Journal of Cancer Therapy, **2012, 3, 768-776**
http://dx.doi.org/10.4236/jct.2012.325096 Published Online October 2012 (http://www.SciRP.org/journal/jct)

Region of Treatment in Radiotherapy and Second Malignancies in Breast Cancer Patients

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Received July 19th, 2012; revised August 21st, 2012; accepted August 31st, 2012

ABSTRACT

A cohort study was conducted based on clinical records for 5248 women treated for breast cancer in Florence (Italy), with continuous follow up from 1965 to 1994. The subjects were categorised into groups such as no radiation treatment; breast dose only; and radiation doses in one, two, three or four of the following fields: namely internal mammary chain, supraclavicular nodes, axillary lymph nodes and chest wall. The Cox proportional hazards model for ungrouped survival data was used to estimate the relative risk for second cancer after radiotherapy delivered to different regions. The relative risk for all second cancers combined was statistically significantly raised if the internal mammary chain and supraclavicular nodes were irradiated. However, we found that the relative risk of the second malignancies could be reduced if all the locoregional lymph nodes (the internal mammary chain, supraclacicular nodes, axillary nodes) and chest wall are irradiated at the same time. If this finding can be verified by other large cohort studies or randomized clinical trials, it may have implications in clinical practice when deciding upon the targeted areas for radiotherapy; partial radiation treatment of the locoregional lymph nodes could raise the risk of second malignancies and should ideally be avoided.

Keywords: Second Cancer; Radiotherapy; Breast Cancer

1. Introduction

Many patients are diagnosed with breast cancer each year and are often treated with surgery followed by adjuvant radiation therapy [1]. With advances in early diagnosis and treatment, breast cancer is becoming an increasingly survivable disease resulting in a large population of long-term survivors. Recent trials have shown an overall survival benefit in favour of adjuvant radiotherapy for breast cancer [2-4]. Nevertheless, there is clear evidence for the association between radiation exposure and cancer, especially from epidemiological studies of survivors of the atomic bombings in Japan [5-6], as well as from various studies of medically-exposed groups [7]. In particular, irradiation of surrounding tissues during breast radiotherapy can cause second malignancies to develop within these tissues [8-9]. The second malignancy refers to a new primary cancer in a person who has survived an earlier cancer. The probability of a radiation induced second malignancy after radiotherapy is a topic that has been widely discussed [9-15]. While the benefit of radiotherapy should outweigh the risks of developing subsequent cancers, it is important to evaluate the long-term consequences of breast cancer treatment.

Our study involved the analysis of clinical records for female breast cancer patients treated at the University of Florence (Italy) with radiotherapy and/or chemotherapy and/or hormonal therapy from 1965 to 1994 and who were subsequently followed-up [16]. Previous analysis of this cohort [17] compared the incidence of second primary cancers in a group of patients treated with radiation therapy for breast cancer to breast cancer patients not treated in this way. In that analysis, an increased relative risk of all second cancers combined following radiotherapy was found. The increased relative risk appeared five or more years after radiotherapy and appeared to be highest among women treated after the menopause. Increased relative risks were observed specifically for leukaemia and other solid cancers that exclude leukaemia and contralateral breast cancer. For contralateral breast cancer, no raised relative risk was observed during the period more than 5 years after radiotherapy.

Recent randomized trials [18] have demonstrated that

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locoregional nodal irradiation after mastectomy reduces locoregional recurrence and improves overall survival at 5 years after radiation therapy in women with node positive breast cancer. However, Obedian *et al*. [19] reported that the region of radiation treatment may affect the risk of the second cancer and suggested that this risk might be higher when the internal mammary nodes were irradiated. In our cohort, 26% of those patients given radiotherapy had the mammary chain and supraclavicular nodes or chest wall irradiated. This provides an opportunity to examine further the relationship between the region of treatment and second cancers. In this paper, we evaluate the effect that the region of treatment in radiotherapy may have had on the subsequent risk of second malignancies among patients treated in Florence, based on categorising the patients into the following groups such as no radiation treatment, breast dose only, or radiation dose in one, two, three or four of the following fields: namely, internal mammary chain, supraclavicular nodes, axillary lymph nodes and chest wall.

2. Materials and Methods

Data were collected on 5248 patients with breast cancer who were submitted to radiotherapy, chemotherapy, hormonal therapy or no additional therapy at the University of Florence from June 1965 to December 1994 [17]. All of the patients had received surgery for breast cancer.

A treatment schedule of 2 Gy/day, 5 days/week, for a total dose up to 60 Gy was used. However, the regions treated with radiation differed from patient to patient. The exposed volume for a large number of patients was the breast only, while other patients had also other regions irradiated, such as internal mammary chain, supraclavicular nodes, axillary lymph nodes and chest wall.

Details of the method of follow-up and collection of data on second malignancies have been presented previously [17]. The end of follow-up for the subjects was chosen to be the earliest of: date of second cancer incidence, date of loss to follow-up, date of death and 31 December 1994. The follow-up time among surviving patients ranged from a minimum of 1 year to a maximum of 30 years, with a mean of 8 years. The overall average age at treatment was 54.7 years. The researchers carrying out the study had no identifiable details of patients forwarded to them and therefore ethical approval was not required under Italian laws when the project was initiated in 1996.

The Cox proportional hazards model for ungrouped survival data [20] was used to estimate the relative risk of second cancers after radiotherapy treatment and to evaluate how the risk varied according to other factors. Parameter estimation and significance testing were carried out using the Epicure software [21]. Since some patients also received chemotherapy and/or hormonal therapy, the relative risks of second cancers due to radiotherapy were reported both unadjusted and adjusted for chemotherapy and hormonal therapy to check if there were any confounding effects from these therapies. The analyses are stratified by age-at-treatment and age at outcome categories.

As well as all second cancers combined, leukaemia, contralateral breast cancer (*i.e*. cancer in the opposite breast to that in which cancer had previously been diagnosed) and all other cancers combined were considered. For leukaemia, the follow up period was chosen to be two years or more following treatment, in view of the evidence from other studies showing a short latency period for radiation-induced leukaemia [7]. For other cancers and for all second cancers combined, the follow-up period was chosen to be five years, in line with the pattern reported by Zhang *et al*. [17].

3. Results

As shown in **Table 1**, among the 5248 patients in the cohort, 261 patients (5%) developed contralateral breast cancer, 8 patients (0.15%) developed leukaemia and a total of 118 patients (2.25%) developed other types of second cancers during the period of follow-up. The details of other second cancer types were presented previously by Zhang *et al.* [17]. The median time to development of a second malignancy was 3 years for contralateral breast cancer, 4.5 years for leukaemia and 4.4 years for other cancers combined.

Table 2 summarises the number of subjects based on the region of radiation treatment. Among the 3080 subjects who had a follow-up of 5 or more years, 1813 subjects had no radiation treatment and 804 subjects received breast dose only. 14 subjects were irradiated in only one of the four following fields: internal mammary chain, supraclavicular nodes, axillary lymph nodes and chest wall, 138 subjects were irradiated in only two of the above fields (87% were internal mammary chain and supraclavicular nodes), 190 subjects received doses in three of the above fields (97% were internal mammary chain, supraclavicular nodes and axillary nodes) and 114 subjects received doses in all four fields. A very small number of subjects received breast doses in addition to doses in "other fields", as indicated by + in **Table 2** and

Table 1. Sites of second malignancies.

Second cancer type	Numbers of total second cancer patients	Numbers of second cancer patients with radiotherapy
Contralateral breast cancer	261	103
Leukaemia	8	7
Other type of cancers combined	118	54

they are grouped together with patients who only received doses to "other fields" in the analyses. Seven subjects had radiation treatment but without information on the field of treatment, therefore they are included in the any radiation treatment group but are excluded in the field-specific treatment groups in the analyses.

Table 3 shows the relative risks of all second cancer combined amongst patients given radiotherapy according to the region of radiation treatment, based on a follow-up of 5 or more years and both unadjusted and adjusted for chemotherapy and hormonal therapy. The reference category consists of unirradiated patients. The relative risk was below one for radiation treatment of the breast only and greater than one for patients who received radiation dose in one, two or three of the other fields. In particular, the relative risk was statistically significantly raised for patients who received radiation dose in two fields, which—among 87% of the patients—were the internal mammary chain and supraclavicular nodes. However, the relative risk dropped below one for subjects irradiated in all four fields (internal mammary chain, supraclavicular nodes, axillary nodes and chest wall). After adjustment for chemotherapy and hormonal therapy, there was strong evidence of differences in the relative risk between the radiation treatment groups ($p = 0.002$).

The relative risks for some specific types of second cancer have been studied previously [17]. We further analysed the relative risk of leukaemia, contralateral breast cancer and other cancers respectively, according to the region of radiation treatment. **Table 4** shows the relative risks for leukaemia amongst patients given radiotherapy according to the region of radiation treatment based on a follow-up of 2 or more years. Although the numbers of leukaemia cases were small, the relative risks were statistically significantly raised for patients having either one or three other fields irradiated, based on 1 and 2 cases in the corresponding irradiated groups. In contrast, the relative risks appeared to be smaller amongst patients who received a breast dose only or who received doses in either two or all four fields other than the breast, compared to other the irradiated groups. The differences in relative risk between the radiation treatment groups were statistically significant ($p = 0.04$, after adjusting for chemotherapy and hormonal therapy).

Table 5 shows the relative risk of contralateral breast cancer amongst patients given radiotherapy according to the region of radiation treatment based on a follow-up of 5 or more years. The relative risks were below one for patients who received a breast dose only, or who had either three or all four of the non-breast fields irradiated. In particularly, the relative risk was statistically significantly less than one for patients with radiation exposure only of the breast. The relative risks for patients who received radiation doses to either one or two of the

Table 2. Region of treatment and corresponding number of subjects, based on the follow-up of 5 or more years. The numbers of subjects who received breast dose in addition to other fields are represented as + numbers.

Fields exposed	Number of subjects	Percentage (%)
None	1813	58.86
Breast only	804	26.10
One other field exposed		
Internal mammary nodes	2 + 1	
Supraclavicular nodes	4 + 1	
Chest wall	5	
Axillary nodes	1	
subtotal	14	0.45
Two other fields exposed		
Internal mammary nodes and chest wall	1	
Internal mammary nodes and supraclavicular nodes	118 + 2	
Supraclavicular nodes and axillary nodes	12 + 1	
Supraclavicular nodes and chest wall	4	
Subtotal	138	4.48
Three other fields exposed		
Internal mammary nodes, supraclavicular nodes and axillary nodes	178 + 6	
Internal mammary nodes, supraclavicular nodes and chest wall	5	
Supraclavicular nodes, chest wall and axillary nodes	1	
Subtotal	190	6.17
Four other fields exposed		
Internal mammary nodes, supraclavicular nodes, chest wall and axillary nodes	111 + 3	
Subtotal	114	3.70
Fields unknown	7	0.23
Total	3080	100

Table 3. Relative risk of all second cancers combined among patients given radiation therapy, by region of radiation treatment and based on a follow-up of 5 or more years.

Region of radiation treatment	RR unadjusted for chemotherapy and hormonal therapy (95% CI)	RR adjusted for chemotherapy and hormonal therapy (95% CI)	Cases/women
None	1	1	94/1813 (5.2%)
Any radiation treatment	1.22 (0.88, 1.69)	1.14 (0.82, 1.58)	73/1267 (5.8%)
Subgroups			
Breast only	0.79 (0.49, 1.28)	0.70 (0.43, 1.14)	24/804 (3.0%)
One other field**	2.95 (0.71, 12.14)	3.13 (0.76, 12.91)	2/14 (14.3%)
Two other fields**	1.99 (1.15, 3.43)*	2.05 (1.19, 3.56)*	16/138 (11.6%)
Three other fields**	1.59 (0.93, 2.74)	1.50 (0.87, 2.56)	18/190 (9.5%)
Four other fields**	0.83 (0.36, 1.94)	0.76 (0.33, 1.77)	6/114 (5.3%)
Test for heterogeneity in RR between radiation treatment subgroups	p = 0.054	p = 0.002	

*p < 0.05, ** defined in **Table 2**.

Table 4. Relative risk of leukaemia among patients given radiation therapy, by region of radiation treatment and based on a follow-up of 2 or more years.

Region of radiation treatment	RR unadjusted for chemotherapy and hormonal therapy (95% CI)	RR adjusted for chemotherapy and hormonal therapy (95% CI)	Cases/women
None	1	1	1/2377 (0.04%)
Any radiation treatment	8.13 (0.96, 69.10)	6.67 (0.76, 58.00)	7/2339 (0.3%)
Subgroups			
Breast only	4.17 (0.41, 42.62)	3.27 (0.32, 33.72)	3/1691 (0.18%)
One other field**	72.09 (4.05, 1284)*	88.61 (4.54, 1728)*	1/25 (4%)
Two other fields**	NC	NC	0/187 (0%)
Three other fields**	24.71 (3.44, 278.90)*	18.85 (1.69, 210.80)*	2/252 (0.8%)
Four other fields**	15.13 (0.92, 247.60)	9.58 (0.57, 161.30)	1/176 (0.6%)
Test for heterogeneity in RR between radiation treatment subgroups	p = 0.03	p = 0.04	

*p < 0.05, **defined in **Table 2**. NC: not calculated due to zero cases.

Table 5. Relative risk of contralateral breast cancer among patients given radiation therapy, by region of radiation treatment and based on a follow-up of 5 or more years.

Region of radiation treatment	RR unadjusted for chemotherapy and hormonal therapy (95% CI)	RR adjusted for chemotherapy and hormonal therapy (95% CI)	Cases/women
None	1	1	67/1813 (3.7%)
Any radiation treatment	0.87 (0.58, 1.32)	0.82 (0.54, 1.24)	41/1267 (3.2%)
Subgroups			
Breast only	0.57 (0.31, 1.08)	0.52 (0.27, 0.98)*	13/804 (1.6%)
One other field**	2.20 (0.30, 16.22)	2.33 (0.32, 17.13)	1/14 (7.1%)
Two other fields**	1.25 (0.59, 2.66)	1.28 (0.60, 2.73)	8/138 (5.8%)
Three other fields**	0.94 (0.43, 2.04)	0.89 (0.41, 1.94)	8/190 (4.2%)
Four other fields**	0.68 (0.24, 1.94)	0.63 (0.23, 1.80)	4/114 (3.5%)
Test for heterogeneity in RR between radiation treatment subgroups	p = 0.43	p = 0.06	

*p < 0.05, **defined in **Table 2**.

fields were greater than 1, but were based on small numbers of cases and were not statistically significantly raised. The differences in relative risk between the radiation treatment groups were close to being statistically significant (p = 0.06), after adjusting for chemotherapy and hormonal therapy).

Table 6 shows the relative risk of all second cancers other than leukaemia and contralateral breast cancer among patients given radiotherapy according to the region of radiation treatment based on a follow-up of 5 or more years. The relative risk was close to 1 for patients who received a breast dose only or who were irradiated in all four of the other fields. There were no cases amongst the 14 patients who received a radiation dose in only one of the fields. However, for patients who received radiation doses in two or three of the fields, statistically significantly raised relative risks were observed. The test for heterogeneity in the relative risk between radiation treatment groups was borderline statistically significant (p = 0.05, after adjusting for chemotherapy and hormonal therapy).

4. Discussion

In this study, we have used a clinical records-based cohort to analyse the effects of region of treatment in radiotherapy for breast cancer on the incidence of subsequent second cancers. All patients in this cohort received surgery for breast cancer. An advantage of restricting the cohort to women treated for breast cancer is to minimize any possible systematic difference between the study groups. Such an approach has been used in other epidemiological studies of a similar nature, as reported by Roychoudhuri *et al*. [13].

Our cohort contains 26% of radiotherapy patients who had the mammary chain and supraclavicular nodes or chest wall irradiated. This provided an opportunity to examine the relationship between the region of treatment and second cancers. Based on a follow-up of five or more years, the relative risk of all second cancers was highest for patients who received radiation to one or two fields apart from the breast; in particular, the risk was statistically significantly raised for patients irradiated in two fields. Amongst them, 87% received radiation exposure in internal mammary chain and supraclavicular nodes. This result is consistent with the finding of Obedian *et al*. [19], which suggested a raised risk of second cancer when the internal mammary chain was exposed. Furthermore, we also found that the relative risk started to decrease when axillary lymph nodes was also irradiated and was less than one (although not significantly so) for those subjects irradiated in all four fields. Thus, in order to reduce the risk of second cancer following radiotherapy for breast cancer, it might be important when irradiating the internal mammary chain and supraclavicular nodes to also irradiate the chest wall and axillary lymph nodes.

An increased risk of leukaemia can start to arise two to five years after exposure to radiation [22] and raised leukaemia risks have been reported in previous epidemiological studies of breast cancer patients treated with radiation [23]. This raised risk might be associated with regional radiation therapy that includes an internal mammary node field, which may expose the thoracic spine to a relatively high radiation dose [9]. In our previous

Table 6. Relative risk of second cancers other than leukaemia and contralateral breast cancer among patients given radiation therapy, by region of radiation treatment and based on a follow-up of 5 or more years.

Region of radiation treatment	RR unadjusted for chemotherapy and hormonal therapy (95% CI)	RR adjusted for chemotherapy and hormonal therapy (95% CI)	Cases/women
None	1	1	29/1813 (1.6%)
Any radiation treatment	1.84 (1.06, 3.16)	1.70 (0.98, 2.94)	29/1267 (2.3%)
Subgroups			
Breast only	1.34 (0.63, 2.82)	1.17 (0.55, 2.50)	11/804 (1.4%)
One other field**	NC	NC	0/14 (0.0%)
Two other fields**	3.65 (1.63, 8.21)*	3.88(1.72, 8.77)*	8/138 (5.8%)
Three other fields**	2.36 (1.02, 5.48)*	2.19 (0.94, 5.08)	8/190 (4.2%)
Four other fields**	1.08 (0.25, 4.65)	0.98 (0.23, 4.20)	2/114 (1.8%)
Test for heterogeneity in RR between radiation treatment subgroups	p = 0.06	p = 0.053	

*p < 0.05, **defined in **Table 2**. NC: not calculated due to zero cases.

analysis [17], there was suggestion of a raised incidence of leukaemia among radiotherapy patients in the period two or more years after radiotherapy. There were seven cases in the radiotherapy group compared with only one case in non-radiotherapy group, with a relative risk of 6.67 (95% CI 0.76, 58.00) after adjustment for chemotherapy and hormonal therapy. The raised risk was not statistically significant, reflecting the small number of cases in this cohort. In the current analysis, the relative risk of leukaemia peaked when one of the fields other than the breast was irradiated, albeit based on only one case. The relative risk was lower if more fields were irradiated, or if only the breast was irradiated. There were no leukaemia cases among the subjects who was irradiated in two of the fields; this might be due to chance, since there was only a total of 7 cases in the irradiated groups.

Raised risks of breast cancer has been reported in various studies of women exposed to radiation; for example, Japanese atomic bomb survivors [5,6,24], female tuberculosis patients who received multiple fluoroscopies [25,26], and female patients who received radiotherapy for various benign conditions [27]. Raised risks have also been seen specifically in women who had direct breast exposure prior to the age of 30 years [26-30]. However, the causes of contralateral breast cancer amongst breast cancer patients given radiotherapy are less obvious. In the Early Breast Cancer Trialists' Collaborative Group report which evaluated the effects of radiotherapy, a significantly increased risk of contralateral breast cancer was found [31]. However, in another large case-control study from Denmark, there was no significant raised risk of contralateral breast cancer among women who received radiotherapy [32]. A more recent large-scale study included 13,472 women also failed to show an increased risk of contralateral breast cancer for those received radiotherapy [33]. The WECARE study [34] also reported that no excess risk was observed in women who received radiotherapy at more than 40 years of age, but a relative risk of 3.0 (95% CI: 1.1 - 8.1) was reported in women aged < 40 years with follow up greater than 5 years. Further analysis of data from the WECARE study found a raised risk of contralateral breast cancer among nulliparous (but not parous) women who received radiotherapy [35]. In some studies, it was reported that the increased risks of contralateral breast cancer were most likely observed within the first year following diagnosis of the primary breast cancer [36], or associated with patients with more advanced stage disease [37-39]. This suggests metastatic disease in the opposite breast could be mistakenly classified as a new primary second breast cancer. Since some patients selected for post-mastectomy radiation have a poorer prognosis than other patients, there may well be bias in estimates of the risk of contralateral breast cancer that can be attributed to radiotherapy. In order to minimise any effect of metastatic disease in the opposite breast, our analyses excluded the first five years following treatment. In our previous analysis [17], no raised relative risk for contralateral breast cancer was observed during the period five or more years after exposure. This is in agreement with previous epidemiological studies [9,32,33,40]. However, our current analysis showed that the relative risk was significantly below one for patients who received radiation exposure of the affected breast only. In contrast, the relative risk for patients irradiated in one or more other fields was not statistically significantly different from one. However, it has to bear in mind that our findings are based on small numbers of cases and should be verified by a larger study of similar kind.

Other solid cancers have also been reported to link with radiotherapy following breast cancer [10,41,42]. In our previous analysis, the relative risk of all second cancers excluding leukaemia and contralateral breast cancer appeared to be increased five or more years after radiotherapy, particularly amongst those women treated at ages 50 - 64 years age-at-treatment group. This may indicate an association with menopausal status [17]. The current analysis showed that the relative risk of all second cancers excluding leukaemia and contralateral breast cancer was statistical significantly raised among patients who received radiation dose in two fields, even after adjustment for chemotherapy and hormonal therapy. The relative risk was lower if three fields were exposed and dropped to around one when all four fields were exposed. These results are similar to those for all second cancers combined.

The findings in this paper could have clinical implications if they can be verified by other large cohort studies or randomised clinical trials. In this cohort study, we have no information on how the decisions were made about nodal irradiation treatment, which limits our interpretation of the results. With a fairly small total number of second cancers in this cohort, the excess risk associated with radiotherapy was small over the period of follow-up. Nevertheless, since many of the women were still alive at the end of follow-up, the possibility of raised risks continuing several decades over radiotherapy cannot be ruled out and—based on other studies (e.g. Preston *et al.* [6])—would be expected.

5. Conclusion

This study indicated a raised risk of second malignancies associated with region of treatment in radiotherapy for breast cancer, particularly among women irradiated in the internal mammary chain and supraclavicular nodes. The relative risk was lower if the axillary nodes and

chest wall were also irradiated. This may have implications in clinical practice when deciding upon the targeted areas for radiotherapy; partial radiation treatment of the locoregional lymph nodes could raise the risk of second malignancies and should ideally be avoided. The interpretation of patterns in risk for specific cancers, such as leukaemia and contralateral breast cancer, was complicated by the small numbers of cases. However, for both of these type of cancer, the similar risk patterns exist and the relative risk varied significantly between radiotherapy groups, after adjusting for chemotherapy and hormonally therapy.

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