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Second malignancies following conventional or combined ^{252}Cf neutron brachytherapy with external beam radiotherapy for breast cancer

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We retrospectively evaluated the risk of second malignancies among 832 patients with inner or central breast cancer treated with conventional external beam schedule (CRT group), or neutron brachytherapy using Californium-252 (^{252}Cf) sources and hypofractionated external beam radiotherapy (HRTC group), between 1987 and 1996 at the Institute of Oncology, Vilnius University. Patients were observed until the occurrences of death or development of a second malignancy, or until 31 December 2009, whichever was earlier. Median follow-up time was 10.4 years (range, 1.2–24.1 years). Risk of second primary cancers was quantified using standardized incidence ratios (SIRs). Cox proportional hazards regression models were used to estimate hazard ratios (HRs). There was a significant increase in the risk of second primary cancers compared with the general population (SIR 1.3, 95% CI 1.1–1.5). The observed number of second primary cancers was also higher than expected for breast (SIR 1.8, 95% CI 1.3–2.4) and lung cancer (SIR 3.8, 95% CI 2.0–6.7). For second breast cancer, no raised relative risk was observed during the period ≥10 or more years after radiotherapy. Compared with the CRT group, HRTC patients had a not statistically significant higher risk of breast cancer. Increased relative risks were observed specifically for age at initial diagnosis of <50 years (HR 2.9, 95% CI 1.6–5.2) and for obesity (HR 2.8, 95% CI 1.1–7.2).

Keywords: second cancer; breast cancer radiotherapy; ^{252}Cf neutron brachytherapy

INTRODUCTION

Breast cancer is the commonest cancer and the major cause of cancer-related mortality among women worldwide [1]. One of the most serious events experienced by cancer survivors is the diagnosis of a new cancer. 12–26% of cancer survivors aged >60 years were diagnosed more than once with another cancer [2]. With major improvement of long-term survival, the long-term risks from treatments, including the risk of developing a second cancer after radiotherapy, becomes more significant [2, 3]. Previous trials have shown that most second cancers have a long latency, and the second cancers worsen survivorship in patients who have survived breast cancer [3–5]. Most radiation-associated second cancers develop within or at the edge of the radiation field [6–8]. The risk of occurrence is related to the amount of dose deposited in specific organs, inherent tissue sensitivity and the age at irradiation [9, 10]. Some animal and human data suggest a decrease at higher doses, usually attributed to cell killing. Other data suggest that small radiation doses to the organs located far from the tumor volume can induce secondary cancers as well [11]. Radiation to the breast can induce a wide spectrum of histological types of tumors, including sarcomas, carcinomas of thyroid, esophagus, lung and breast, as well as some types of leukemia and lymphomas [9, 10]. Some recent research has shown that the characteristics of radiation types such as neutrons, protons, photons and electrons differ, with respect to individual cancer susceptibility and types of interactions with tissues [11, 12]. Improved understanding of treatment-related malignancies should result in the formulation of customized therapeutic approaches. Knowledge is therefore required concerning the second primary cancer risk associated with neutron radiotherapy in breast cancer

patients. We have collected retrospective data on hypofractionated EBRT with postoperative intraluminal brachytherapy using ^{252}Cf sources for internal mammary lymph nodes.

The aim of this cohort study was to evaluate the risk of second primary cancers in a group of patients treated with hypo-fractionated preoperative ionizing radiation therapy and brachytherapy using ^{252}Cf sources for breast cancer in comparison with patients treated with conventional ionizing radiation therapy.

MATERIALS AND METHODS

Between 1987 and 1996, 991 female patients with operable breast cancer of inner or central breast site were treated at our institution. All patients underwent surgical resection (either radical mastectomy or breast conserving), received adjuvant systemic, and radiation therapies (either conventional or combined hypofractionated external and internal radiotherapy) at the Institute of Oncology, Vilnius University during the period January 1987 to December 1996. Eligibility criteria for the study included female gender, histologically confirmed diagnosis, no prior breast carcinoma, nor diagnosis of cancer of any type, and no distant metastases. Patients with two cancers at different sites diagnosed on the same day or patients with cancers occurring within 1 year of the initial cancer were excluded from the standardized incidence analysis. Accordingly, 832 female patients met the criteria and were entered into this study.

Information about surgery, radiotherapy, chemotherapy and hormonal therapy was abstracted from registry records, and oncology clinic records. The following data were collected: age at initial diagnosis, clinical stage of first breast cancer, pathological report, primary tumor treatment, the occurrence of second cancers, time interval between the primary tumor and second cancer, patient status, height and weight.

The schedule of radiotherapy was divided into two groups. Of the 832, 621 patients (74.6%) received 2.0 Gy daily fractions for 25 fractions to a total dose of 50 Gy to the treated breast, and was designated the conventional (CRT) group. A cohort of 211 patients underwent preoperative hypofractionated external beam radiotherapy EBRT (7 Gy twice or 4–5 fractions by 5 Gy), postoperative EBRT (10–14 Gy by 2 Gy daily) and brachytherapy by ^{252}Cf sources, and was designated the HRTC group. ^{252}Cf neutron sources were indicated for patients with inner and central breast-located tumors after surgery. On the first or second post-operative day, two flexible ^{252}Cf sources with active length of 60 mm and with total activity 5–15 μg of ^{252}Cf were inserted into the catheters. An empirical radiobiological model by Ryabukhin was used for the isoeffective doses (Gy eq) of ^{252}Cf brachytherapy [13]. A relative biological effectiveness for late and early normal tissue damage (RBE) of 5.5–6.8 was used for calculating the equivalent dose. The irradiation dose at a distance of 1 cm from the centre of the sources was in the range 34–40 $Gy_{eq,}$ (median 40 Gy_{eq}) ~ 42–96 hours. More detailed information about the treatment has been published elsewhere [14].

Adjuvant treatment consisted of cyclic administration of CMF (cyclophosphamide; methotrexate; 5-fluorouracil) in 52 patients, FAC (5-fluorouracil, doxorubicin, cyclophosphamide) in 79 patients, and AC [adriamycin (doxorubicin) and cyclophosphamide] in 40 patients. A total of 351 women (42.2%) received of tamoxifen for 3–5 years. Adjuvant tamoxifen was generally considered for postmenopausal, hormone receptor-positive patients with node-positive or high-risk node-negative disease. Based on the values for height and weight, body mass index was computed as weight in kilograms divided by the squared value of height in meters (kg/m^2). Body mass index was categorized to be consistent with the World Health Organization obesity classification: <25 kg/m^2 (normal), 25–29 kg/m^2 (overweight), ≥30 kg/m^2 (obese). The first coding grouped 'normal weight' and 'overweight' whilst the second coding defined obese patients using 30 kg/m^2 as a cut-off. Information regarding hormone receptor status was not available for >49% of the patients. Estrogen receptor and progesterone receptor status were therefore not included in our analysis.

Follow-up

The follow-up time (person-years at risk) for second cancers for each individual began one year after the date of initial cancer diagnosis and ended at the date of diagnosis of any second malignant cancer, last known vital status, death or the end of study (31 December 2009), whichever occurred first. Follow-up for second malignancies was mainly conducted through direct contact with the patients at regular visits at out-patient clinics. For this study data were collected retrospectively. The information on second malignancies (coded according to the ICD-9) was collected from the Cancer Registry of the Institute of Oncology, Vilnius University, by record linkage to the database. The Cancer Registry of the Institute of Oncology, Vilnius University has kept information on date of diagnosis, histology, stage and death for all patients in Lithuania since 1978. The occurrence of any subsequent cancer was ascertained by pathology, reports, hospital or physician records, or death certificates. Pathology reports confirmed 82.5% of second breast cancers cases. During the follow-up period, the vital status of each subject was determined using resident registration records available from the Lithuanian Death and Population Registers, and causes of death were confirmed by death certificate at the Archives Department under the government of the Republic of Lithuania. The median follow-up time (person-years at risk) among surviving

CRT patients was 10.4 years (range, 1.2–24.1 years), and 10.1 years (range, 1.0–21.8 years) for HRTC patients. After 8297 person-years of follow-up, there were 532 (63.9%) deaths: 447 (53.7%) from the first breast cancer, 55 (6.6%) from the second primary cancer and 30 (3.6%) from other causes.

This examination of retrospective data was approved by the Regional Biomedical Research Ethical Committee in Vilnius (2008-09-03, No. 52).

Statistical methods

For the purpose of this study, second malignancies were defined as a second breast malignancy or any non-breast malignancies. Excess risk during the first one year after first cancer diagnosis suggests a surveillance bias. Therefore, incidence calculations were excluded for the first 12 months after the initial breast cancer diagnoses.

External comparisons

To obtain standardized incidence ratios (SIRs) of subsequent cancers following diagnosis of breast cancer, we computed person-years at risk in each cohort and applied appropriate female population-based cancer incidence rates. For a given subsequent cancer site, person-years at risk were calculated from the date of diagnosis of breast cancer to the date of microscopically-confirmed diagnosis of second primary cancer at the specified site, or to the exit date, or date of death, whichever was earlier. SIR was calculated as the ratio of the observed number of second cancer cases divided by the expected numbers as estimated by applying the appropriate numbers of person-years at risk to incidence rates of general population specified by site, 5-years age groups and calendar year groups [15]. We examined effect modification of the risk associated with radiotherapy over time-since-initial-diagnosis. Poisson-based 95% confidence intervals (CIs) were calculated.

Internal comparisons

Cox regression analysis, accounting for competing risks, was used to examine the effect of initial treatment on second breast and non-breast cancers [16]. Initial treatment was entered into the model using three separate binomial variables (yes vs no) for chemotherapy, hormonal therapy, and type of radiotherapy (HRTC vs CRT). We considered several variables as potential covariates, including the age at surgery, stage of initial breast cancer, menopausal status, lymph node metastasis, BMI. All *P*-values were based on two-sided tests and, if < 0.05, considered statistically significant. All statistical analyses were performed using SPSS 19.0 for Windows (IBM Corporation, Somers, NY, USA).

RESULTS

The selected background characteristics of the study subjects are shown in Table 1. The median age at initial diagnosis (first primary cancer) was 53.4 years. The age distribution at initial diagnosis of the first primary breast cancer, the presence of lymph nodal metastasis, chemotherapy, and menopausal status were similar in both treatment groups ($P = 0.40$, $P = 0.29$, $P = 0.12$, respectively). During

Table 1. Selected clinical characteristics of study subjects by radiotherapy for breast cancer

Characteristic	HRTC *n* (%)	CRT *n* (%)	*P* value
Age at diagnosis (y)			
≤49	76 (36.0)	252 (40.6)	
50–59	54 (25.6)	177 (28.5)	
≥60	81 (38.4)	192 (30.9)	0.153
Mean (y, SD)	54.6 (10.8)	53.0 (11.1)	0.914
Stage			
I–II	175 (82.9)	442 (71.2)	
III	36 (17.1)	179 (28.8)	0.02
Tumor size, cm			
0–2	41 (19.4)	254 (40.9)	
>2	170 (80.6)	367 (59.1)	<0.001
Lymph nodal metastasis			
None	76 (36.0)	227 (36.6)	
Yes	135 (64.0)	394 (63.4)	0.40
Menopausal status			
Premenopausal	71 (33.6)	247 (39.8)	
Postmenopausal	140 (66.4)	374 (60.2)	0.12
Body mass index (kg/m^2)			
<25	108 (51.2)	277 (44.6)	
25–29	82 (38.9)	245 (39.5)	
≥30	21 (9.9)	99 (15.9)	0.016
Chemotherapy			
No	93 (44.1)	240 (38.6)	
Yes	118 (55.9)	381 (61.4)	0.29
Tamoxifen			
No	140 (66.4)	341 (54.9)	
Yes	71 (33.6)	280 (45.1)	0.15
Person-years at risk	2012	6285	

HRTC = hypofractionated radiotherapy with ^{252}Cf intraluminal neutron therapy, CRT = conventional radiotherapy.

Table 2. Frequency of second primary cancers according to treatment group

Site of second primary cancers	HRTC		CRT	
	No. of events	%	No. of events	%
Total	35	100.0	116	100.0
Breast	12	34.3	36	31.0
Non-breast	23	65.7	80	69.0
Lung	0	0.0	12	10.3
Gastrointestinal	4	11.4	20	17.2
Gynecological	7	20.0	32	27.6
Skin	6	17.1	3	2.6
Thyroid	2	5.7	0	0.0
Urinary	1	2.9	7	6.3
Hematological/lymph system	0	0.0	3	2.6
Other	3	8.6	3	2.6

HRTC = hypofractionated radiotherapy with ^{252}Cf intraluminal neutron therapy, CRT = conventional radiotherapy.

the follow-up period a total of 151 second primary cancers were identified. The median time interval between the initial diagnosis and that of the second primary cancer was 7.4 years (range, 3–24 years). All second primary cancers identified are shown in Table 2. The most common types of second non-breast cancer malignancies were gynecological malignancies (39 cases, 25.2%) and gastrointestinal cancers (24 cases, 15.9%). The total numbers of second primary cancers were 112 in CRT patients and 38 in HRTC patients. Extremely rare mediastinum cancer occurred among patients who received hypofractionated radiotherapy with HDR-brachytherapy for internal lymph nodes using ^{252}Cf sources, and one case of mediastinal lymphoma occurred for a CRT-treated patient > 20 years after radiotherapy. The age-adjusted incidence rate for second breast malignancies was 6 per 1000 person-years, and 15 cases per 1000 person-years of other primary cancer malignancies.

Table 3 shows the observed and expected numbers of breast, lung, stomach and other sites of cancer with corresponding standardized incidence ratios (SIRs). A higher than expected number of second primary cancer was observed in all patients given combined therapy compared with the general female population (SIR 1.3, 95% CI 1.1–1.5). The observed number of second primary cancers was also higher than expected for lung (SIR 3.8, 95% CI 2.0–6.7) and stomach cancer (SIR 2.0, 95% CI 1.0–3.4). There was a significantly elevated risk of second primary breast cancer (SIR 2.1, 95% CI 1.4–2.9) in the first 9 years after diagnosis. The SIR of lung cancer was 4.7 in the first 9 years after diagnosis, and 3.4 for ≥10 years after diagnosis.

The effect of radiotherapy adjusted for covariates of second primary cancer, and the prognostic significance of individual covariates, are shown in Table 4. After adjusting for chemotherapy, hormonal therapy and other potentially confounding factors, HRTC patients had a higher risk of breast cancer (HR 1.2, 95% CI 0.6–2.3), though this was not statistically significant. This group had the same risk of other second primary cancers as CRT patients (HR 0.9, 95% CI 0.5–1.4). In tamoxifen-treated women, there was a decreased risk of second breast cancer (HR 0.4, 95% CI 0.2–1.1; $P = 0.06$) and a non-significant increase of other cancer (HR 1.3, 95% CI 0.8–1.9; $P > 0.05$). The patient's age at treatment time plays a major role. Age at initial diagnosis of < 50 years was associated with an increased risk of second breast cancer (HR 2.9, 95% CI 1.6–5.3, $P = 0.001$). Obesity was also associated with an increased risk of second breast primary cancer during long-term follow-up (HR 2.8, 95% CI 1.1–7.2, $P = 0.04$).

DISCUSSION

Our study quantified the risk of second primary cancers in a clinical records-based cohort of breast cancer survivors treated with surgery, and compared two different radiotherapy schedules. Our analyses confirmed that the risk of all second primary malignancies and breast cancers is higher for breast cancer patients compared with that of the general female population. Raised risks of breast cancer have been reported in various studies of women exposed to radiation [17–19]. In agreement with several prior studies, increased risks were also seen for lung and stomach cancer [3, 5]. In our analysis, the raised risk for second breast cancer was not statistically significant during the period of ten or more years after radiotherapy. A similarly decreased incidence ratio with the duration of follow-up has been reported in other studies [20, 21]. These variations are probably partly explained by the selection of the populations studied, which mostly excluded patients with a high risk of early contralateral breast cancer [20]. The risk of second primary cancers was similar after conventional and hypofractionated external beam radiotherapy with brachytherapy by ^{252}Cf sources after adjustment for age, lymph nodal metastasis, chemotherapy, hormonal therapy and other potentially confounding factors. It can also be argued that some of the second cancers might have occurred due to factors other than radiotherapy, such as genetic predisposition, endogenous hormones, combination of treatment modalities, genetic predisposition toward cancers or treatment, and external factors such as lifestyle. We did not have information on genetics, lifestyle or reproductive risk factors for breast

Table 3. Observed and expected numbers of selected second primary cancers, and standardized incidence ratios with 95% CIs in patients with breast cancer diagnosed by follow-up interval after first diagnosis of breast cancer

Second primary cancer site	<10 years			≥10 years			Total		
	O	E	SIR (95% CI)	O	E	SIR (95% CI)	O	E	SIR (95% CI)
Total	74	53.2	1.4 (1.1–1.7)	77	61.59	1.2 (1.0–1.6)	151	114.79	1.3 (1.1–1.5)
Breast	34	16.38	2.1 (1.4–2.9)	14	10.13	1.4 (0.8–2.3)	48	26.51	1.8 (1.3–2.4)
Lung	5	1.07	4.7 (1.5–10.9)	7	2.08	3.4 (1.4–6.9)	12	3.15	3.8 (2.0–6.7)
Stomach	7	2.46	2.8 (1.1–5.9)	5	3.63	1.4 (0.5–3.2)	12	6.09	2.0 (1.0–3.4)
Other	28	33.29	0.8 (0.6–1.3)	51	45.12	1.1 (0.8–1.5)	79	78.41	1.0 (0.8–1.3)

SIR = standardized incidence ratio, O = observed numbers of second primary cancers, E = expected numbers of second primary cancers.

Table 4. Multivariate Cox regression analysis of association of breast cancer treatment and risk of second breast or non-breast cancers, adjusted for competing risk

Characteristic	Second breast cancer		Second non-breast malignancies	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Radiotherapy				
HRTC vs CRT	1.2 (0.6–2.3)	0.30	0.9 (0.5–1.4)	0.56
Age				
<50 years vs ≥50	2.9 (1.6–5.2)	0.001	0.4 (0.2–1.2)	0.11
Lymph nodal metastasis				
yes vs no	0.8 (0.3–1.7)	0.97	1.1 (0.7–1.5)	0.66
Menopausal status				
pre- vs postmenopausal	1.5 (0.3–3.2)	0.53	0.9 (0.4–2.00)	0.76
Body mass index				
≥30 kg/m^2 vs < 30 kg/m^2	2.8 (1.1–7.2)	0.04	1.4 (0.9–2.3)	0.13
Chemotherapy				
yes vs no	0.6 (0.3–1.2)	0.13	1.1 (0.7–1.5)	0.76
Tamoxifen therapy				
yes vs no	0.4 (0.2–1.0)	0.06	1.3 (0.8–1.9)	0.34

HR = hazard ratio, CI = confidence interval, HRTC = hypofractionated radiotherapy with ^{252}Cf intraluminal neutron therapy, CRT = conventional radiotherapy.

cancer. Women with breast cancer at a young age are more likely to be genetically predisposed to breast cancer ,and they have a greater susceptibility to radiation-induced cancer [22, 23]. The etiology of stomach cancer includes causes such as *Helicobacter pylori* infection (for distal gastric cancer but not for cardia cancer), dietary imbalance, smoking and genetic factors. Previous studies have shown that the genetics of stomach cancer are likely to be similar to breast and colon cancers: breast carcinomas are increased in BRCA1and BRCA2 mutation carriers, who also have an increased risk of gastric carcinoma [24, 25].

The other potential explanation for the difference in risk between cancer survivors and the general population is that some factors may not be comparable between the two groups. Although the relative risks were based on calculations matched by age group and time period, it is possible that other qualities, such as socioeconomic status, may vary between people who have been diagnosed with cancer and those who have not. Schottenfeld cautioned that the diagnosis of a second primary cancer may be subject to lead-time bias because cancer patients are under closer medical surveillance than the general population, which

may result in an inflation of SIRs of second primary cancer [19]. Conventional treatment for invasive breast cancer includes high concentrated doses of radiation to the chest wall and to the regional lymph nodes. Most investigators have attributed the increased risk to post-mastectomy radiotherapy, which typically delivers high radiation doses to thoracic organs [26]. Smoking may further heighten the risk of radiation-related lung cancer [27]. The carcinogenic effects of radiation on the lung may be synergistic with the carcinogenic effects of cigarette smoking.

Studies in experimental animals show sufficient evidence that exposure to neutrons increases the incidence of myeloid leukemia, malignant lymphoma, mammary tumors, lung carcinomas, subcutaneous fibrosarcomas, basal cell tumors of the skin, and malignant lymphoma in experimental animals [28–30]. There are only a small number of facilities for neutron beam therapy in the world, which has led to a limited number of scientific studies, and difficulty in comparing outcomes due to the variation in the delivery of neutron beam therapy. The majority of the patients were treated for cancer of the uterine cervix, prostate, or head and neck. Studies of patients treated with neutrons are limited and difficult to evaluate due to the small numbers of survivors and the complex dosimetry, often combined with X-rays and chemotherapy agents**.** Recently, MacDougall *et al*. (2006) conducted a review of long-term follow-up sites in Scotland, UK, of fast-neutron therapy for various cancers among 620 patients [31]. Three cases of sarcoma, developing within the treatment volume, were observed among patients treated some years earlier using fast neutrons. This incidence was 111 times what would have been expected in the normal population, and 15 times the incidence in a comparable photon-treated group of patients. The present study is small and its dosimetry is not detailed enough to establish an exact dose-response for each part of the body. The shape of the dose-response curve is uncertain for cancer effects. Neutron ionizing radiation often produces downwardly curving dose-responses, where the risk initially grows with dose, but eventually stabilizes or decreases (inverse dose-rate effect) [32]. In contrast with an inverse dose-rate effect with neutron exposure, γ-rays in the same mouse strain produce a relatively linear dose-response.

In our study a protective effect against risk of second breast cancer was observed when radiotherapy was combined with hormonal (tamoxifen) therapy . Most clinical trials in the past decade have demonstrated an approximately 39–50% decrease in the risk of subsequent breast cancers in women treated with tamoxifen compared with those patients receiving radiotherapy alone [33]. Previous data suggest that tamoxifen is selectively effective in preventing ER-negative second primary cancers in both BRCA1 and BRCA2 carriers [34, 35].

Our analyses also suggest that higher body-mass index (≥30 kg/m^2) is associated with an increased risk of second breast cancer. This finding is consistent with other reports on this topic. Dietary factors, including obesity, a diet low in fruit and vegetables, and a diet high in fat, accompanied by low physical activity have been related to the occurrence of a large number of cancers in the general population [36], and they also seem to account for second primary malignancies involving the breast, female reproductive organs, and lower and upper digestive tract [37]. Obese breast cancer patients had approximately a 2-fold greater hazard of contralateral breast tumors relative to underweight/normal-weight women [36, 37]. Li *et al*. presumed in their report that the mechanisms through which obesity is likely to increase the risk of contralateral breast cancer involve modification of estrogen levels [38]. In addition, there is growing data to suggest that hyperinsulinemia may also be an important contributor to the relationship between obesity and breast cancer [39]. The effective radiation dose is used as an approximate indicator of potential detriment from ionizing radiation. It was estimated that effective dose acquired from computed tomography increased with increasing BMI and increasing amounts of intra-abdominal fat [40]. The increased dose per procedure to overweight individuals is exacerbated by the fact that overweight and obese subjects experience a greater number of health problems and use a greater number of medical services, including radiologic examinations. Additional studies are needed to establish whether the association is due to shared genetic and lifestyle risk factors, and treatment of the first cancer.

When interpreting our results, one must consider the limitations and strengths of the study. The limitations of this study include the unavailable data on potentially confounding factors such as past and present smoking status, alcohol use, endogenous hormones, genetic predisposition and environmental exposures. The relatively small number of patients in our study also does not allow sufficient statistical power to accurately evaluate long-term effects of treatment. Despite these limitations, the major strengths of our study include the long-term follow-up and use of both clinical records and cancer registry data. Strengths of our clinical trial data include the availability of detailed information for protocol therapies, and the potential for direct comparisons between treatment efficacy and second cancer risk**.** To our knowledge, this is the first retrospective cohort study quantifying the risk of second malignancies after combined radiotherapy of external and internal radiotherapy using ^{252}Cf for breast cancer.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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