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Predictive factors for late normal tissue complications following radiotherapy for breast cancer

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Abstract
Background and purpose Radiotherapy after breast-conserving surgery is commonly applied to reduce recurrence of breast cancer but may cause acute and late side effects. To identify prognostic factors for the development of late toxicity after radiotherapy, we conducted a prospective study of breast cancer patients.
Patients and methods We assessed late complications of radiotherapy and collected information on epidemiologic factors in a cohort of breast cancer patients who had received radiotherapy after breast-conserving surgery. Among 416 patients with complete follow-up data, the association between possible risk factors and development of late complications was evaluated using multivariate logistic regression analysis.
Results After a median follow-up time of 51 months, 131 (31.4%) patients presented with telangiectasia and 28 (6.7%) patients with fibrosis. We observed a strong association between development of telangiectasia and fibrosis ($p < 0.01$). Increasing age of the patient was a risk factor for both telangiectasia and fibrosis (p-value for trend <0.01 and 0.03, respectively). Patients with acute skin toxicity (odds ratio (OR) 1.8, 95% confidence interval (CI) 1.0–3.1) were at higher risk to develop telangiectasia. Long-term smoking was associated with a significant increase in risk of telangiectasia compared to non-smokers (OR 2.3, 95% CI 1.2–4.6).
Conclusions Our study revealed several factors other than radiation dose that may predispose to late complications following radiotherapy. Further understanding of differences in response to irradiation may advance individualized treatment and improve cosmetic outcome.

Keywords Breast cancer · Cosmesis · Late side effects · Radiotherapy · Smoking · Telangiectasia

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Introduction

Radiotherapy is commonly applied after breast-conserving surgery to reduce the risk of locoregional recurrence of breast cancer and has been shown to be as effective as radical mastectomy [1]. However, irradiation of the breast may cause acute side effects such

as erythema and desquamation of the skin as well as late normal tissue complications including telangiectasia and fibrosis.

The benefit of radiotherapy following breast-conserving surgery with respect to local recurrence and breast cancer mortality is well established, therefore there has been an effort to optimize irradiation regimen and thus reduce the occurrence of adverse side effects. Although it is known that treatment related factors such as total dose, dose per fraction, irradiated volume and concomitant chemotherapy [2–5] are associated with risk of late complications, the large inter-individual variation in radiosensitivity, which is observed even among patients with the same treatment regimen, is poorly understood.

Several studies have aimed at developing predictive assays for individual radiosensitivity to enable individualized treatment, but so far no such assay is available for clinical use [6, 7]. The literature on patient-related factors that may be associated with risk of late complications tends to be inconsistent and much of the literature is based on case reports or studies with shortcomings in study design and analysis (reviewed in [7, 8]). In addition, findings of studies that were conducted several years ago may not be transferable to current practice, because therapy modalities have changed substantially with the introduction of more sophisticated irradiation techniques such as the use of megavoltage X-rays and CT-based planning.

The main reason for choosing breast-conserving surgery instead of radical mastectomy are psychological aspects and therefore cosmesis and the reduction of late complications such as telangiectasia and fibrosis are of great importance. This emphasizes the need to better understand individual differences in normal tissue tolerance to irradiation.

We therefore evaluated the effect of extrinsic factors that may predispose to development of late normal tissue complications in a prospective study of patients who were treated with radiotherapy after breast-conserving surgery.

Material and methods

Patients and data collection

Between June 1998 and March 2001, 478 female breast cancer patients receiving radiotherapy after breast-conserving surgery were enrolled a study to evaluate acute and long-term toxicities associated with therapy [9]. These women were treated at radiotherapy units of Women's Clinic in Heidelberg, St. Vincentius Clinic in Karlsruhe, City Hospital in Karlsruhe and University Hospital in Mannheim. Patients treated with chemotherapy prior or simultaneously to radiation were not eligible for the study. Information on demographic factors, medical history and lifestyle factors was gathered by means of a self-administered questionnaire. Data on tumor characteristics and treatment regimen were abstracted from patient records. Informed consent was obtained from all participants, and the study was approved by the ethics committee of the University of Heidelberg, the Institutional Review Board for Roswell Park Cancer Institute, and the US Army Medical Research and Materiel Command Human Subjects Research Review Board.

Breast irradiation

Details on the radiotherapy regimen (total dose, dose per fraction, treatment time, boost dose) were abstracted from irradiation protocols. As described previously [9], all patients received a common breast irradiation treatment with conformal tangential irradiation with lateral and medial wedge fields, including CT-based planning, simulation, verification and quality assurance. At three hospitals, the standard regimen included irradiation of the whole breast, either 50 Gy given in 5×2.0 Gy fractions or 50.4 Gy in 5×1.8 Gy fractions per week, followed by a photon or electron boost with doses ranging from 5 to 20 Gy. Three patients were treated with brachytherapy (20 or 25 Gy). In the fourth radiation department, patients received 56 Gy of whole breast irradiation in 5×2.0 Gy fractions without boost.

The occurrence of acute side effects of radiotherapy were monitored and documented by physicians four times during the study (before the beginning of radiotherapy, and at cumulative doses of 36–42 Gy, 44–50 Gy, and at the end of radiotherapy). As previously described [9], acute side effects of radiotherapy were classified according to a modified classification system based on the common toxicity criteria of the National Institutes of Health [10]. For this study, side effects of grade 2c and above (at least one moist desquamation or interruption of radiotherapy due to toxicity) were considered to indicate acute skin toxicity.

Follow-up

Patients were recontacted between June 2003 and July 2005 to assess the course of disease (relapse, metastases,

secondary carcinoma, and death) as well as the occurrence of late adverse effects of radiotherapy. A self-administered questionnaire similar to that applied in the initial study was used to collect information on demographic and epidemiologic risk factors, and to record changes that may have occurred after radiotherapy. Patients were examined to assess the occurrence of late adverse effects of radiotherapy either by the study physician or by their treating physician. Late side effects were classified according to the RTOG/EORTC late radiation morbidity scoring schema [11] supplemented by LENT-SOMA scores and documented using a standardized form. Adverse reactions of the skin (telangiectasia), subcutaneous tissue (fibrosis) and other organ tissues (heart, lung, larynx), weight changes, nausea and development of lymphatic edema (arm or breast) were recorded. The severity of late effects was scored from 0 to 4, whereby the development of side effects of grades ≥2 was considered to indicate late normal tissue complications. The present analysis was restricted to telangiectasia and fibrosis, since these complications are clearly attributable to radiotherapy.

Of the 478 patients, 5 (1.0%) patients refused to participate in the follow-up study and 4 (0.8%) could not be traced. Hence, information on the course of disease was available for 469 patients and could be verified with patient records for 463 patients. Fifty-eight (12.3%) women had developed metastases, a secondary carcinoma or a relapse until follow-up. For 467 patients, details on the radiotherapy regimen (total dose, dose per fraction, treatment time, boost dose) were abstracted from irradiation protocols. Of the 469 patients with follow-up information, 27 (5.8%) women had died (12 due to breast cancer, 7 due to other causes, and 8 women with unknown cause of death), 45 (9.6%) did not complete the questionnaire and 46 (9.8%) did not agree to an examination of late complications of radiotherapy. Thus, data on late effects of radiotherapy as well as information on demographic and epidemiologic factors were available for 421 (89.8%) women.

Statistical analysis

The chi-squared test was calculated for univariate comparisons. Multivariate unconditional logistic regression analysis was used to identify potential risk factors for late complications of radiotherapy. Odds ratios (OR) and 95% confidence intervals (CI) were computed using the LOGISTIC procedure in SAS Version 9.1 (SAS Institute Inc., Cary, NC, USA).

The biologically effective dose (BED) of radiotherapy relative to an irradiation with a fraction dose of 2.0 Gy, i.e., the Normalized Total Dose (NTD), was calculated to account for differences in fractionation according to the following formula:

$$NTD = \frac{BED}{\left(1 + \frac{2Gy}{\alpha/\beta}\right)} = n \times d \frac{\left(1 + \frac{d}{\alpha/\beta}\right)}{\left(1 + \frac{2Gy}{\alpha/\beta}\right)}$$

given the number of fractions n, the fraction size of d, and an α/β ratio of 3 Gy for telangiectasia and 2 Gy for fibrosis.

Multivariate models included NTD, type of boost (photon, electron, no boost), age at the end of radiotherapy, body mass index (BMI) and follow-up time since end of radiotherapy. Mutual adjustment did not substantially influence the risk estimates for any of the risk factors presented here. A two-sided $p < 0.05$ was considered significant.

Three patients with interstitial boost (two of whom developed fibrosis and one telangiectasia, respectively) and two women with missing data on fibrosis were excluded from the analysis. Seven patients who developed fibrosis but not telangiectasia were not included in the analysis of risk factors for the development of telangiectasia.

Results

Characteristics of the 421 breast cancer patients who participated in the follow-up study are shown in Table 1. After a median follow-up time of 51 months (range 36–77 months), the most common symptoms of grade ≥2 which were observed included telangiectasia, impairment of the general condition, fibrosis, lymphatic edema, and pain (Table 2). Of the 416 patients who were included in the analysis, 28 (6.7%) patients presented with fibrosis and 131 (31.4%) with telangiectasia of grades ≥2, whereby 21 patients (5.0%) presented with both adverse reactions. Hence, there was a strong association between development of telangiectasia and fibrosis ($p < 0.0001$).

In the multivariate analysis of factors predisposing to telangiectasia (Table 3), our findings confirmed that higher NTD has a significant adverse effect on cosmetic outcome (p for trend 0.002), whereas application of boost therapy (in the dose range up to 56 Gy) was not significantly associated with risk for telangiectasia. Increasing age of the patient was a risk factor for the development of telangiectasia (p for trend 0.001). For instance, women who were 70 years and above were at a twofold increased risk to develop telangiectasia

Table 1 Study population and tumor characteristics

	N	%
Age at follow-up		
31–50	19	4.5
51–60	98	23.3
61–70	209	49.6
71–80	80	19.0
81–91	15	3.6
BMI		
18.0–24.9	192	45.6
25.0–29.9	163	38.7
30.0+	66	15.7
Primary tumor		
T0	1	0.2
T1	282	67.0
T2	97	23.0
T4	1	0.2
TX	37	8.8
In situ	3	0.7
Nodal status		
N0	321	76.3
N1	60	14.3
NX	40	9.5
Metastatic status		
M0	270	64.1
M1	1	0.2
MX	150	35.6
Histological type		
Invasive ductal	234	55.6
Invasive lobular	91	21.6
In situ	38	9.0
Other	58	13.8
Prescribed irradiation dose[a]		
50.0–56.4 Gy	92	21.9
56.5–60.4 Gy	158	37.5
60.5–64.4 Gy	71	16.9
64.5+ Gy	100	23.8

[a] Includes irradiation to the whole breast and boost application

Table 2 Late side effects among patients who received radiotherapy after breast-conserving surgery (*N* = 421)

	Score					
	0	1	2	3	4	*Missing*
General condition (*N*)	260	94	61	5	1	
Nausea (*N*)	402	15	4			
Lung (*N*)	414	5	1	1		
Heart (*N*)	413	7	1			
Pain (*N*)	279	119	19	4		
Weight change (*N*)	406	7	4	4		
Larynx (*N*)	418	3				
Fibrosis (at operation site) (*N*)	156	233	25	5		2
Fibrosis (not at operation site) (*N*)	282	132	5			2
Telangiectasia (*N*)	207	79	134	1		
Lymphatic edema (arm) (*N*)	304	97	19			1
Lymphatic edema (breast) (*N*)	345	67	7			2

compared to women who were aged 60 years and below at the end of radiotherapy (OR 2.11, 95% CI 1.11–4.03). In contrast to previous findings for acute skin toxicity [9], high BMI had no significant effect on late complications. However, a non-significant risk increase was observed for women with large breast size (OR 1.74, 95% CI 0.87–3.49).

Patients who had presented with moist desquamation during radiotherapy were at higher risk for telangiectasia (OR 1.77, 95% CI 1.00–3.13), but there was no evidence for an association between moist desquamation and development of fibrosis (OR 0.40, 95% CI 0.09–1.80). Allergy and hypertension were both associated with a 60% increase in risk for telangiectasia, while there were no associations between diabetes and skin type and cosmetic outcome (Table 3).

Women living with a partner were less likely to present with telangiectasia than single women (Table 3). However, single women were older than those living with their partner (median age at end of radiotherapy was 64 and 59 years, respectively), and singles were more likely to be hypertensive (57.4% of single women versus 43.2% of women living with partner). Yet, the positive effect of living with a partner remained significant after adjustment for these confounders. The distribution of other variables such as smoking status, alcohol consumption, BMI or allergies did not differ between single women and women living with a partner (data not shown).

Ever active smoking was associated with a borderline significant increase in risk for telangiectasia (OR 1.64, 95% CI 1.00–2.71). A detailed analysis of smoking showed that cigarette smoking for at least 30 years and the accumulation of at least 20 pack-years were associated with a significant 2.3-fold risk increase (p for trend 0.004 for duration of smoking and 0.05 for pack-years, respectively). Consumption of alcohol was not a significant risk factor for the development of telangiectasia (Table 3).

The analysis of factors that predispose to fibrosis was hampered by the small number of patients who presented with fibrosis at follow-up ($N = 28$). Factors that were significantly associated with susceptibility to fibrosis were patients' age (OR 1.06, 95% CI 1.01–1.11 per year, p for trend 0.03) and allergy (OR 2.45, 95% CI 1.11–5.51). Smoking also seemed to increase the risk of fibrosis, but the estimates were not statistically significant (OR 2.03, 95% CI 0.84–4.90 for ever smoking).

Risk estimates for the investigated factors from multivariate analyses adjusted for the maximum NTD were essentially similar to those adjusted for nominal NTD (data not shown).

Table 3 Association between potential risk factors and development of telangiectasia following radiotherapy for breast cancer

	No telangiectasia		Telangiectasia		OR[a]	95% CI
	N = 278	%	*N* = 131	%		
Age at end of RT (median)	59.5		62.0		1.05	1.02–1.08
Normalized Tumor Dose (median)	61.0		63.0		1.11	1.04–1.19
BMI (median)	25.3		25.5		1.04	0.98–1.10
Boost						
Photon	177	63.7	98	74.8	1	Ref
Electron	67	24.1	27	20.6	0.71	0.42–1.22
No boost	34	12.2	6	4.6	0.91	0.31–2.69
Chemotherapy	0	0	2	1.5	n.c.	
Hormone therapy						
Yes	236	84.9	122	93.1	1	Ref
No	42	15.1	9	6.9	0.53	0.24–1.17
Acute radiosensivity						
No	233	83.8	101	77.1	1	Ref
Yes	45	16.2	30	22.9	1.77	1.00–3.13
Allergy	91	32.7	56	42.8	1.64	1.04–2.58
Hypertension	117	42.1	76	58.0	1.60	1.00–2.56
Diabetes	21	7.6	14	10.7	1.30	0.61–2.76
Skin type						
Always sunburn/no sun tan	75	27.0	28	21.4	1	Ref
Sometimes sunburn/sun tan	150	54.0	80	61.1	1.51	0.88–2.59
Never sunburn/sun tan	49	17.6	18	13.7	0.85	0.41–1.79
Breast size						
Cup A, B	154	55.4	71	54.2	1	Ref
Cup C	73	28.4	31	23.7	0.81	0.48–1.36
Cup D, E, F	27	9.7	20	15.3	1.74	0.87–3.49
Marital status						
Single/widowed/divorced	66	23.7	49	37.4	1	Ref
Married/partner	212	73.3	82	62.6	0.52	0.32–0.85
Alcohol consumption (g/day)						
0	74	26.6	32	24.4	1	Ref
0.1–3.4	71	25.5	30	22.9	1.05	0.57–1.96
3.5–13.2	67	24.1	36	27.5	1.52	0.82–2.83
13.3+	66	23.7	33	25.2	1.41	0.76–2.64
Smoking status						
Non-smoker	185	66.6	82	62.6	1	Ref
Current smoker	29	10.4	12	9.2	1.45	0.66–3.18
Former smoker	54	19.4	30	22.9	1.74	0.99–3.04
Pack-years of smoking						
Non-smoker	185	66.6	82	62.6	1	Ref
1–9	38	13.7	14	10.7	1.33	0.64–2.74
10–19	15	5.4	12	9.2	2.17	0.92–5.16
20+	22	7.9	15	11.5	2.32	1.07–5.00
Duration of smoking (years)						
Non-smoker	185	66.6	82	62.6	1	Ref
1–14	27	9.7	8	6.1	1.06	0.43–2.61
15–29	22	7.9	14	10.7	1.87	0.87–4.02
30+	28	10.1	20	15.3	2.33	1.17–4.64

Percentages for some variables do not add up to 100% due to missing data

n.c. not calculated

[a] Odds ratios adjusted for age at end of RT, boost, NTD, follow-up time and BMI; seven patients with fibrosis only were excluded from the analysis

Discussion

In this study of breast cancer patients treated with radiotherapy after breast-conserving surgery, we identified several factors that increase the risk of telangiectaisa including irradiation dose, age, cigarette smoking, and acute skin toxicity. Overall, however, the applied radiotherapy regimens were well tolerated and severe late complications were rare.

In line with previous studies [12], irradiation dose, specifically the NTD, was significantly associated with risk of telangiectasia. We did not observe an adverse effect of boost on cosmetic outcome [13]. However, the number of patients ($N = 40$) treated with whole breast irradiation only was low in the present study. Likewise, only a small proportion (12%) of the patients did not receive hormone therapy and only two patients were treated with chemotherapy after radiotherapy (patients with chemotherapy prior or during radiotherapy were not eligible for the study).

In contrast to a previous report [14] and our findings for acute toxicity [9], high BMI or large breast size was not significantly associated with risk of telangiectasia in the present study. Possibly, this is due to modern irradiation techniques such as CT-based planning that help to minimize dose inhomogeneities compared to earlier studies.

The literature on the effect of age on late side effects of radiotherapy is inconsistent, and the effect of age seems to vary between sequelae and irradiated sites (reviewed in [8]). For instance, higher age was associated with an elevated risk for impaired shoulder movement after radiotherapy for breast cancer but no association was observed with risk of telangiectasia or fibrosis in the same series of patients [15, 16]. The significant increase in risk of normal tissue complications with increasing age observed in the present study is in line with findings from previous studies [4, 17, 18]. This association was not observed in one other study [12]. Nevertheless, it is conceivable that the age-related accumulation of mutations and decline of DNA repair capacity increase sensitivity to ionizing radiation [19–21].

Our observation of an association between telangiectasia and fibrosis indicates that some individuals may have a generally enhanced radiosensitivity affecting various cell types, analog to patients suffering from genetic syndromes such as ataxia telangiectasia or Nijmegen breakage syndrome [22, 23]. Ionizing radiation exerts its cytotoxic effects mainly through DNA damage leading to cellular responses including apoptosis and cell-cycle arrest. It is thus plausible that genetic variability in cellular response to these lesions could influence radiosensitivity [24]. Indeed, genetic polymorphisms in enzymes involved in DNA repair have been associated with acute and late adverse effects [25–29]. Although in vitro assays have not proven sufficiently accurate for clinical use, the observed associations of in vitro radiosensitivity of peripheral blood lymphocytes with normal tissue reactions to radiotherapy support the notion of a generally enhanced radiosensitivity in a subgroup of the population [30, 31].

The present study confirmed previous reports of an increased risk of telangiectasia among patients with acute skin toxicity [12, 32]. As for the association between telangiectasia and fibrosis, one may hypothesize that this association reflects individuals with a generally increased radiosensitivity, since different target cells are involved in telangiectasia and moist desquamation. However, the lack of an association between acute radiosensitivity and fibrosis, which was also reported by Bentzen and Overgaard [32], does not support this perception. Hence, an alternative hypothesis is that telangiectasia may represent a consequential late effect of the damage to superficial capillaries caused by moist desquamation [12, 32].

We observed an increased risk of telangiectasia among patients with hypertension and among patients who reported to have allergies. Findings on the effect of hypertension on radiosensitivity are inconsistent [12, 33, 34]. It is possible that the increased risk associated with hypertension is attributable to the medication used rather than to hypertension *per se*. Indeed, several diuretics and inhibitors of the angiotensin-converting enzyme are known to exert phototoxic effects and may thus also increase radiosensitivity [35]. Allergy is an inflammatory process with increased expression of several cytokines [36]. Interestingly, some mediators of inflammation such as TGF-beta 1, TNF-alpha and interleukins have been associated with development of late normal tissue damage after irradiation [37, 38].

Cigarette smokers are exposed to a plethora of carcinogens, which may reach the breast tissue via the circulatory system after inhalation [39, 40]. Tobacco carcinogens may induce DNA damage, mainly by formation of DNA adducts [41], and thus add to the cytotoxic effect of ionizing radiation, thereby increasing the risk of late normal tissue complications. Previous studies investigating the effect of smoking have mainly been concerned with organs directly exposed to tobacco smoke. Reports of a higher risk for lanyngeal edema [42] and mucositis [43] after irradiation among smokers than among non-smokers corroborate our findings.

The present study was specifically designed to assess determinants of acute and late side effects of

radiotherapy and hence, radiotherapy modalities were assessed in great detail, women were carefully monitored during radiotherapy, and acute and late toxicity were classified and documented according to standardized scoring schemes. We are thus confident that differences in radiotherapy regimen and follow-up time were adequately controlled for in the analysis and that our findings are unlikely to be due to bias. Unfortunately, the small number of patients presenting with subcutaneous fibrosis at follow-up did not provide sufficient power for a detailed analysis of factors that predispose to fibrosis. However, since late effects of radiotherapy may have a very long latency period [44], more cases may accumulate with extended follow-up time.

In summary, this prospective study revealed several patient-related factors that are associated with late normal tissue complications after radiotherapy for breast cancer. However, these extrinsic factors are not sufficient to explain patient-to-patient variability. Thus, to fully understand differences in radiosensitivity and eventually enable individualized treatment, further research on intrinsic factors and predictive assays is warranted.

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