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The Incidence and Risk Factors for occurrence of Arm Lymphedema after Treatment of Breast Cancer

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Rezumat

Incidența și factorii de risc pentru apariția limfedemului brațului după tratamentul cancerului mamar

Introducere: Limfedemul brațului este raportat ca fiind cea mai frecventă reacție tardivă și complicație care afectează calitatea vieții pacientelor cu neoplasm mamar după limfadenectomie și radioterapie (RTE). Scopul studiului este identificarea factorilor de risc în apariția limfedemului brațului la pacientele cu neoplasm mamar care au efectuat chirurgie radicală/conservatoare, chimioterapie și radioterapie.
Material și Metodă: Am analizat 305 paciente cu neoplasm mamar care au efectuat tratament în Serviciul de Radioterapie și Oncologie al Spitalului Clinic de Urgență "Sf. Ap. Andrei" Galați, în perioada 01.01.2010 - 31.12.2012. Am analizat incidența și factorii de risc pentru apariția limfedemului brațului după efectuarea tratamentului pentru cancerul mamar: asocierea radioterapiei cu chirurgia, chimioterapia, hormonoterapia, numărul ganglionilor invadați, numărul ganglionilor extirpați, bolile comorbide asociate (obezitate, hipertensiune arterială, diabet zaharat tip II).
Rezultate: Studiul nostru evidențiează faptul că asocierea RTE adjuvante după chirurgie radicală sau conservatoare cu limfadenectomie, reprezintă un factor de risc semnificativ, riscul relativ, RR=1.87, 95%C.I.=1.39–3.51, p<0.001. Numărul ganglioni limfatici extirpați a fost găsit ca factor de risc independent: > 25 ganglioni limfatici extirpați, RR=1.95 (95%C.I.=1.79–4.51) iar pentru 16-25 ganglioni limfatici extirpați – RR=1.78, 95% C.I. = 1.46 – 3.23, p<0.001. Alți factori de risc analizați dar care nu au influențat apariția limfedemului brațului, au fost: asocierea chimioterapiei, hormonoterapiei, prezența bolilor asociate comorbide.
Concluzii: Dezvoltarea limfedemului reprezintă un fenomen nepredictibil care se poate manifesta și tardiv după chirurgia axilară. Atât edemul brațului cât și edemul sânului sunt reacții tardive asociate cu tratamentul neoplasmului de sân care pot fi reduse prin practicarea tehnicii biopsiei ganglionului santinelă cu evitarea limfadenectomiei axilare atunci când ganglionul santinelă este negativ, ținând cont de faptul că riscul de limfedem post-biopsie a ganglionului santinelă este de 5% comparativ cu riscul de limfedem post limfadenectomia axilară care este de 16%, evitarea obezității și utilizarea tehnicilor moderne de radioterapie.

Cuvinte cheie: limfedemul brațului, neoplasm de sân, radioterapie, factori de risc

Abstract

Background: The arm lymphedema is reported as being the most frequent late reaction and complication that influences breast cancer patients' quality of life after lymph node dissection and radiotherapy. The aim of the study is to identify the risk factors in arm lymphedema occurrence in breast cancer patients who performed radical / conservatory surgery, chemotherapy and radiotherapy.
Material and Methods: We analysed 305 breast cancer patients who underwent treatment in the „Sf. Ap. Andrei" Emergency Clinical Hospital, Galati, Radiotherapy and Oncology

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Department, between the 1st of January 2010 and 31st of December 2012. We tried to find the risk factors for arm lymphedema development after treatment of breast cancer: the association of adjuvant radiotherapy with surgery, chemotherapy, hormonal therapy, number of removed lymph nodes, and number of lymph nodes with metastases, the co-morbid illnesses (obesity, diabetes mellitus and high blood pressure).
Results: Our study evidences that the association of adjuvant radiotherapy, including the lymph node regions, with radical or conservatory surgery with lymph node dissection represents a statistically significant risk factor, with relative risk, RR = 1.87, 95%C.I.=1.39–3.51, $p<0.001$. The number of removed lymph nodes was found to be a risk factor with statistical significance. For more than 25 removed lymph nodes, the relative risk for arm lymphedema development was RR=1.95 (95%C.I. =1.79–4.51) and for 16-25 removed lymph nodes the relative risk, RR = 1.78, 95% C.I. = 1.46 – 3.23. Other analysed risk factors, which did not influence lymphedema development, were: associated chemotherapy or hormonal-therapy, presence of co-morbid illnesses.
Conclusions: The development of arm lymphedema is an unpredictable occurrence that can happen years after axillary surgery. Breast and arm oedema continue to be late reactions that can be reduced by use of biopsy sentinel technique with avoiding of axillary lymph node dissection, when the sentinel lymph node is negative, knowing that lymphedema risk after sentinel lymph node is 5% comparative with lymphedema risk after axillary lymph node dissection which is 16%, by avoiding obesity, and performing modern therapy techniques.

Key words: arm lymphedema, breast neoplasm, radiotherapy, risk factors

Introduction

Breast cancer treatment is a multimodal treatment and involves surgery, radiotherapy, chemotherapy and hormonal-therapy. Axillary lymph-node dissection and/or external beam radiotherapy (EBRT) represent an important component in the treatment of the great majority of invasive breast cancer. Arm lymphedema represents one of the most important late reactions after axillary lymph-node dissection. Arm lymphedema frequently occurs after lymph node dissection and causes physical and psychological distress and leads to reduction of functional ability (functional impotence of respective member), pain, infections (1); it can also cause repeated cellulitis episodes, erysipelas, lymphangitis, and occasionally lymph-angiosarcoma. There are two types of arm lymphedema: acute lymphedema – transitory and developed after surgery and chronic lymphedema – developed years after breast cancer treatment (2). Even if axillary lymph-node dissection does not influence the breast cancer patient's survival, the axillary lymph-node status represents one of the most important prognostic factors.

Figure 1. *Female patient with right arm lymphedema who underwent adjuvant radiotherapy including the lymph node regions*

Arm lymphedema represents the increase of the arm volume over 10% (2 cm) which occurs in the first 3 months after surgical treatment (1,3). Dates about lymphedema incidence vary between 5 and 66% and the incidence is directly related to axillary lymph-node dissection and strongly influenced by the association of external beam radiotherapy. Axillary external beam radiotherapy is associated with low incidence of late-reactions. There are limited data about risk factors of lymphedema related to breast cancer treatment. The arm lymphedema is reported as the most frequent late reaction and the most frequent complication that influences breast cancer patients' quality of life after lymph node dissection and radiotherapy (4).

The aim of the study is to identify the risk factors for arm lymphedema occurrence in breast cancer patients who underwent radical / conservatory surgery, chemotherapy and radiotherapy.

Material and Method

We analysed 305 breast cancer patients who underwent treatment at the „Sf. Ap. Andrei" Emergency Clinical Hospital, Galati, Radiotherapy and Oncology Department, between 1st of January 2010 and 31st of December 2012. We excluded from this study the patients with systemic disease, loco-regional recurrence and bilateral breast cancer. The median age of the patients was 59 years (range 28-82 years), with a majority of urban cases (68.85%). A percent of 40.33% of patients presented loco-regional advanced disease, being in IIIB stage, and 38.03% of cases were in II B stage of disease. The clinical characteristics are shown in *Table 1*. Of all 305 breast cancer patients, 18 (5.9%) developed arm lymphedema, with more cases in the left arm (55.56%).

In patients with more than 4 metastatic lymph nodes or in cases with extra-capsular invasion of the nodal metastases, adjuvant radiotherapy was recommended. The chest wall,

Table 1. *Clinical characteristics*

Parameters	No. patients (%) N=305	No. lymphedema patients (%) N=18 /305
Median age (years) at the time of surgery	59 (range 28-82)	55 (range 37-77)
Sex		
Female	300 (98.36)	18 (100)
Male	5 (1.64)	0
Environment		
Urban	210 (68.85)	12 (66,67)
Rural	95 (31.15)	6 (33.33)
Disease stage		
I	15 (4.92)	1 (5.56)
IIA	26 (8.52)	3 (16.67)
IIB	116 (38.03)	5 (27.78)
IIIA	20 (6.56)	1 (5.56)
IIIB	123 (40.33)	7 (38.89)
IV	5 (1.64)	1 (5.56)
Left arm lymphedema		10 (55.56)
Right arm lymphedema		8 (44.44)
Number of removed lymph nodes		
<15	148 (48.52)	3 (16.67)
16-25	103 (33.77)	6 (33.33)
>25	54 (17.70)	9 (50)
Metastatic lymph nodes		
Yes	220 (72.13)	13 (72.22)
No	85 (27.87)	5 (27.78)
Surgical Treatment		
- mastectomy + lymph node dissection	236 (77.5)	13 (72.22)
- conservatory surgery + lymph node dissection	69 (22.5)	5 (27.78)
Radiotherapy technique		
- thoracic wall / mammary gland	67 (21.88)	4 (28.57)
- thoracic wall/ mammary gland + lymph regions	238 (78.03)	14 (77.78)
Chemotherapy (CMT)		
Yes	265 (87)	16 (89)
No	40 (13)	2 (11)
Hormonal therapy (HT)		
Yes	244 (80)	13 (72.22)
No	61 (20)	5 (27.78)
Obesity		
Yes	82 (26,89)	10 (55.56)
No	223 (73.11)	8 (44.44)
Diabetes Mellitus		
Yes	29 (9.51)	5 (27.78)
No	276 (90.49)	13 (72.22)
High blood pressure		
Yes	59 (19.34)	6 (33.33)
No	246 (80.66)	12 (66.67)

supraclavicular regions, internal mammary lymph nodes, axillary regions were included in the radiotherapy field. Radiotherapy was performed after the patients signed the informed consent in accordance to the „Sf. Ap. Andrei" Emergency Clinical Hospital, Galati protocol.

Statistical analysis

The categorized probable risk factors were introduced into the logistic regression analysis as categorical covariates using a different reference category for each risk factor. The XLSTAT 2013 computer program was used for data analysis. Risk factors associated with arm symptoms were tested in univariate analyses by performing the chi-square test. Multivariate logistic regression model was used for the multivariate analysis; relative risks and odds ratio were reported with a 95% confidence interval. All p values reported are two sided; statistical significance is defined as $p < 0.05$.

Results

During the follow-up period, 18 patients (5.9%) developed arm lymphedema. The mean age of the patients in the lymphedema group at the time of surgery was 55 years, compared with 59 years for the entire lot of patients.

Our study evidences that adjuvant radiotherapy including lymph node regions association after radical or conservatory surgery with lymph node dissection represents a statistically significant risk factor, with relative risk RR = 1.87 (95%C.I.=1.39–3.51, $p < 0.001$). The radiotherapy technique which did not involve the axillary regions did not represent a risk factor for arm lymphedema development. A value of RR > 1 means that arm lymphedema is more likely to occur in the lymph node radiotherapy group than in the non-lymph node radiotherapy group.

The number of excised lymph nodes was found to be a risk factor with statistical significance. For more than 25 removed lymph nodes, the relative risk for lymphedema development was RR=1.95 (95%C.I. = 1.79–4.51, $p < 0.001$) and for 16-25 removed lymph nodes the relative risk, RR = 1.78, (95% C.I. = 1.46 – 3.23) (*Table 2*). A value of RR 1.87 and 1.95, respectively, means that the arm lymphedema is more likely to occur in the group of patients in which the number of removed

lymph nodes is between 16 - 25, and even higher when the number of removed lymph nodes is more than 25, respectively, in comparison with less than 16.

Another analysed risk factor was association of chemotherapy and hormonal – therapy and none of these parameters were found to be risk factors for lymphedema development, RR = 0.34 (95%C.I.= 0.16–1.03) for chemotherapy association and RR=0.6 (95%C.I= 0.31–1.35) for hormonal therapy association. Therefore, the risk of developing late lymphedema appears to be unrelated to chemotherapy and hormonal - therapy. We also analysed the presence of co-morbid illnesses as risk factors for occurrence and development of arm lymphedema (obesity, diabetes mellitus and high blood pressure). But none of these associated diseases were found to be risk factors: RR = 0.9 (95%C.I. =0.41–1.85) for obesity, RR = 0.67 (95%C.I = 0.15–1.02) for diabetes mellitus and RR = 0.45 (95%C.I. = 0.22–1.06) for high blood pressure.

In the multivariate analysis we included the number of lymph nodes removed, adjuvant radiotherapy, chemotherapy association, and obesity. Logistic regression evidenced that only the number of excised lymph nodes and adjuvant radiotherapy including the lymph node regions association after radical or conservatory surgery with lymph node dissection represent statistically significant risk factors for arm lymphedema developing (*Table 3*).

Table 2. *Relative risk for arm lymphedema development*

Risk factors	RR (95%CI)
Number of removed lymph nodes	
<15	1*
16-25	1.78 (1.46-3.23)
>25	1.95 (1.79–4.51)
Radiotherapy technique	
- thoracic wall / mammary gland	1*
- thoracic wall/ mammary gland + lymph regions	1.87 (1.39–3.51)
Chemotherapy (CMT)	
Yes	0.34 (0.16–1.03)
No	1*
Hormonal therapy (HT)	
Yes	0.6 (0.31–1.35)
No	1*
Obesity	
Yes	0.9 (0.41–1.85)
No	1*
Diabetes Mellitus	
Yes	0.3 (0.1–0.9)
No	1*
High blood pressure	
Yes	0.45 (0.22–1.06)
No	1*

1* - reference category

Discussions

The arm lymphedema risk is associated with axillary lymph node dissection, with external beam radiotherapy and with combination of EBRT with axillary surgery. The incidence of arm lymphedema after axillary lymph node dissection is reported as varying between 10 and 37% and increases with the number of removed lymph nodes. The differences in arm lymphedema incidence are mainly related to the different definitions used and different patient groups with varying profiles that are included in studies (1, 2). In our study adjuvant chemotherapy, hormonal–therapy, high blood pressure and diabetes mellitus did not influence lymphedema occurrence.

The cause of arm lymphedema may be fibrosis development after radiotherapy, which induces lymphatic vessel constriction, subsequently decreasing the filter function of the lymph nodes and altering the immune response (5,6). Lymphatic obstruction does not represent the only physicopathological mechanism for lymphedema occurrence (7,8). Body mass index (BMI) represents an important risk factor for arm lymphedema occurrence. Ozaslan el al. (1) found in their study that a BMI > 25 is an important risk factor with statistical significance for lymphedema occurrence. But Larson et al. (5) did not find the BMI to be an important risk factor for lymphedema occurrence. The number of removed lymph nodes may be a cause of lymphedema development. Authors like Larson et al. (5), Kiel et al. (9) and Senofsky et al. (10) found in their studies that the number of removed lymph nodes is an important risk factor with statistical significance for lymphedema occurrence. Studies like Ozaslan et al. (1), Eduard et al. (11), Roses et al. (12), do not report the number of removed lymph nodes as being a risk factor correlated with lymphedema occurrence. Roses et al. (12) find only in univariate analyses that the number of removed lymph nodes is a risk factor for lymphedema occurrence, but at multivariate analysis this parameter was not found to be an independent related factor. In our study, the number of removed lymph nodes was found to be an independent statistically significant risk factor for development and lymphedema occurrence. Suneson et al. (13) found the presence of axillary lymph node metastasis to be a risk factor in lymphedema development.

Our study evidences that the association of adjuvant EBRT after radical or conservatory surgery with lymph node dissection represents a significant risk factor for lymphedema development. This statement is confirmed by many literature studies: Ozaslan et al. (1), Kiel et al. (9), Senofsky et al. (10), Mortimer et al. (14), Brismar et al. (15).

The specialized literature evidenced the statistically significant factors for arm lymphedema development: number of removed lymph nodes, advanced stage disease, particularly axillary lymph node metastasis; postsurgical radiotherapy

Table 3. *Logistic regression for predictive factors of arm lymphedema*

Risk factors	OR	95%CI*	p
Number of removed lymph nodes			
16-25	1.85	1.27-2.71	
>25	4.88	2.25–10.58	<0.001
Radiotherapy technique			
- thoracic wall / mammary gland	1.06	0.95-2.54	
- thoracic wall/ mammary gland + lymph regions	3.87	1.39–6.51	0.01
Chemotherapy (CMT)	1.45	1.12-2.24	
Obesity	0.81	0.46-1.44	

* CI = confidence interval

increases breast oedema risk and arm oedema risk after conservatory surgical treatment, EBRT dose administrated in the axillary lymph nodes, obesity, high blood pressure, soft tissues infections, old age (in some studies), chemotherapy (in some studies)

The risk of arm lymphedema as a function of the extent of axillary dissection in patients not receiving axillary radiotherapy is controversial. Specialized studies show that the unique axillary biopsy involves a low risk or an absent risk for lymphedema occurrence, total or partial lymph node dissection involves a 22% risk of arm lymphedema occurrence, axillary biopsy with EBRT presents a 6-9% risk for arm lymphedema occurrence, total or partial lymph node dissection has a 9-44% risk for lymphedema development and occurrence, and this risk increases with the number of removed axillary lymph nodes (16,17). Arm lymphedema occurs late after the axillary EBRT in patients without axillary lymph node dissection comparative with lymphedema that occurs after combined treatment – axillary lymph node dissection and EBRT.

Another aspect which must not be forgotten is the breast lymphedema after EBRT, after conservatory treatment that can lead to physical and psychological distress, pain, repeated cellulitis episodes, cosmetically modified aspect of conservatory treated breast.

The treatment that can be administrated in order to prevent the arm lymphedema development and occurrence consists in: physical exercises at short time after surgery, self-massage, compressive contention, medication – flavonoids like diosmina that facilitate the microcirculation, daily hygiene and diet.

We can also talk about the prevention of arm lymphedema taking into consideration the following aspects: development of arm lymphedema cannot be prevented after axillary lymph node dissection, the symptomatology occurs in the first 3 years after treatment in 77% of cases and at more than 3 years in 25% of patients, sentinel lymph node biopsy being performed as an alternative to axillary lymph node dissection, avoiding axillary lymph node dissection when the sentinel lymph node is negative. The arm lymphedema risk after sentinel lymph node biopsy is 5% compared with arm lymphedema risk after lymph node dissection, which is 16%, increasing with conservatory surgical treatment frequency. When possible, post-treatment biopsy, which increases the risk of cellulitis and breast oedema, can be avoided. The total dose administrated must be limited to 45-50Gy in conventional fractionation and the administration of EBRT must be restricted in patients older than 55 years old, especially in overweight patients. Health education of patients regarding skin care, avoiding breast infections, ipsilateral arm and chest wall trauma, obesity, play an important role in lymphedema preventing. Health education of patients regarding early diagnosis, presuming that low stage disease treatment involves a decreased risk of arm lymphedema and performing modern high technology EBRT, which confers increased dose homogeneity in the treatment field, are also important.

Conclusions

The development of arm lymphedema is an unpredictable occurrence that can happen years after axillary surgery. Breast and arm oedema continue to represent late reactions that can be reduced by using biopsy sentinel technique with avoidance of axillary lymph node dissection when the sentinel lymph node is negative, knowing that lymphedema risk after sentinel lymph node is 5% comparative with lymphedema risk after axillary lymph node dissection, which is 16%, by avoiding obesity, and submitting oneself to modern therapy techniques.

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