

The frequency and risk factors of developing lymphedema of the upper extremity after breast conserving therapy

Anna Niwińska¹, Hanna Tchórzewska², Małgorzata Procner², Ewa Kraszewska³

Aim. The aim of the study was to evaluate the frequency of lymphedema of the upper extremity in breast cancer patients after breast conserving therapy (BCT) and to assess the risk factors influencing this complication.

Material and methods. We evaluated 174 patients with breast cancer, mean age 53 yrs, stage 0, I and II undergoing BCT at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw between the years 1995 and 1999. Mean follow-up time was 50 months. Adjuvant chemotherapy or hormonotherapy had been administered to 83 pts. The circumference of both arms was measured by tape 10 cm above the lateral epicondyle, 10 cm below it and at the metacarpal level. A difference of 2-4 cm was recognized as mild; of 4-6 cm as moderate and over 6 cm as severe lymphedema. In order to assess the risk factors of lymphedema we performed a statistical analysis of the following elements: age, tumour location, number of excised nodes, number of metastatic lymph nodes, radiotherapy to lymph node areas and adjuvant systemic therapy.

Results. We observed 17/174 (10%) cases of lymphedema – 15/17 mild; 1/17 moderate and 1/17 severe. On statistical analysis we found, that the only factor affecting lymphedema was irradiation to the lymph node areas.

Conclusion. The incidence of lymphedema of the upper extremity after breast conserving therapy is low (10%), similar to published data. Radiotherapy of the lymph node areas is the only factor increasing the risk of lymphedema.

Ocena częstości występowania i czynników ryzyka obrzęku limfatycznego kończyny górnej u chorych na raka piersi po leczeniu oszczędzającym

Cel. Celem pracy była ocena częstości występowania i stopnia nasilenia obrzęku limfatycznego kończyny górnej u chorych na raka piersi po leczeniu oszczędzającym oraz analiza czynników ryzyka wystąpienia obrzęku.

Materiał i metoda. Poddano analizie 174 chore na raka piersi w stopniu zaawansowania klinicznego 0, I i II, leczonych w Centrum Onkologii w Warszawie w latach 1995-1999. Średni czas obserwacji wynosił 50 miesięcy. U wszystkich chorych wykonano tumorektomię lub kwadrantektomię z limfangiektomią pachową oraz napromienianie na piersi. U 83 chorych przeprowadzono chemioterapię lub hormonoterapię uzupełniającą. W trakcie leczenia pierwotnego wszystkie chore odbyły instruktaż w Zakładzie Rehabilitacji, dotyczący profilaktyki przeciwobrzękowej. Po średnim czasie obserwacji 50 miesięcy wykonano pomiary obwodów kończyny górnej po stronie leczonej i porównano je z obwodami po stronie zdrowej. Pomiary przeprowadzono na wysokości ramienia, przedramienia i śródreżcza. Obrzęk uznano za niewielki, jeśli różnica pomiarów wynosiła 2-4 cm, średni – 4-6 cm i duży >6 cm. Poddano analizie wielowariantowej regresji logitowej następujące czynniki, mogące mieć wpływ na wystąpienie obrzęku: wiek, lokalizację raka w piersi, stopień zaawansowania, liczbę usuniętych węzłów chłonnych, liczbę zmienionych przerzutowo węzłów chłonnych, napromienianie okolic węzłowych, chemioterapię i hormonoterapię uzupełniającą.

Wyniki. Obrzęk kończyny stwierdzono u 17 chorych (10%). U 15 z nich (88%) obrzęk był niewielki, u 1 – średnio zaawansowany, u 1 – duży. Na podstawie analizy wieloczynnikowej wykazano, że jedynie napromienianie okolic węzłowych w sposób statystycznie znamienny zwiększało ryzyko wystąpienia obrzęku.

Wnioski. Obrzęk kończyny górnej u chorych po leczeniu oszczędzającym, przeprowadzanym w Centrum Onkologii w Warszawie, występuje rzadko i nie stanowi istotnego problemu klinicznego. Zadowalające wyniki mogą mieć związek z rutynowym stosowaniem w Centrum Onkologii w Warszawie profilaktyki przeciwobrzękowej. Wyniki są porównywalne

¹ Department of Breast Cancer and Reconstructive Surgery

² Department of Rehabilitation

³ Department of Biostatistics

Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland

z danymi z piśmiennictwa. Radioterapia uzupełniająca okolic węzłowych (zwłaszcza okolicy pachy) ponad 4-krotnie zwiększa ryzyko wystąpienia obrzęku.

Key words: breast cancer, arm lymphedema, breast conserving therapy

Słowa kluczowe: rak piersi, obrzęk limfatyczny, oszczędzające leczenie piersi

Introduction

Lymphedema is the most common complication observed in patients treated for breast cancer. It is caused by the narrowing or destruction of lymphatic vessels, which may occur in the course of surgery, radiotherapy, infections and/or phlebitis.

One may discern acute and chronic lymphedema [1, 2]. The acute form is transient in character, appears during the first six weeks after surgery, lasts for some 3 to 6 months and usually disappears without treatment. The chronic form appears at some point between 6 months and many years after surgery and takes on the form of permanent cutaneous changes. The severity of lymphedema is divided into three grades – in grade I (the acute phase) edema disappears when the extremity is elevated; in grade II (the onset of the chronic phase) edema appears due to changes in the albumin/globulin ratio in the subcutaneous tissue, which in turn causes an increase in interstitial pressure and connective tissue proliferation. In grade III (the chronic phase), often referred to as elephantiasis, one observes massive edema and hardening of the extremity.

The percentage of patients with lymphedema varies in different literature reports – from 6.7% to 89% [1, 3-12]. Such discrepancies may arise from a variety of surgical modalities, from different combinations of surgery and radiotherapy and may also depend on the time gap after which the measurements were performed, counting from the termination of treatment [2]. An analysis of 1650 patients treated at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw between the years 1950 and 1970 has revealed that lymphedema was observed in 21.6% of patients after the Patey procedure, in 43.2% of patients after the Halsted procedure and in 42.4% after Urban procedure. After perioperative irradiation this ratio increased to 30.8%, 62.1% and 57.5%, respectively [4]. American authors publishing over that very time period report from 6.7% to 62.5% of cases with lymphedema [5], while British – between 41% and 70%.

After BCT lymphedema is observed in 10% of patients on average – varying between 2% and 24% and depending upon the extent of surgery, irradiation and the observation period [6-9, 11]. There exist no Polish literature reports concerning the frequency of lymphedema after BCT.

Aim

The aim of this study was to evaluate the frequency and the degree of lymphedema in breast cancer patients after

BCT and to analyse the factors which may affect the development of this complication.

Material and method

174 breast cancer patients, median age 53 years (range: 28-76 yrs) were treated according to the BCT protocol at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw between the years 1995 and 1999. Follow-up ranged between 24 and 78 months; median 50 yrs. The first stage of treatment was tumorectomy (quadrantectomy) with axillary lymphadenectomy; then the breast was irradiated conventionally; i.e. 4-6 MeV of photons or Co-60 from two tangential fields up to a total dose of 50 Gy in 25 fractions (2 Gy per fraction). Patients with invasive carcinoma received an additional boost to the tumour site of with an individually calculated electron beam or from Ir192 implantation. A majority of patients received adjuvant treatment – either chemotherapy or tamoxifen. Patients treated according to the CMF protocol (cyclophosphamide, methotrexate, fluorouracil) were irradiated during chemotherapy, while patients treated according to anthracycline containing regimens were irradiated after the completion of chemotherapy. The characteristics of patient material are presented in Table I.

Table I. Patient characteristics

No. of patients	174
Age in yrs.	28-76 mean 52
Follow-up duration in mos.	24-78
Mean	50
Median	50
Grade of clinical advancement	T0N0M0- T2N1M0
0	17
I	132
II a	21
II b	4
Tumour localisation:	
Upper external quadrant or Spence's tail	122
Other	52
Type of operation:	
Quadrantectomy and lymphadenectomy	13
Tumorectomy and lymphadenectomy	150
Tumorectomy	11
Radiotherapy:	
Breast only	164
Breast and nodal fields	10
Chemotherapy:	
Yes	47
No	127
Hormonotherapy:	
Yes	36
No	138

In the course of treatment all patients completed a course of rehabilitation training at the Dept. of Rehabilitation of the Maria Skłodowska-Curie Memorial Cancer Center.

Circumference measurements were compared on both extremities 10 cm above the lateral epicondyle, 10 cm below it and at the metacarpal level. Edema was recognized if the difference between the circumference was equal to or greater than 2 cm at least at one measurement level.

Statistical methods

Patient characteristics were presented using standard methods – mean value and standard deviation and frequency tables. The influence of the different clinical factors (patient age, tumour localization, TNM advancement, number of excised nodes, number of metastatic nodes, irradiation of nodal areas, chemotherapy and radiotherapy) on the frequency of lymphedema of the upper extremity was analysed according to a multivariate model of logit regression. Stepwise elimination allowed us to identify statistically significant factors at a level of 0.05.

Results

We observed 10% of cases of lymphedema (17/172) in patients after BCT. A majority of these – 88% (15/17) were pronounced as grade I. In 12/17 pts (70%) edema was discernible only on one measurement level. Results are presented in Table II.

We performed an analysis of the factors which could affect the development of lymphedema – age (under 50 vs over 50 yrs.); tumour localization (upper external quadrant and Spence's tail vs all other); TNM advancement; number of excised nodes (10 vs more than 10), nodal

Table II. The number of patients with lymphedema of the upper extremity – including the grade of the edema (acc. to the criteria applied at the Dept. of Rehabilitation of the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw)

Total number of patients with lymphedema	17 / 174 – 10%
Grade of edema	
I (2-4 cm difference in circumference)	15 (88%)
II (4-6 cm difference in circumference)	1
III (>6 cm difference in circumference)	1
Edema in 1 measurement	12 (70%)
Edema in 2 measurements	4
Edema in 3 measurements	1

metastases, irradiation of lymph node fields, chemotherapy and hormonotherapy. Multivariate analysis has revealed that the only factor which achieved statistical significance in its influence on the frequency of lymphedema was irradiation of the nodal fields after lymphadenectomy. Patients who were irradiated to the nodal fields had a 4.6 higher risk of developing lymphedema than patients without nodal field irradiation (chance quotient 4.62, confidence interval 1.07 to 19.88; $p = 0.040$). Patient characteristics as regarding the distribution of risk factors are presented Table III, while the results of the logit analysis are presented in Table IV.

Table III. An analysis of the factors affecting the development of lymphedema of the upper extremity in breast cancer patients after BCT

Factor	Pts without lymphedema (n = 157)	Pts with lymphedema (n = 17)
Age:		
50 yrs. and less	82 / 157 (52%)	9 / 17 (53%)
51 yrs. and over	75 / 157	8 / 17
Quadrant of the breast:		
Upper external and Spence's tail	110 / 157 (70%)	12 / 17 (70%)
Other	47 / 157	5 / 17
No. of excised lymph nodes:		
Mean	15	16
Median	15	15
Nodal metastases on histopathological examination:		
Yes	29 / 157 (18%)	5 / 17 (29%)
No	128 / 157	12 / 17
Hormonotherapy:		
Yes	30 / 157 (19%)	3 / 17 (18%)
No	127 / 157	13 / 17
Chemotherapy:		
Yes	43 / 157 (28%)	4 / 17 (24%)
No	114 / 157	13 / 17
Nodal irradiation:		
Yes	7 / 157 (5%)	3 / 17 (18%)
No	150 / 157	14 / 17

Table IV. The results of multivariate analysis – logit regression model

Risk factor of lymphedema	Chance quotient	Standard deviation	P	Confidence interval 95%
Radiotherapy of nodal fields	4.62	3.44	0.040	1.07- 19.89

Discussion

Methods applied for the measurement of lymphedema

Measurements of lymphedema of the upper extremity may be performed according to three different methods. The first method is limited to the comparison of the circumferences measured at different levels on both extremities. The second method involves the measurement of the volume of the extremities basing upon their immersion in measurement vessels filled with water. The third method bases upon the evaluation of the tonus of the skin and the subcutaneous tissue – i.e. the measurement of bioelectric resistance in the affected extremity [11, 13]. The Dept. of Rehabilitation of the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology applies the first of these methods, with measurements taken with measuring tape at three points – 10 cm above the lateral epicondyle, 10 cm below it and at the metacarpal level, excluding the thumb. The difference between the extremities is then calculated at each level.

The consistency of the edematous tissue is evaluated at different points and referred to as “soft” edema and “hard” edema. Three grades of edema are recognized – a difference in circumference of 2-4 cm is recognized as mild edema; of 4-6 cm as – moderate and over 6 cm – as severe lymphedema [14]. Some authors accept different criteria; acc. to which a difference in circumference of up to 3 cm is recognized as mild edema; of 3-5 cm as moderate and over 5 cm – as severe lymphedema, with differences in volume reported as 150-400 ml; 400-700 ml and over 750 ml, respectively [2]. When applying these criteria one must make a certain allowance for the dominant extremity which, usually, has a larger diameter.

Prevention and treatment

Due to the fact that the treatment of lymphedema is long-lasting and, in more advanced cases, achieves relatively poor results, its prevention becomes an important issue. The basic element of prophylaxis is automassage and elements of Vooder massage (lymphatic drainage) [15]. The patients are advised to take the following preventive measures: elevate the affected extremity during sleep and when resting, avoid blood pressure measurements and all kinds of injections on the affected extremity, refrain from more extreme physical exercise, avoid tight sleeves or watch straps and avoid excessive heat (hot baths, balms) and lesions (cuts, burns, insect bites etc) on the

affected extremity. Every-day physical exercise adequately chosen in view of the patient's possibilities is also an important preventive measure, as it allows to maintain complete movement in the joints and provides lymphatic drainage and circulation thanks to the muscle pump.

Kinetotherapy (movement exercises) is also a good method for the complex treatment of lymphedema, as well as various forms of massage which increase lymphatic circulation: lymphatic drainage, specialistic compression sleeves which adapt to the grade of edema (elastic sleeves), underwater whirl massage and pulsating pneumatic pressure. Surgical treatment is not very effective; its principle lie in either creating anastomoses of the lymphatic vessels into veins or on the liposuction of the edematous fatty tissue from the affected extremity [11]. Pharmacological treatment is ineffective – among the different drugs used the most popular are diuretics, flavonoids and cumarin derivatives [11].

Frequency

The frequency of the development of lymphedema in patients with breast cancer has significantly diminished over the last few years. This probably arises from the growing popularity of less extensive surgical methods and from the fact that breast cancer is now often diagnosed at an earlier stage. In patients treated with BCT the risk of lymphedema varies between 2% and 24%, approx. 10% on average [6-9, 11, 16]. According to Larson et al. 6 years after the completion of treatment in patients who had undergone BCT without axillary lymphadenectomy the risk of lymphedema is 4%; after dissection of the inferior level – only 7%, and after dissection of the three levels of axillary lymph nodes – 13%; while after dissection of the three levels of axillary lymph nodes and irradiation of the nodal fields this increases to 36% [10]. In the paper of Meric et al. the frequency of lymphedema observed 7 yrs. from treatment completion was 10% after axillary lymphadenectomy and 18% after axillary lymphadenectomy and irradiation [17]. Kwan et al. have estimated the frequency of lymphedema at 12% in a group of 744 pts. after BCT. The probability of developing lymphedema increased in patients who had undergone axillary lymphadenectomy with irradiation [18]. Voogdt et al. have evaluated a group of 465 pts, finding 2 cm differences in diameter in 26% of patients [19], while Beaulac et al. have analysed 151 patients after BCT or mastectomy without irradiation and estimated the risk of lymphedema at 27.8% [20].

In our material we observed lymphedema in 10% of patients. This is a satisfactory result when compared with literature data, all the more in view of the fact that all

patients underwent lymphadenectomy of all the three levels of axillary lymph nodes. It is also necessary to stress that in a vast majority of patients (70%) we observed differences in the diameter of the extremities only at one level, while in 88% of these patients the difference was between 2 and 4 cm. We believe that such good results arise from the fact that all BCT patients had completed a course in lymphedema prevention at the Dept. of Rehabilitation of the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw.

Risk factors

The risk factors responsible for the development of lymphedema may be divided into three groups. The first group consists of treatment-related risk factors, especially in the case of combined treatment modalities: surgery, systemic therapy and irradiation. The extent of surgery is an important element – especially within the axilla. There exists a linear relationship between the number of excised nodes (lower level vs two levels vs three levels of axillary nodes) and the probability of developing lymphedema [1, 11]. The frequency of lymphedema reaches 2-27%, at an average of 10% [16]. Irradiation of the axillary fossa after dissection of the three levels of the axillary nodes increases this risk to 12-30% [1, 12, 16, 21, 22]. Isolated irradiation of the axillary fossa without lymphadenectomy carries a 2-5% risk of lymphedema, although it appears at a later stage than in the case of isolated surgery or combined surgery and irradiation [16]. The second group of risk factors combines disease-related issues – advancement, the number of involved lymph nodes and the location of the tumour within the breast. The probability of developing lymphedema increases with the size of the primary tumour and the number of involved nodes [1, 2, 12]. The third group consists of patient-related risk factors – age [23], obesity [6], arterial hypertension, phlebitis, over-exercising the affected extremity, appearance of early lymphedema after surgery and the time laps since treatment completion [2, 11, 23]. The risk of developing lymphedema increases with the age of the patient [23], although this is not confirmed by all authors [6].

It is a common belief that of all these risk factors the most significant one is extensive surgery (especially involving the dissection of all three levels of axillary lymph nodes) combined with irradiation of the lymph node areas [16].

In our material the extent of surgery was comparable – tumorectomy and lymph node dissection of all the three levels of the axillary nodes. In the case of 10 patients irradiation involved not only the breast, but also the nodal areas and in the case of these patients there was a 4.6 times greater risk of developing lymphedema. Radiotherapy to the nodal fields was one of the seven analysed factors, which significantly increased the risk of lymphedema of the upper extremity. We did not confirm the influence of patient age, tumour size, tumour localization within the breast, the number of excised lymph nodes

and the number of metastatic nodes, chemotherapy nor hormonotherapy on the risk of developing lymphedema.

Conclusions

1. In the case of breast cancer patients treated with conserving therapy at the Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Warsaw the risk of developing lymphedema of the upper extremity is estimated at 10%. In a majority of cases (88%) the extent of lymphedema is mild.
2. The most important risk factor affecting the development of lymphedema after breast conserving therapy in this patient group is irradiation of the nodal fields.

Anna Niwińska MD, PhD

Department of Breast Cancer and Reconstructive Surgery
Maria Skłodowska-Curie Memorial Cancer Center
and Institute of Oncology
Roentgena 5, 02-781 Warsaw
Poland

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