Journal of Radiotherapy & Medical Oncology

ORIGINAL REPORT

Clinical and Therapeutical Aspects of Contralateral Breast Cancer after Treatment of Breast Neoplasm

Laura Rebegea[1,2], Dorel Firescu[2,3], Rodica Anghel[4], Mihaela Dumitru[1]

1) „Sf. Ap. Andrei" Emergency Clinical Hospital, Galati, Radiotherapy Department, Galati; 2) „Dunarea de Jos" University of Galati, Faculty of Medicine, Clinic Department, Galati; 3) „Sf. Ap. Andrei" Emergency Clinical Hospital, Galati; 4) "Prof. Dr. Alexandru Trestioreanu" Institute of Oncology, Bucharest, Romania

Purpose: identifying the potential risk factors for contralateral breast cancer, (CBC) in patients who undergo specific treatment for breast neoplasm. **Patients and methods**. This is a retrospective study and evaluates 507 patients who underwent treatment in the Radiotherapy Department of "Sf. Ap. Andrei" Emergency Clinical Hospital, Galati, between 1995 and 2002. The following parameters were taken into consideration: age of the patient at the time of treatment, disease stage, histologic type, surgical treatment, radiotherapy technique, chemotherapy and/or schemas. The relative risk (RR) for CBC was estimated for the following risk factors: hormonal therapy, age at the time of treatment, histologic type. **Results**: The median follow up was 12 years (range 9-16 years). 19 women developed CBC, out of 507 analyzed cases (3.75%). The median time of CBC occurrence was 5.22 years (range 1-12 years). The chemotherapy did not increase the risk for CBC; statistically, patients under 50 years (RR=1.35), with infiltrating ductal carcinoma (RR=1.89) and who had not received hormonal therapy (RR=0.58), presented a significantly increased rate of CBC. **Conclusions**: The administration of hormonal therapy proved to be a protection factor regarding CBC occurrence. The risk factors for CBC were the following: age under 50 years and histologic type of infiltrating ductal carcinoma. Women with breast cancer evidenced an increased risk for the second primary cancer development, not only as contralateral breast, but also in other organs (colon, ovary, thyroid, corpus uteri and malignant melanoma), thus, monitoring breast cancer patients is of major importance

Key words: contralateral breast cancer, radiotherapy

Introduction

Patients with breast cancer present an increased risk of developing second primary cancer, not only in contralateral breast, but also in other organs [1]. Many studies indicated that women with breast cancer have an increased risk of developing cancer in the ovary, colon, corpus uteri, thyroid and malignant melanoma [2].

The aim of the current study is to identify the potential risk factors for contralateral breast cancer (CBC), in women who performed specific treatment for breast cancer.

Patients and methods

We included, in this retrospective study, 507 breast cancer patients that received external radiotherapy, between January 1995 and December 2002, at Radiotherapy Department of „Sf.Ap.Andrei" Emergency Clinical Hospital, Galati.

For the purpose of this study, contralateral breast cancer was considered to be the cancer that occurs at over 3 months after the primary breast cancer diagnosis.

89.74% of cases were treated with chemotherapy. The chemotherapy scheme was CMF (Ciclofosfamide 600mg/m^2 day 1, Methotrexate 40mg/m^2 day 1, 5FU 600mg/m^2 day 1), FAC (5FU 600mg/m^2 day 1, Doxorubicin 60mg/m^2 i.v. day 1, Ciclofosfamide 600mg/m^2 day 1) and EC (Epidoxorubicine 80 mg/m^2 i.v. day 1, Ciclofosfamide 600mg/m^2 day 1), in 43.98%, 34.71% (176 patients) and respective 11.05% (56 patients) of cases. A number of 52 patients (10.26%) did not undergo chemotherapy. 328 women received hormonal therapy with Tamoxifen; against the 35.31% that did not receive this particular treatment hormonal therapy was administrated in a dose of 20mg/day, for a period of 2-5 years.

Radiotherapy was performed at Rokus M40 and Theratron Elite 100 units. The chest wall or mammary gland was irradiated throughout two tangential opposed fields, including internal mammary lymph nodes. The radiotherapy technique included the exposure of supraclavicular and axillary lymph nodes throughout anterior axillary-

Journal of Radiotherapy & Medical Oncology
December 2013 Vol. 19 No 2: 45-48
Address for correspondence: Laura Rebegea
„Sf.Ap.Andrei" Emergency Clinical Hospital, Galati, Radiotherapy Department, Brailei St. 177, 800830 Galati Romania
Email: laura_rebegea@yahoo.com

supraclavicular field and posterior axillary field. The head of the humerus and larynx were shielded from the radiation beam with lead blocks. The prescribed doses were TD = 50 Gy/25 fractions /30-35 days in 436 cases (86.0%) or TD = 40Gy /20 fractions / 25 days in 66 patients (13.02%). Higher doses >50 Gy were received by 5 patients (1.0%).

The Cox proportional hazards regression model was used to estimate the relative risk of developing CBC; all reported p values were two sided and considered statistically significant if $p<0.05$.

Results

Clinical and therapeutical parameters of the studied population are shown in table I. The mean age of the patients included in the study was 56 years old (range 25-89 years). Histology of ductal carcinoma was present in 92.7% of the cases (470 patients), followed by lobular and medullary carcinoma, each present in 15 cases (2.96%), papillary carcinoma (0.99%) and tubular (0.4%). Radical surgical treatment (total mastectomy with axillary clearance), conservatory breast surgery, and respective simple mastectomy was performed on 259 patients (51.08%), 147 patients (28.99%), and respectively 55 women (10.85%), 9.07% of the cases did not undergo surgical treatment.

Median follow up was 12 years (range 9-16 years), 19 cases developed CBC, out of 507 patients. Median time for CBC development was 5.22 years (range 1-21 years). Clinical parameters of CBC patients are given in Table II. Mean age at the time of diagnosis of second breast cancer was 58 years (range 36-89 years).

Table I. Clinical and therapeutically parameters

Parameters	Nr. patients (%) N = 507
Mean age (years) (range)	56 (25-89
Hystologic type	
Ductal	470 (92.7)
Lobular	15 (2.96)
Medullary	15 (2.96)
Papillary	5 (0.99)
Tubular	2 (0.4)
Surgical treatment	
radical treatment, mastectomy with clearance axillary	259 (51.08)
conservative treatment	147 (28.99)
simple mastectomy	55 (10.85)
without surgical treatment	46 (9.07)
Chemotherapy	
CMF[1]	223 (43.98)
FAC or FEC[2]	176 (34.71)
EC[3]	56 (11.05)
without chemotherapy	52 (10.26)
External beam radiotherapy	
two tangential fields + internal mammary + anterior axillary-supraclavicular field + posterior axillary field	502 (99)
two tangential fields + internal mammary	5 (1)
Total doses prescribed	
40 Gy	66 (13.02)
50 Gy	436 (86.0)
> 50Gy	5 (1.0)
Hormonal therapy	
Tamoxifen	328 (64.69)
without hormonal therapy	179 (35.31)

1-CMF=Ciclofosfamida 600mg/m^2 day 1, Metotrexat 40mg/m^2 day 1, 5FU 600mg/m^2 day 1); 2-FAC=5FU 600mg/m^2 day 1, Doxorubicin 60mg/m^2 i.v. day 1, Ciclofosfamida 600mg/m^2 day 1); 3-EC = Epidoxorubicina 80 mg/m^2 i.v. day 1, Ciclofosfamida 600mg/m^2 day 1.

Table II. Clinical and therapeutical parameters of CBC patients

Parameters	Nr. patients (%) N = 19
Mean age (years) (range)	58 (36-89)
Histologic type	
Ductal	15 (78.95)
Lobular	3 (15.79)
Medullary	1 (5.26)
Papillary	0
Tubular	0
Surgical treatment	
radical treatment, mastectomy with clearance axillary	5 (26.32)
conservative treatment	4 (21.05)
simple mastectomy	2 (10.53)
without surgical treatment	8 (42.11)
Chemotherapy	
CMF[1]	8 (42.11)
FAC or FEC[2]	4 (21.05)
EC[3]	2 (10.53)
without chemotherapy	5 (26.32)
External beam radiotherapy	
two tangential fields + internal mammary + anterior axillary-supraclavicular field + posterior axillary field	15 (78.95)
two tangential fields + internal mammary	4 (21.05)
Total doses prescribed	
40 Gy	2 (10.53)
50 Gy	17 (89.47)
Hormonal therapy	
Tamoxifen	16 (84.21)
without hormonal therapy	3 (15.79)

1-CMF=Ciclofosfamida 600mg/m^2 day 1, Metotrexat 40mg/m^2 day 1, 5FU 600mg/m^2 day 1); 2-FAC=5FU 600mg/m^2 day 1, Doxorubicin 60mg/m^2 i.v. day 1, Ciclofosfamida 600mg/m^2 day 1); 3-EC = Epidoxorubicina 80 mg/m^2 i.v. day 1, Ciclofosfamida 600mg/m^2 day 1

Histology of ductal carcinoma was present in 78.95% of the cases (15 patients), followed by lobular carcinoma which developed in 3 cases (15.79%) and medullar carcinoma presented in 1 case (5.26%). Histology of papillary and tubular carcinoma was not found in CBC patients. For the second breast malignancy in contralateral breast, radical surgical treatment (total mastectomy with axillary clearance), conservatory breast surgery, and simple mastectomy was performed on 5, 4 and respectively 2 patients; 42.11% of cases (8 patients) did not undergo surgical treatment.

Chemotherapy was performed on 73.68% of the cases. The chemotherapy schemes were: CMF on 42.11% of the patients, FAC on 21.05% of the cases and EC on 10.53% of the cases. A percentage of 26.32% of patients did not undergo chemotherapy. 84.21% of CBC women received hormonal therapy with Tamoxifen, in contrast with 35.31% of the patients, who did not receive the treatment.

All CBC patients performed external radiotherapy at the same radiotherapy units and conforming to the same techniques ; for CBC patients, the following fractionation scheme was administered: TD = 45 Gy/22 fractions /27-28 days, and TD = 50Gy/25 fractions /30-35 days for 17 patients.

Estimation of relative risk highlighted the risk factors for CBC development. The age under 50 years at the moment of first primary cancer diagnosis represents a risk factor statistically significant (RR=1.35, p=0.02) (Table III).

Histology of ductal carcinoma was also a risk factor, but without significance (RR = 1.89, p = 0.32). Total radiation doses of 50 Gy and, respective > 50Gy were found to be risk factors without an important impact for CBC development (RR = 1.3, p=0.4 and respective RR=1.9, p=0.8).

The relative risk for CBC development at 40 Gy was smaller in comparison with the relative risk for CBC development at higher irradiation doses (50Gy and >50Gy); the differences were considered irrelevant, from a statistical point of view (RR = 0.8, p=0.46).

Table III. Relative risk for CBC development

Risk factors	RR	p
Age		
< 50 years	1.35	0.02
≥ 50 years	1	
Histology		
ductal	1.89	0.32
Hormonal therapy		
Yes	0.27	0.03
No	0.58	
Delivered doses		
40 Gy	0.8	0.46
50 Gy	1.3	0.8
> 50 Gy	1.9	0.4

The hormonal therapy represented a protector factor with significance for CBC development (RR=0.27, p=0.03).

Discussions

There are many studies which show that breast cancer patients present a very high risk for second cancer development. The study performed by Budhi Singh Yadav et al. [3] on 1084 breast cancer patients indicates the contralateral breast cancer (CBC) presence in 4% of the cases; the incidence rate of CBC at 15 years was 9.5%. In specialized literature, the incidence rate of CBC at 15 years, varies between 9.1 and 14% [4, 5]. An epidemiological study of Chen et al [6] reported that between 2 and 11% of breast cancer women will develop CBC during their life time. Breast cancer patients present a risk of 2-6 times higher of developing CBC in comparison with the general population of patients who develop a primary tumor.

It is well known that during the breast cancer radiotherapy, the contralateral breast receives a radiation dose of 0.5 – 4 Gy, corresponding to 1 – 8% of the total administrated dose of 50 Gy [7, 8, 9]. Boice et al [9] has demonstrated that a dose of 7.1 Gy received by the contralateral breast is sufficient for breast cancer to occur [10].

Radiation exposure at a young age can initiate cancerogenesis because of mutational negative effects, which, in time, and in combination with promotional factors (estrogen) can cause breast cancer to develop. On the contrary, radiation exposure in postmenopausal patients is not followed by hormonal change and does not develop in breast cancer

In the literature, there are conflicting studies, regarding the influence of age, at the time of the first tumor site diagnosis upon CBC occurring. Thus, the studies performed by Budhi Singh Yadav et al. [3], Boice et al. [9], Mariana et al. [12] and Kurtz et al. [13] identified the age under 45 years as being a risk factor for CBC development in the case of patients undergoing radiotherapy.

Boice et al [9] found that radiotherapy was involved in a relative risk increasing by a factor of 1.9 for CBC development, for women under 45 years The study of Budhi Singh Yadav et al. [3] performed in 2003, indicated that radiotherapy plays a minor role in CBC occurring in postmenopausal patients, but women under 45 years of age which performed radiotherapy for primary breast cancer, presented a higher risk for CBC development.

Also, there are studies which affirm that the age under 55 years, at the moment of the first breast cancer diagnosis is associated with an increased risk of CBC development. These are the studies of Broet et al [11] from Cuire Institute and the studies of Gao et al. [4] which reported that not only ages <45 years present an increased risk for CBC development [RR = 1.32] but, patients > 55 years have also, an increased risk of developing CBC [RR = 1.15].

Other analyzed risk factors in the literature for CBC are family history, histological type, chemotherapy and hormonal therapy.

A limit to our study is the lack of family history and comorbidities analysed as risk factors for CBC development.

Family history of breast cancer was an important potential risk factor for CBC in the study of Budhi Singh Yadav et al. [3]. The 15 years risk for CBC development in patients with family history of breast cancer was 12.4%. In varied analyses performed by Storm et al [14], the family history, nulliparity and obesity were discovered to be favorable factors for contralateral cancer, without any change in the estimation of radiotherapy-induced risk.

The patients with lobular carcinoma histology present a high risk for CBC development [15,16]. The study of Budhi Singh Yadav [3] evidenced that women with medullary carcinoma had a risk for CBC of 15% higher than patients with infiltrative ductal carcinoma. Gao's et al [4] study also showed an 18% increased risk for CBC for patients with medullary carcinoma in comparison with patients with infiltrative ductal carcinoma.

Another study confirmed that the hormonal therapy with Tamoxifen reduces the risk of CBC development [17]and the chemotherapy does not influence in a negative way the CBCdevelopment .

Budhi Singh Yadav's et al research on 1084 patients evidenced that breast cancer radiotherapy does not have a significant effect upon CBC incidence. The breast cancer family history and later age of the first birth of a child are important risk factors for CBC incidence, while hormonal therapy reduces the risk of CBC. The premenopausal status and the age under 45 years at the time of diagnosis of the primary breast cancer, represent also, other risk factors.

Conclusions

The study reveals that the age < 50 years represents a risk factor in the occurrence of CBC. Moreover, hormonal therapy with Tamoxifen, having a protection effect, reduces the risk of patients developing CBC. Chemotherapy does not represent a risk factor for the development of a second malignancy. The follow-up of the primary breast cancer appearance in patients is of major importance for identifying or preventing relapses and, also, for CBC diagnosis.

Our aim for future studies is to analyse the family history of cancer and radiotherapy technology as risk factors for CBC incidence. The modern treatment procedures increase the survival rate on one hand, but on the other hand, enhance the risk of a second malignancy or contralateral breast cancer to appear, none having to be overseen.

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