ORIGINAL RESEARCH

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Assessment of Arm Lymphedema and Late Skin Side Effects in Breast Cancer Patients Who Recieved Postoperative Adjuvant Radiotherapy

Postoperatif Adjuvan Radyoterapi ile Tedavi Edilen Meme Kanserli Olgularda Geç Cilt Yan Etkiler ve Kol Lenf Ödemin Değerlendirilmesi

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ABSTRACT Objective: To investigate factors leading to arm lymphedema and late side effects involving the skin in breast cancer patients who received postoperative adjuvant radiotherapy (RT). **Material and Methods:** Arm lymphedema and late skin side effects were investigated using the LENT/SOMA scales in 87 women with breast cancer treated by breast conservative surgery and RT. **Results:** Median age of patients were 52 years (range: 27-84). Factors that increased the risk of arm lymphedema included age >60 years, large RT volume, axillary dose ≥50 Gy and supraclavicular dose ≥50 Gy. Axillary dissection, dissected lymph nodes number >10 and lack of hormonal therapy increased fibrosis risk. Use of Co-60 machine for RT increased retraction atrophy risk. Axillary dissection, dissected lymph nodes number >10, and Co-60 use increased telangiectasia risk. **Conclusion:** In our study, to be over 60 years of age, large RT volume and high dose axillary RT were significant risk factors for arm lymphedema. Sentinel lymph node biopsy, small number of axillary lymph nodes dissected, RT by lineer accelarator reduced late skin reactions. Menopausal status, obesity, diabetes mellitus, stage of tumor and chemotherapy administration did not impact arm lymphedema and late skin side effects.

Keywords: Breast cancer; breast conservative surgery; radiotherapy; arm lymphedema; late radiation toxicity

ÖZET Amaç: Postoperatif adjuvan radyoterapi (RT) alan meme kanserli olgularda cilt geç yan etkileri ve kol ödemini değerlendirmek. **Gereç ve Yöntemler:** Kol ödemi ve geç cilt yan etkiler meme koruyucu cerrahi ve radyoterapi ile tedavi edilen meme kanserli 87 kadın olgu LENT/SOMA yan etki ölçeği kullanılarak değerlendirildi. **Bulgular:** Hastaların ortanca yaşı 52 (aralık: 27-84) idi. Kol ödemini arttıran faktörler 60 üstü yaş, geniş radyoterapi volümü, aksillanın ve supraklavikular fossanın aldığı 50 Gy ve üstü dozdur. Aksiller diseksiyon, diseke 10' dan fazla lenf nodu sayısı ve hormonal tedavi yokluğu meme fibrozis riskini arttırdı. Co-60 cihazı ile tedavi meme retraksiyon atrofi riskini arttırdı. Aksiller diseksiyon, diseke 10' dan fazla lenf nodu sayısı ve Co-60 cihazı ile tedavi meme telenjektazi riskini arttırdı. **Sonuç:** Çalışmamızda, 60 yaşın üzerinde olmak , geniş RT volüm ve yüksek aksiller RT doz kol ödemi için anlamlı risk faktörleridir. Sentinal lenf nodu biyopsisi, diseke edilen aksiller lenf nodu sayısının azlığı, lineer akselerator cihazı ile RT cilt geç yan etkileri azaltıltır. Menopoz durumu, obezite, diabetes mellitus, tümör evresi ve kemoterapi yönetimi kol ödemi ve geç cilt yan etkileri etkilemedi.

Anahtar Kelimeler: Meme kanseri; meme koruyucu cerrahi; radyoterapi; kol lenf ödemi; geç radyasyon toksisitesi

Breast cancer is the most common type of cancer among women and it is the second-leading cause of cancer-associated mortality.[1] Recently, there has been a reduction in causes of death secondary to breast cancer. Factors leading to this improvement include successful application of screening methods, increase in long-term survival due to advances in systemic treatment and developments in radiotherapy (RT) techniques enabling reduction in long term cardiac mortality. RT is important in the treatment of breast cancer as a primary and adjuvant treatment. It also impacts survival favorably as well as providing local and regional control.[2-5] Breast-conserving surgery (BCS) followed by RT is currently considered standard of care for early-stage breast cancer.[6] Several prospective randomized trials have found that breast conserving therapy (BCT), comprising segmentectomy followed by RT, is an oncologically safe treatment and is therefore commonly used in breast cancer treatment.[7] Although BCT has tremendously improved patient quality of life, some patients suffer from chronic late side effects, such as unfavourable cosmetic outcomes, atrophy of the breast, skin damage, breast oedema, lymphedema of the arm or pain.[8,9]

In breast cancer, late side effects are mainly fibrosis and atrophy due to the replacement of adipose tissue by collagen, resulting in a negative impact on the appearance of the breast.[10]

Improvements in RT techniques such as conformal radiation therapy (3D-CRT) and intensity-modulated RT (IMRT) allow for more homogenous dose distribution in the breast, resulting in better cosmetic results.[11] Moreover, the extent of surgery and tumor- and treatment-related factors can negatively influence cosmetic outcomes, such as an increased resected breast volume, inferior tumour location and the pathological tumour size.[12,13]

In our study, we aimed to determine factors that cause late side effects in breast cancer patients treated by BCS and adjuvant RT.

MATERIAL AND METHODS

PATIENTS

87 women diagnosed with invazive ductal carcinoma (stage I–III) or ductal carcinoma in situ (DCIS) who underwent a segmentectomy. All patients were irradiated at the Department of Radiation Oncology of Ege University Medical School between October 1994 and December 2010. The median age of **the cohort was** 52 (range: 27-84). The distribution of the patients characteristics is shown in (Table 1).

TABLE 1: Characteristics of the patients.

n=87		Number of cases	Percentage
Age (years)	Median 52 range: 27-84		
Diabetes Mellitus	Yes	4	4.6
	No	83	95.4
Menopause	Pre	26	29.8
	Post	61	70.2
Obesity	No	14	16.1
	Yes	73	83.9
Tumor Stage	DCIS	12	13.8
	1	31	35.6
	2	35	40.2
	3	9	10.3
Axillary Surgery	No	13	14.9
	Sentinel	27	31.1
	Axillary	47	54
Radiotherapy Fields	Breast	54	62.1
	BSA	33	37.9
Radiotherapy Machine	Co-60	10	11.5
	Linac	77	88.5
Chemotherapy	Yes	43	49.9
	No	44	50.6
Hormonal Therapy	No	11	12.6
	Yes	76	87.4
Follow up	Median 24 (range 6-144) months		

Abbreviations: RT: Radiotherapy; BCS: Breast Conservative Surgery; BSA: Breast Supraclavicular Axillary Field; Co-60: Cobalt-60 teletherapy unit; Linac: Linear accelerator; DCIS: Ductal carsinoma in situ.

SURGERY

The study patients received segmentectomy according to the surgeon's decision considering a good tumor-to-breast ratio.

CHEMOTHERAPY AND HORMONOTHERAPY

In total, 43 women were treated with chemotherapy. Trastuzumab was only given to those who received chemotherapy and had tumors overex pressing human epidermal growth factor receptor 2. Hormonal therapy was indicated for all hor-

monal receptor positive tumor patients (n=76). Tamoxifen with or without luteinizing hormone releasing hormone analogues or only aromatase inhibitors were prescribed depending on menopausal status of the patient. Chemotherapy was applied before RT and hormonal therapy was initiated after RT.

RADIATION TECHNIQUE

All patients received 3D-CRT. The dose prescription volumes were identified following the recommendations of International Commission on Radiation Units and Measurements report No. 62.[14] Treatment planning of the patients was performed with a CT-simulation slice thickness of 3 mm. The surgery scar was marked with radiopaque contrast medium. Dose calculations and optimizations were performed using Elekta Precise Planning System. Radiation was delivered by a linear accelerator (linac) or a Cobalt-60 unit. Breast irradiation plan consisted of equally weighted opposed symmetrical tangential two photon beams, dose distribution being corrected by wedge filters. Every patient received daily single dose of 2.0 Gray (Gy) to a total dose of 50.0 Gy to whole breast with conventional fractionation. A boost dose to tumour bed up to a total dose of 60.0 Gy (n= 66) or 66.0 Gy (n=21) was given. Of thirtythree patients who received additional breast supraclavicular axillary (BSA) field irradiation, thirtythree were irradiated only by a restricted BSA field at a dose of 50 Gy in 25 fractions, while seven were irradiated by extended anterior supraclavicular axillary field, with a complementary posterior axillary field if necessary: Twentysix of them received 50.0 Gy, one recieved 54 Gy and six patients recieved a total dose of 56.0 Gy to level I-III axillary nodes.

FOLLOW-UP AND ASSESSMENT

All patients who were monitored for ≥6 months following postoperative RT underwent physical examination in order to determine late side effects using the LENT/SOMA (Late Effects Normal Tissue Task Force- Subjective, Objective, Management and Analytic) assessment system. Follow up time was median 24 range (6-144) months.

The evaluation for statistical significance was performed by taking into consideration the following variables: axillary surgery, number of lymph nodes dissected from the axillary, menopausal status, stage, diabetes mellitus, age, obesity, type of treatment machine, hormonal therapy, RT dose, and field of irradiation. Measurements for arm lympedema were performed in both forearms, upper arms, and above the wrists. Breast oedema, lymphedema of the arm, fibrosis, retraction athropy and telangiectasia of the skin as late side effects were assessed using the LENT-SOMA scale. Physical examination of the patients was performed by one staff member independent radiation oncologist. All patients signed an informed consent form to participate and the study was approved by the Ethical Committee of Ege University Medical School.

STATISTICAL ASSESSMENT

Arm lymphedema and late skin side effects were scored according to the LENT/SOMA scoring system. Variables affecting these late side effects were evaluated using the chi-square and fisher's exact tests. The level of significance was set at $p<0.05$. The calculations were performed with SPSS 18.0 (SPSS Inc, Chicago, Illinois).

LENT/SOMA AND RTOG LATE SIDE EFFECTS SCORING

Compared to the RTOG (Radiation Treatment Oncology Group) scale, LENT/SOMA criteria appear to be a better scale for late-radiation toxicity classification and recording. Thus in our study we preferred to use LENT/SOMA scoring system that should be considered as a standard reporting scale for late-radiation morbidity assessment.[15]

STATISTICAL ANALYSIS

The level of significance was set at $p <0.05$. The calculations were performed with SPSS 18.0 (SPSS Inc, Chicago, Illinois). Variables affecting the late side effects were evaluated using the chi-square and fisher's exact test. The study was approved by the Ethical Committee of Ege University Medical School.

RESULTS

We retrospectively analysed late side effects of postoperative RT in 87 breast cancer patients treated with BCS. The distribution of patients with arm lymphedema and late skin side effects is shown in Table 2. The detailed number of events according to LENT-SOMA are listed in Table 3.

The detailed number of events according to LENT-SOMA are listed in Table 3.

Lymphedema of arm ≥grade 2 was observed in 4.5% of patients (n=4). Grade 2 and upper arm lymphedema was higher in patients over 60 years of age compared to ≤60 years (p=0.027). Breast cancer patients with stage III had higher ≥grade 2 arm lymphedema (p=0.052). Dissected lymph nodes number >10 (p=0.055) were significantly correlated with increased ≥ grade 2 arm lymphedema. Compared with RT to breast field, RT to BSA field was increased grade 2 and upper arm lympedema (p=0.018). Axillary dose ≥50 Gy (p=0.018) and supraclavicular dose ≥50 Gy (p=0.018) were significantly correlated with increased grade 2 and upper arm lympedema. Diabetes mellitus, menopause status, obesity, axillary dissection/sentinel lymph node biopsy and no axillary dissection, machine type for RT, chemotherapy, hormonal therapy, prescribed radiation dose including boost to breast were not significant risk factors for arm lymphedema (p>0.05). Factors leading to arm lymphedema of breast cancer patients treated with BCS and adjuvant RT are shown in Table 4.

Breast fibrosis ≥ grade 2 was observed in 13.8 % of patients (n=12). Grade 2 and upper skin fibrosis was lower in patients with sentinel lymph biopsy and without axillary dissection compared to axillary dissection (p=0.028). Compared with dissected lymph nodes number 10≤, the presence of more than 10 dissected lymph nodes increased ≥ grade 2 skin fibrosis (p=0.011). Patients without hormonal therapy had more ≥ grade 2 skin fibrosis (p=0.01). Breast retraction atrophy ≥grade 2 was observed in 3.4 % of patients (n=3). Grade 2 and upper skin retraction athropy was higher in patients treated with Co-60 machine than patients treated with lineer accelarator machine (p=0.00).

Breast telangiectasia ≥grade 2 was observed in 23% of patients (n=20). Axillary dissection (p=0.032), dissected lymph nodes number >10 (p=0.009), use of Co-60 machine for RT (p=0.001) were significantly correlated with increased ≥grade 2 telangiectasia. Age, diabetes mellitus, menopause status, obesity, stage, radiation volume, supraclavicular dose, axillary dose, prescribed radiation dose including boost to breast, chemotherapy were not

TABLE 2: The distribution of patients with arm lymphedema and late skin side effects.

n=87	Case	Percent
No arm lymphedema (Grade 0)	n=73	83.9%
Arm lymphedema (Grade 1-3)	n=14	16.1%
No breast fibrosis (Grade 0)	n= 33	37.9%
Breast fibrosis (Grade 1-3)	n=54	62.1%
No breast retraction atrophy (Grade 0)	n=70	80.5%
Breast retraction atrophy (Grade 1-3)	n=17	19.5%
No breast telangiectasia (Grade 0)	n= 67	77%
Breast telangiectasia (Grade 1-3)	n=20	23%
No breast pigmentation (Grade 0)	n=75	86.2%
Breast pigmentation (Grade 1-3)	n=12	13.8%
No breast pain (Grade 0)	n=39	44.8%
Breast pain (Grade 1-3)	n=48	55.2%

TABLE 3: Late side effects according to the LENT-SOMA scoring system.

Late side effect	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Arm lymphedema	73 (83.9%)	10 (11.5%)	1 (1.1%)	3 (3.4%)
Fibrosis	33 (37.9%)	42 (48.3%)	11 (12.6%)	1 (1.1%)
Retraction atrophy	70 (80.5%)	14 (16.1%)	2 (2.3%)	1 (1.1%)
Telangiectasia	67 (77%)	-	7 (8%)	13 (14.9%)
Breast pigmentation	75 (86.2%)	12 (13.8%)	-	-
Breast pain	39 (44.8%)	43 (49.4%)	2 (2.3%)	3 (3.4%)

TABLE 4: Arm lymphedema of breast cancer patients treated with BCS and adjuvant RT.

	Grade 0-1		≥ Grade 2		
n=87	**n**	**Percent**	**n**	**Percent**	***p value***
Age ≤ 60 years	68	98.6%	1	1.4%	**p=0.027**
Age >60 years	15	83.3%	3	16.7%	
DCIS and stage I-II	76	97.4%	2	2.6%	**p=0.052**
Stage III	7	77.8%	2	22.2%	
Dissected lymph nodes number ≤ 10	44	100%	0	0%	**p=0.055**
Dissected lymph nodes number >10	39	90.7%	4	9.3%	
Breast field	54	100%	0	0%	**p=0.018**
BSA field	29	87.9%	4	12.1%	
Axillary no dose	54	100%	0	0%	**p=0.018**
Axillary dose ≥ 50 Gy	29	87.9%	4	12.1%	
Supraclavicular no dose	54	100%	0	0%	**p=0.018**
Supraclavicular dose 50 Gy	29	87.9%	4	12.1%	

Abbreviations: RT: Radiotherapy; BCS: Breast Conservative Surgery; BSA: Breast Supraclavicular Axillary Field.

significant risk factors for late skin radiation toxicities (p>0.05).

Factors leading to late skin radiation toxicities of breast cancer patients treated with BCS and adjuvant RT are shown in Table 5.

No patients had breast oedema nor breast ulcer. Breast pigmentation ≥grade 2 was not observed in our patients (n=0). Breast pigmentation was apparent in 12 patients out of 87 patients. Breast pain ≥ grade 2 was observed in 5.7% of patients (n=5). Fourtythree (49.4%) had grade 1 breast pain and 5 patients (5.8%) had grade 2-3 breast pain. There was not any statistical correlation for breast pigmentation and breast pain.

TABLE 5: Late skin radiation toxicities of breast cancer patients treated with BCS and adjuvant RT N& Percent Rate & P value of Patients.

n=87	**Fibrosis Grade 0-1**	**Fibrosis ≥ Grade 2**	**Retraction atrophy Grade 0-1**	**Retraction atrophy ≥ Grade 2**	**Telangiectasia Grade 0-1**	**Telangiectasia ≥ Grade 2**
Sentinel lymph biopsy and no axillary dissection	38 (95%)	2 (5%)			35 (87.5%)	5 (12.5%)
	p=0.028		***p> 0.05***		***p=0.032***	
Axillary dissection	37 (78.7%)	10 (21.3%)			32 (68.1%)	15 (31.9%)
Dissected lymph nodes number 10 ≤	42 (95.5%)	2 (4.5%)			39 (88.6%)	5 (11.4%)
	p=0.011		***p>0.05***		***p=0.009***	
Dissected lymph nodes number 10 >	33 (76.7%)	10 (23.3%)			28 (65.1%)	15 (34.9%)
Co-60 machine	***p>0.05***		7 (70%)	3 (30%)	3 (30%)	7 (70%)
			p=0.00		***p=0.001***	
Linac machine			77 (100%)	0 (0%)	64 (83.1%)	13 (16.9%)
No hormonal therapy	7 (58.3%)	5 (41.7%)				
	p=0.01		***p>0.05***		***p>0.05***	
Hormonal therapy	68 (90.7%)	7 (9.3%)				

DISCUSSION

Arm lymphedema was detected to be common complication of breast cancer treatment and resulted in functional impairment and psychological morbidity who have axillary dissection and radiation therapy.[8,16-19] In their study, Dewar et al. reported the rates of upper-extremity arm lymphedema to be 33.7%, 26%, and 7.2%, respectively, in patients undergoing axillary surgery and radiotherapy, radiotherapy alone, and axillary dissection alone.[20] In a study by Sener et al. lymphedema was reported in 9 of the 303 patients (3%) who received sentinel lymphadenectomy and in 20 of the 117 patients (17%) who received sentinel lymphadenectomy combined with axillary dissection.[12,21] Lucci et al. found no difference in the frequency of lymphedema of the arm after axillary surgery versus sentinel-lymphonodectomy by arm measurements 12 months after surgery.[22] Our finding that 16.1% of the patients developed lymphedema is higher according to the prevalence reported in other studies.[23,24] In our study, number of axillary lymph node (p=0.055), axillary dissection (p>0.05) were not significant factors regarding lymphedema in the arm.

RT related factors affecting cosmesis included large treatment volumes (tangential breast fields only vs. three or more fields) as our findings.[8,12] In a large cohort of breast cancer patients prospectively screened for lymphedema, peripheric lymphatic irradiation significantly increased the risk of lymphedema compared with breast/chest wall radiation alone. When considering use of peripheric lymphatic irradiation, clinicians should weigh the potential benefit of peripheric lymphatic irradiation for control of disease against the increased risk of lymphedema similar with our findings.[25]

In our study, patients over 60 years of age had most grade 2 and upper arm lymphedema. Menopausal status was not significant for arm lymphedema. Taylor et al. reported that lower proportion of excellent cosmetic scores were showned in patients with age>60 years (p=0.001) and postmenopausal women (p=0.02).[12]

Markiewicz et al. reported that chemotherapy or hormonal therapy did not influence arm lymphedema as is the findings from our study.[26] The rate of lymphedema in patients with advanced breast cancer was higher than patients with early stage breast cancer (p=0.018) similar with our findings.[27]

Obesity as a significant factor of lymphedema of the arm is controversially discussed in the literature.[19,23,25] Obesity was important factor for lymphedema but we did not find any significance.[27]

Fibrosis was proposed to have a dose-dependent relationship with radiotherapy.[28] Axillary irradiation increased the incidence of moderate to severe breast fibrosis in both premenopausal and postmenopausal patients. Due to a strong interaction between tamoxifen administration and radiation to the regional lymph nodes, the effect of tamoxifen on the development of fibrosis could not be fully discerned.[29] We did not find any relationship with radiotherapy dose, age, chemotherapy, and menopausal status for breast fibrosis. In our study, hormonal therapy did not increase breast fibrosis risk.

The reported incidence of telangiectasia in the literature ranges from 3.1-32.1 %.[30,31] In our study, incidence of telangiectasia was 23%. Telangiectasia was associated with use of Co-60 machine for RT, axillary dissection, number of dissected lymph nodes. Retraction athropy was associated with use of Co-60 machine for RT in our patients. We think that since the Co-60 gamma rays has a little skin sparing effect with respect to 6 Mv linac x Rays, skin associated late effects with mostly seen with C0-60 usage.

No patients of all our patients had breast oedema. Breast oedema was associated with axillary surgery.[32]

Radiotherapy after Breast Conservative Treatment is associated with more intense chronic breast pain.[33,34] Ishiyama et al. identified additional boost irradiation as a predictive factor of breast pain.[35] In a recently published multivariate analysis by Mak et al. the volume treated to≥110% of the prescribed dose (PTV110) and hormonal therapy were statistically significant predictors of pain.[36] Breast pain ≥

grade 2 was observed in 5.7% of all our patients. There was not any statistical correlation for breast pain.

The limitations of our study include its retrospective nature. In addition, late side effects and the cosmetic result were assessed only once. We do not know whether the same low rate of chronic side effects would have been observed if periodically follow-up visits had been carried out.

CONCLUSIONS

In our study, to be over 60 years of age, large radiotherapy volume and high dose axillary RT were significant risk factors for arm lymphedema. Sentinel lymph node biopsy, a small number of axillary nodes dissected, RT by lineer accelarator reduced late skin reactions. Hormonal therapy did not increase breast fibrosis risk. Menopausal status, obesity, diabetes mellitus, stage of tumor and chemotherapy administration did not impact arm lymphedema and late skin side effects. The findings from our study are in good correlation with the literature. The limitations of our study include its retrospective nature and the small number of patients.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Zeynep Özsaran, Halil Sağınç;* ***Design:*** *Halil Sağınç;* ***Control/Supervision:*** *Zeynep Özsaran, Halil Sağınç;* ***Data Collection and/or Processing:*** *Halil Sağınç, Özgür Yıldırım;* ***Analysis and/or Interpretation:*** *Halil Sağınç, Bahar Baltalarlı;* ***Writing the Article:*** *Halil Sağınç;* ***Critical Review:*** *Zeynep Özsaran;* ***References and Fundings:*** *Ege University Faculty of Medicine, Department of Radiation Oncology;* ***Materials:*** *Ege University Faculty of Medicine, Department of Radiation Oncology.*

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