 vs. 60 %, log rank: 13.49; p=0.0002) (Table 2).

Tumor characteristics

Half of the patients (184 patients – 50%) had their tumors in the right breast whereas the other half in left side. 17 of right sided breast cancers had LRR (9.2%) while 11 (5.9%) left sided breast cancer recurred locoregionally. Location was not a statistically significant factor for LRR (X^2=1.392 p=0.238). DFS had no significant difference between two groups (Table 3).

Considering the localization, LRR were lowest in tumors located in the upper outer quadrant (UOQ) and in tumors under the areola. While 12 (5.4%) of 219 UOQ cases were encountered with LRR, LRR occurred in 39 upper inner quadrant (UIQ), in 60 lower inner quadrant (LIQ), in 18 lower outer quadrant (LOQ) and in 32 periareolar tumors, the rate of LRR incidence were 10.3%, 11.6%, 16.6%, and 6.3% respectively (X^2= 11.2 p=0.048). By contrast, survival analyses showed that periareolar cancers had the longest DFS, but UOQ localization had the shortest DFS. This was probably due to unequal distribution of the groups. Consequently, this difference was not statistically significant (log rank: 6.87; p=0.230).

Assessing the tumor diameter of the recruited patients, 60 cases (16.3%) had tumors < 2 cm, in 278 cases (75.5%) tumors were ranging from 2 to 5 cm, and remaining 30 patients (8.2%) had tumors > 5 cm. Number of patients with LRR occurring in these groups were five (9%), 20 (7.2%), and three (10%) respectively. Mean tumor diameter was 3.4±2.0 cm in cases with LRR, while it was 3.1±1.7 cm in cases without LRR (t=0.734; p=0.469). Statistical

Table 3. Comparison of tumor characteristics for locoregional recurrence *(LRR: Locoregional recurrence)*

Tumor	*LRR (n=28)*	*p*	*Disease-free survival (mean±S.E) (95% CI)*	*Median follow-up (range)*	*5-year survival*	*Log rank p*
Localization						
Right	17 / 184 (9.2%)	0.238	133±6 (121;145)	82 (10-199)	66%	0.02
Left	11 / 184 (5.9%)		118±6 (107;129)	79 (6-205)	68%	0.900
Outer Upper Quadrant	12 / 219 (5.4%)	**0.048**	117±7 (104;130)	78 (6-205)	64%	
Inner Upper Quadrant	4 / 39 (10.3%)		132±10 (111;152)	101(42-175)	69%	6.,87
Outer Lower Quadrant	7 / 60 (11.6%)		126±9 (108;144)	81 (21-165)	72%	0.230
Inner Lower Quadrant	3 / 18 (16.6%)		111±15 (81;141)	85 (28-165)	72%	
Areola	2 / 32 (6.3%)		145±12 (122;168)	80 (23-181)	76%	
Tumor size						
< 2 cm	5 / 60 (9%)	0.837	144±8 (127;160)	81 (23-181)	78%	23.10
2-5 cm	20 / 278 (7.2%)		126±6 (113;138)	82 (6-205)	69%	**0.00001**
> 5 cm	3 / 30 (10%)		59±9 (42;76)	66 (21-128)	30%	
Axillary lymph node						
Negative	8 / 118 (6.7%)		145±8 (129;162)	86 (23-205)	78%	24.51
1-3 positive	8 / 114 (7.0%)	0.796	130±7 (116;143)	83 (21-181)	72%	**0.00001**
> 3 positive	12 / 136 (8.8%)		93±6 (81;105)	68 (6-170)	54%	
Surgical Margin (245)						
< 1 cm	6 / 30 (20%)	**0.007**	68±10 (49;88)	83 (6-205)	43%	12.22
> 1 cm	13 / 215 (6%)		126±5 (115;137)	65 (16-134)	72%	**0.0005**
Grade (177)						
I	1 / 17 (5.8%)	0.994	104±9 (87;121)	76 (54-120)	82%	2.92
II	6 / 109 (5.5%)		93±5 (82;103)	79 (21-150)	62%	0.2325
III	3 / 51 (5.8%)		83±6 (70;95)	78 (13-120)	61%	
Estrogen Receptor						
Negative	2 / 37 (5.4%)	1.0	62±7 (49;75)	79 (23-150)	51%	6.30
Positive	5 / 77 (6.5%)		101±5 (90;111)	81 (25-141)	72%	**0.0121**
Progesterone Receptor						
Negative	4 / 61 (6.5%)	1.0	84±7 (71;98)	79 (23-116)	57%	3.83
Positive	3 / 46 (6.5%)		103±6 (90;115)	79 (25-150)	76%	**0.0502**

analysis showed that mean tumor diameter was not significantly different among patients with or without LRR (X^2=0.357; p=0.837). However, in terms of DFS, especially in patients with tumors greater than 5 cm, DFS was significantly lower than that in other groups (log rank: 24.51; p=0.00001) (Table 3).

Whenever there was no enlarged lymph node in Level III group, standard axillary dissection including level I and II lymph node groups was done. Mean total removed lymph node was 18.2±7.1 in patients with LRR, and 19.1±7.6 in patients without LRR. Mean metastatic lymph node was 5.5±7.3 and 4.6± 6.5 respectively. When comparing, overall and metastatic lymph nodes were not statistically significant between patients with and without LRR (p=0.49 and p=0.50). When axillary LN status was assessed and it was found that LRR was encountered in eight cases (6.7%) of 118 node negative patients, another eight cases (7.0%) of 114 patients with one to three LN positivity, and in twelve (8.8%) of 136 patients with ≥ 4 LN. Statistical analysis revealed that axillary LN status had no effect on LRR occurrence (X^2=0.458; p=0.796).

In only 177 patients (48.1%), tumor grade could be assessed. Of those, ten (5.6%) have experienced LRR. One of 17 grade I patients (5.8%), six of 109 grade II patients (5.5%) and three of 51 grade III patients (5.8%) have had LRR. Grade differences also did not influence LRR (X^2=0.011; p=0.994).

As estrogen receptor (ER) and progesterone receptor (PR) could be studied later, we only have information of PR status in 107 patients (29.1%) and ER status in 114 patients (30.1%). While five of 77 ER positive patients (6.5%) have had LRR, 5.4% of ER negative patients have experienced LRR. Three of 46 PR-positive patients (6.5%) and four PR-negative patients (6.5%) have had LRN (Fisher' s exact chi-square test, p=1.0) (Table 3).

Kaplan-Meier analysis revealed that positive axillary lymph node, tumor differentiation, and positive estrogen receptor were significantly associated with disease-free survival, but positive PR had borderline significance (Table 3).

Surgical margin

Information on surgical margin could be defined in only 245 patients (66.5%) at histopathological diagnosis. In 19 (7.8%) patients of this group LRR developed. Closest margin from tumor to cut surface was below 1 cm in 30 patients whose 29 underwent MRM, and the last one RM (3.3%), while of 215 patients with close margin greater than 1 cm, 17 underwent RM (7.9%). Two surgical methods were not statistically significant in obtaining safe close margin (X^2=0.809 p=0.462).

Six of patients with surgical margin closer than 1 cm (20%) developed LRR while 13 of 215 patients with safe surgical margin (6%) have had LRR. Considering the surgical margin of 1 cm as critical cut-off value, LRR was statistically significantly higher in patients with closer margin (X^2=7.165; p=0.007) (Table 3).

Survival analysis

Mean follow-up of patients in the study was 81 months (range: 6-205 months). The two and 5-year overall survival rates were 96.4% and 72.3% in patients with isolated LRR while these were 97.3% and 85.1% respectively in patients without LRR (log rank: 10.79 p=0.001). The two and 5-year disease-free survival rates were 79.5% and 50.6% in patients with LRR, while 93.3% and 82.1% in patients without LRR (log rank: 18.09 p=0.00001).

When survivals were compared with patients' stage, the two and 5 – year overall survival rates of locally advanced breast cancer patients were 94.4% and 78.7% respectively, while those of Stage I and IIA patients 99.3% and 92.4% respectively (log rank: 15.65 p=0.0001).

Patients were also compared according to surgical margin status. The 5-year overall survival rate was 88.6% and DFS rate was 72.0% in patients with safe surgical margin. However, in patients with surgical margin closer than 1 cm, the 5-year overall and disease-free survival rates were 78.3% and 43.0% respectively (log rank: 9.53 P=0.0085 for overall survival rates, and log rank: 12.22 p=0.0005 for DFS) (Figure 1).

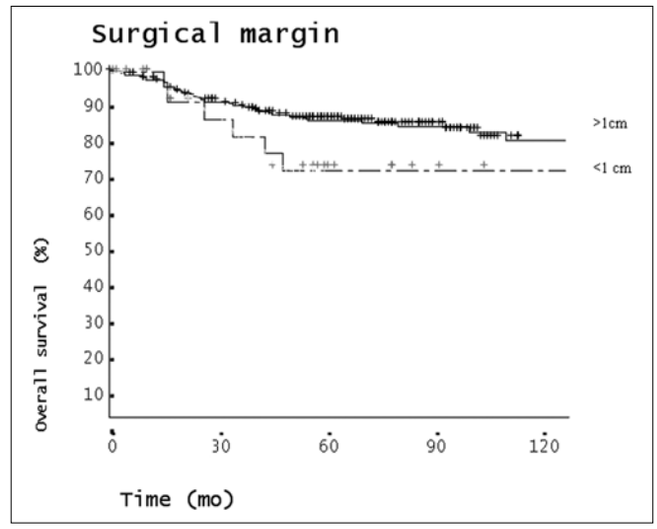

Figure 1. The effect of surgical margin on overall survival (log rank: 9.53 p=0.0085).

In the analysis of the effect of lymph node involvement on survival between patients with or without LRR, an overall survival rate for 340 patients without LRR was 81.8%. Of these, 110 have had negative ALN. 200 patients have had one to three positive ALN and the remaining 30 patients equal or more than four positive ALN. On the other hand, overall survival rates of the 28 patients with isolated LRR was 57.1% and among them, nine were node-negative, 14 had 1-3 positive ALN, and five had ≥ 4 ALN. There was statistically significant difference in overall survival between two groups (log rank: 27.4 p=0.00001) (Figure 2).

Although limited, the effect of tumor diameter on survival was statistically significant. In tumors < 2 cm, the two and 5-year survival rates was 98.3% and 91.5% respectively, while this was 97.5% and 83.9% in patients with 2-5 cm tumors. When the tumor diameter exceeded 5 cm, 2-year overall survival was not so much dif-

Table 4. Cox regression analysis; independent factors for locoregional recurrence-free survival.

Factor	*Beta*	*SE*	*Wald*	*p*	*Relative risk*	*CI (95%)*	
						Min	*Max*
Stage	-0.281	0.415	0.458	0.498	0.755	0.334	1.704
Tumor size	0.486	0.242	4.039	0.044	1.626	1.012	2.612
Lymph node positivity	0.596	0.160	13.977	0.0001	1.816	1.328	2.482
Surgical margin	-0.278	0.123	5.095	0.024	0.757	0.594	0.964

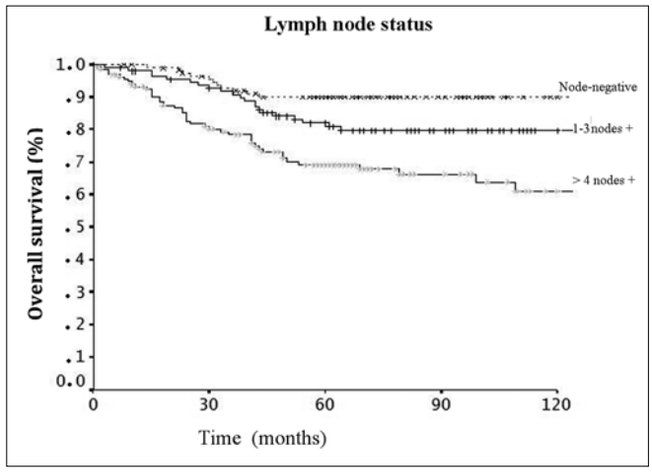

Figure 2. The effect of lymph node status on overall survival (log rank: 21.47 p=0.00001).

ferent (96.7%), however 5-year survival rates decreased to 71.8% (log rank: 6.56 p=0.0376).

In Cox regression analysis, tumor > 5cm, positive lymph node, close surgical margins were found to be independent prognostic factors for survival without locoregional failure (Table 4).

Discussion

The fact that postmastectomy LRR has no ideal definition, studies enquiring its frequencies run into some difficulties. In studies using different characteristics in staging, follow-up, and inclusion criteria, the occurrence of LRR has been reported to be from 6.2 to 29%(26-32). Especially seen earlier after surgery, LRR has a close relationship with distant metastasis (31,33-35). This association of LRR with systemic dissemination supports the hypothesis of being a precursor of metastasis, hence indicator of the poor prognosis, and increased risk.

For earlier stage cancer, more LRR is reported to be seen after BCS (10.8%) than that after mastectomy (5.9%)(36). It is shown that, in mastectomy patients, a direct correlation exists between tumor size and LRR occurrence (10.5% in pT1, and 15.6% in pT4)(33). On the other hand, in a study by Timothy et al. comparing mastectomy patients with those having a rather large tumor, and undergoing postmastectomy radiotherapy, LRR and 5-year survival rate were found to be similar (37). Subsequently, it is demonstrated that radiotherapy has no benefits on LRR in tumors > 5cm(38). In our study, tumor size, although significant with survival, was not directly associated with LRR occurrence. The importance of tumor size is obvious as it is a prognostic factor affecting the LRR-free survival. Possibly adjuvant radiotherapy for tumors > 5 cm in our study might affect the occurrence of LRR.

Beside uncontrollable tumor characteristics such as ALN involvement, and tumor grade (39), a controllable feature like surgical margin becomes prominent, especially in BCS (40,41). In the International Breast Cancer Study Group (IBCSG) study aiming the definition of risk factors for LRR in patients without postmastectomy irradiation, vascular invasion, and tumor size greater than 2 cm were found to be significant factors in node negative patients. Beside these features, the number of positive lymph nodes was also prominent in node positive women (21). Other studies revealed that the amount of positive lymph node (22,27,28,42), tumor size (27,28,42,43), ER status and the number of examined lymph nodes (27), close or positive surgical margin (28,42), multicentricity (28), and age (22,43) were predictors of LRR occurrence. In early breast cancer and ductal carcinoma in situ patients, while age, tumor diameter, and lymph node status are still significant factors, postoperative adjuvant therapy is becoming a new factor on LRR for BCS (44,45). The German Breast Cancer Study Group emphasized the importance of interval time from both mastectomy and BCS to isolated LRR and defined as significant prognostic factor (26).

It seems that the amount of removed lymph nodes is a prognostic factor for LRR. Suboptimal surgical technique leads to under-staging and poor performance of axillary treatment (27,29,30). LRR incidence increases with the number of lymph nodes involved (22,23). In our study, the number of involved lymph nodes was not statistically significant for LRR. However, it was the most prominent factor in LRR-free and disease free survival.

Nowadays, adjuvant radiotherapy strongly proven for patients with four or more positive lymph nodes is also investigated in patients with one to three positive lymph nodes. Van der Hage et al. showed that early breast cancer patients were the women who have had the most benefit from adjuvant radiotherapy (36). Studies mostly impressed the profits of radiotherapy on lowering LRR rates. However, Woodward et al. found these benefits for T1-T2 tumors and 1 to 3 involved lymph node patients and pretended that close or positive surgical margins, highly extracapsular invasion, and ALN dissection containing more than 10 lymph nodes are highly associated with LRR. Beside the number of dissected lymph nodes, a great number of positive lymph nodes, greater tumor size, negative ER are all good predictors of LRR in patients receiving radiotherapy (23). Feigenberg et al. revealed that T stage and the number of positive lymph nodes are highly related to the survival (32). It has been clearly showed that c-erb B-2 and p53 were investigated, and the negativity of bcl-2, a new biological marker, was a poor prognostic factor for predicting LRR (46).

According to the endocrine response of the tumor, more aggressive adjuvant therapies induce a decrease in LRR (47,48). Before the advent of systemic adjuvant therapies, more radical surgery was being applied to the chest wall, and subsequently radiotherapy was added in order to maintain local control. Radiotherapy lowered the death from breast cancer and achieved good locoregional control, however, beside two studies with limited mean dissected lymph nodes, its effect on overall survival has not been shown (18, 37, 49-54). In Danish Breast Cancer Study Group (DBCSG 82B) and British Columbia studies with their fewer mean lymph node number (7

and 11 respectively) and high LRR rates, it has been asserted that postmastectomy radiotherapy had a significant contribution to survival in high-risk premenauposal women (17,29,30). Due to the side effects such as lymphedema and radiation pneumonia as much as 21%, radiotherapy is advised only to the patients with high risk for LRR (18,32). In another study in which no patient received radiotherapy, timing for chemotherapy was investigated and LRR rates was found to be 27% in patients receiving neoadjuvant therapy and 15% in patients receiving adjuvant therapy (55). Thus, although surgical and systemic therapies were applied, risk factors associated with LRR should be determined.

In our study, tumor characteristics did not seem to be a significant factor for LRR occurrence beside lower inner quadrant localization. For example, patients' age seemed to be a significant factor for LRR and survival in some studies (22,36,56), however this was not so in our study. It is emphasized that surgical margin is named as "close" if it is closer than 1 mm (41,57,58). In another study, of patients re-excised for positive surgical margin 52.5% was found to have residual tumor (59). While the surgical margin was the most attractive and prominent factor for BCS (40,41), only one study including mastectomy patients stated that the surgical margin was an important factor for LRR (42). Comparing the LRR occurrence, although LRR in radical mastectomies were lesser than that in modified radical mastectomies, there was no statistically significant difference between two surgical modalities (22).

During the classical mastectomy incision, there are difficulties for tumors situated in inner lower quadrants, especially in neighborhoods of the skin or the fascia. It has been recently demonstrated that tumors localized in inner quadrants recurred more often than those situated in outer quadrants, and these localizations have shown poor prognostic features (60,61). By the way, the significance of upper outer quadrant localization for LRR occurrence can be the result of the fact that these tumors could be managed more conveniently preoperatively. At the other hand, lower inner quadrant localization can be a prominent factor in LRR as lymphatic drainage of these tumors is towards parasternal and internal mammarian lymph nodes (IMLN). So metastatic lymph nodes left in place during surgery could raise locally recurrent disease. Beside this, IMLN metastasis can only be detected with the techniques such as computerized tomography or dynamic breast MR rarely used for the diagnosis and management of the breast cancer, and these examinations clearly show the systemic spread.

As a conclusion, close surgical margins and tumor localization were found to be significant risk factors for LRR despite adjuvant therapies in this study. In tumors situated close to the skin flaps, mastectomy incision should specifically be modified for safer margins. For tumors in proximity of the pectoral muscles, modification of the surgical technique aiming the total or at least partial excision of the muscle can reduce the future LRR risk. Considering the high risk of LRR in tumors situated close to or excised with positive the surgical margin, or localized in inner quadrants of the breast, different oncological approaches during follow-up schedule and adjuvant therapies should be searched for local control.

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