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SHORT COMMUNICATION

Correlation between anthropometric parameters and acute skin toxicity in breast cancer radiotherapy patients: a pilot assessment study

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Objective: The objective of the present study was to identify acute skin toxicity risk factors linked to the anthropometric characteristics of patients with breast cancer treated with radiation therapy.

Methods: Consecutive patients with breast cancer were enrolled after breast-conserving surgery and before radiotherapy course. Acute skin toxicity was assessed weekly during the 7 weeks of radiotherapy with the International Classification from National Cancer Institute. Grade 2 defined acute skin toxicity. Patient characteristics and anthropometric measurements were collected.

Results: 54 patients were enrolled in 2013. Eight patients (14.8%) had grade ≥ 2 toxicity. The average weight and chest size were 65.5 kg and 93.6 cm, respectively. Bra cup size is significantly associated with a risk of grade 2 dermatitis [odds ratio (OR) 3.46, 95% confidence interval

(CI) (1.29–11.92), $p = 0.02$]. Anthropometric breast fat mass measurements, such as thickness of left [OR 2.72, 95% CI (1.08–8.26), $p = 0.04$] and right [OR 2.45, 95% CI (0.99–7.27), $p = 0.05$] axillary fat, are correlated with an increased risk. Distance between the pectoral muscle and nipple is a reproducible measurement of breast size and is associated with acute skin toxicity with significant tendency (OR = 2.21, 95% CI (0.97–5.98), $p = 0.07$).

Conclusion: Breast size and its different anthropometric measurements (thickness of left and right axillary fat, nipple-to-pectoral muscle distance) are correlated with the risk of skin toxicity.

Advances in knowledge: The present article analyses several characteristics and anthropomorphic measurements of breast in order to assess breast size. A standardized and reproducible protocol to measure breast volume is described.

INTRODUCTION

Breast cancer is the most frequent female cancer in France with 48,763 new cases in 2012.¹ It is now considered as a favourable prognosis cancer, since therapeutic progress has increased survival time to at least 5 years for 83% of patients.² It is estimated that 72.8% of the patients who develop, nowadays, a breast cancer in France will be cured.³ Clearly, one of the next challenges is how to reduce side effects of treatments. Radiotherapy plays a leading role in breast conservation strategy in adjuvant setting, with a significant reduction of local recurrence risk.^{4,5} Acute radiotherapy skin toxicity, or radiodermatitis, is defined by the occurrence of a dermal lesion in the days or weeks following the beginning of radiation therapy, which will heal in the following months.^{6,7} Acute radiodermatitis is ranked from one (erythema) to four (necrosis) in terms of

severity following the International Classification from the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).⁸ Acute skin toxicity is defined by a grade ≥ 2 toxicity. Acute skin toxicity is a frequent radiotherapy complication: grade 1 radiodermatitis occurs in 50–58% of cases, grade 2 in 32% of cases and grade 3 in 4% of cases.^{9,10} It can lead to a pause in the treatment, with significant loss of therapeutic benefit.^{11–13} Radiation parameters, such as total dose, dose per fraction, time between fractions, total treatment time and total treated volume, have an influence on acute skin toxicity.¹⁴ Nevertheless, patients receiving similar radiation treatments can develop toxicities of various intensities.^{15,16} Therefore, factors other than radiation technique can influence the variability of dermal side effects.¹⁷ These factors are probably environmental and associated with individual

radiosensitivity. Individual radiosensitivity is a complex polygenic phenomenon, resulting from the interaction of numerous genes implicated in numerous intracellular signalling pathways.¹⁸ However, it has been shown that patient characteristics, such as smoking, malnutrition or obesity, also has an influence on skin toxicity linked to radiotherapy.¹⁹ We know that a high body mass index (BMI) is a predictive indicator of acute skin toxicity [hazard ratio (HR) = 1.09 for 1 kg m^{-2} with 95% confidence interval (CI) (1.05–1.13)].¹² Besides obesity, breast size is significantly correlated with the risk of radiodermatitis.¹⁷ This leads us to the necessity of measuring precisely large breasts, in order to identify patients with high-risk toxicity.^{10,11,20,21} Bra cup sizes vary depending on the models of bras, and patients are generally unfamiliar with this. So cup sizes cannot be a scientific reproducible and reliable breast measure tool. However, no study has yet developed a standardized protocol to measure the breast fat mass. The primary objective of the present observational prospective study was to analyse acute skin toxicity risk factors linked to anthropometric and clinical characteristics of patients with breast cancer treated with radiation therapy. The secondary objective was to develop a reliable and reproducible measure of breast size and breast fat mass, which can help to identify high-risk groups of acute skin toxicity.

METHODS AND MATERIALS

Population

The present study has been performed at the Radiotherapy Department of Lucien Neuwirth Comprehensive Cancer Care Center, Saint Priest on Jarez France. The inclusion criteria were patients with breast cancer treated with conservative surgery and adjuvant radiotherapy. The protocol respected the ethic guidelines enounced in the Helsinki Declaration.

Procedure

Age, medical history, medical treatments (especially hormonal therapy), co-morbidities (especially diabetes, blood pressure, actual or past smoking), breast cancer characteristics (TNM stage, histological type, Scarff–Bloom–Richardson grade, hormonal receptors, Her2 status) and treatment characteristics (type of energy, total dose, bolus dose, dose per fraction, time between fractions, total treatment time) were collected. Clinical morphological characteristics (bra cup, arm size and BMI), Type I skin on Fitzpatrick scale (pale white skin, blue/hazel eyes, blond/red hair) and the last haemoglobin level were also noted. The radiotherapist (SMN) weekly evaluated acute skin toxicity during the 7 weeks of the treatment and at 3 months after the beginning of radiation therapy.

Tools

Acute skin toxicity was evaluated with the NCI-CTCAE.⁸ Acute skin toxicity was defined by a grade ≥ 2 toxicity.^{12,20,21} Breast size was systematically evaluated before the beginning of the radiotherapy. Bra cup sizes were collected. Breast anthropometric parameters were measured on simulation CT. Breast size was defined by the distance between the pectoral muscle and the nipple, namely the tangent to the pectoral muscle passing through the nipple. Nipple-to-pectoral muscle distance was measured on the mammography image of the healthy breast nipple, since surgery probably alters breast fat mass. Furthermore, subcutaneous

fat thickness was assessed with the distance between skin and spinous process, distance between skin and sternum and the bilateral axillary fat thickness. Axillary fat was assessed as this volume may increase in overweighted females and could cause dose inhomogeneity as it is located at the entrance of radiation therapy external field. Figure 1 is a detailed illustration of these measures. Dosimetric parameters [planning target volume (PTV), clinical target volume, minimum dose ($D_{\min}$), maximum dose ($D_{\max}$), mean dose (D_{mean}), skin hot spots, homogeneity index] were reported. Dose calculation was performed systematically on Varian Eclipse™ treatment planning system (Varian® Medical Systems, Palo Alto, CA) and Dosigray® treatment planning system (Dosisoft, Cachan, France). Homogeneity index was based on the Radiation Therapy Oncology Group definition.²² Skin hot spot was defined by a dose $>107\%$ of the prescribed dose located in the first centimetre below the skin surface.

Statistical analyses

Statistical analyses was performed with R software (The R Foundation for Statistical Computing Vienna, Austria).²³ We analysed the correlation between skin toxicity emergence and several risk factors with a univariate logistic regression. The Wald test was also used. The significant value was set to $p < 0.05$.

RESULTS

Population characteristics

We enrolled 54 patients, with an average age of 62 years. Mean weight was 65.5 kg (47–95 kg), average BMI was 24.9 kg m^{-2} ($19\text{--}37.6 \text{ kg m}^{-2}$) and mean chest size was 93.6 cm (80–115 cm). Medical and physical patient characteristics are summarized in Table 1 and Table 2, respectively. Anthropometric parameters of the whole set of patients are described below: skin-to-xiphoid mean distance was 16 mm (5–33 mm), nipple-to-pectoral muscle mean distance on ipsilateral side was 41 mm (14–69 mm), nipple-to-pectoral muscle mean distance on contralateral side was 42 mm (19–77 mm), left axillary fat mean thickness was 20 mm (5–57 mm), right axillary fat mean thickness was 17 mm (6–63 mm) and skin-to-spinous process mean distance was 15 mm (4–38 mm).

Figure 1. Anthropological assessment on dosimetric CT scan: 1 and 2: nipple-to-pectoral muscle distance on healthy/treated side; 3: skin-to-xiphoid distance; 4: skin-to-spinous process distance; 5: right axillary fat thickness; 6: left axillary fat thickness.

Table 1. Medical patient characteristics

Medical characteristics	Population (<i>n</i> = 54)
Treated breast	
Left	20
Right	34
Smoker status	
Active	9
Former	11
No	34
Fitzpatrick phototyping scale	
Pale	32
Easily tanned skin	21
Unknown	1
Familial history of cancer	
Yes	24
No	29
Unknown	1
Personal history of cancer	
Yes	14
No	40
High blood pressure	
Yes	19
No	34
Unknown	1
Hormone therapy	
Concomitant	9
After radiation therapy	30
No	15
Location	
Upper outer quadrant	25
Upper inner quadrant	7
Lower outer quadrant	2
Lower inner quadrant	3
Other	17
Axillary lymph node dissection	
Yes	22
No	24
Unknown	8
Sentinel lymph node dissection	
Yes	47
No	4
Unknown	3

(Continued)

Table 1. (Continued)

Medical characteristics	Population (<i>n</i> = 54)
Tumour size	
1	43
2	11
Lymph nodes	
0	31
1	21
Unknown	2
Histological type	
Ductal invasive cancer	40
Lobular invasive cancer	7
Other	7
Scarff–Bloom–Richardson	
1	7
2	23
3	24
Hormone receptor status	
Positive	39
Negative	11
Unknown	4
Her2 status	
Positive	11
Negative	37
Unknown	6
Adjuvant chemotherapy	
Yes	36
No	18
Node radiotherapy	
Yes	20
No	34

32 patients had a Type I skin, 9 patients were active smokers and 11 were former smokers. 9 patients were prescribed hormonotherapy simultaneously with radiation therapy, and 36 patients were prescribed chemotherapy.

Skin toxicity and anthropometric risk factors

Eight patients (14.81%) were diagnosed with a grade ≥ 2 toxicity (*i.e.* at least severe erythema). Axillary fat thickness is significantly correlated with acute skin toxicity, whenever ipsilateral or contralateral sides are assessed [left side: odds ratio (OR) 2.72, 95% CI (1.08–8.26), $p = 0.04$; right side: OR 2.45, 95% CI (0.99–7.27), $p = 0.05$]. Bra cup size is significantly associated with a risk of radiodermatitis [OR 3.46, 95% CI (1.29–11.92), $p = 0.02$]. We also found the following trends: radiodermatitis occurrence may be correlated with nipple-to-pectoral muscle

Table 2. Physical patient characteristics

Physical characteristics	Average	Median	Minimum	Maximum
Weight (kg)	65.5	62.0	47.0	95.0
Height (m)	1.61	1.62	1.42	1.75
BMI (kg m ⁻²)	24.9	23.2	18.8	37.6
Chest measurement (cm)	93.6	93.0	80.0	115.0
Brachial perimeter (cm)	29.4	29.0	22.0	46.0

BMI, body mass index.

distance [OR 2.21, 95% CI (0.97–5.98), $p = 0.07$], and actual or past smoking may have fostered the appearance of skin toxicity [OR 4.09, 95% CI (0.86–22.89), $p = 0.08$]. Skin toxicity and correlations data are given in Table 3.

Data on dosimetry

No hot spot was located within the skin surface. No minor/major deviation was reported based on Radiation Therapy Oncology Group homogeneity index. Mean PTV was 1026.7 cm³ (range: 333–2178 cm³), mean PTV among patients suffering from acute skin toxicity was 1264.9 cm³ (range: 540.5–2106 cm³). Data on dosimetry are reported in Table 4.

DISCUSSION

Three new predictive anthropometric characteristics seem to be linked to acute skin toxicity risk: left axillary fat thickness, right axillary fat thickness and nipple-to-pectoral muscle distance. This last measure could be considered as a new, reliable and reproducible assessment of breast size. However, owing to the limited number of patients and of patients with grade ≥ 2 toxicities, comparison between the groups is difficult and results are to be taken cautiously. Big bra cup size is a well-known predictive factor of acute skin toxicity, yet. When we

can foretell the acute skin toxicity risk with those objective anthropometric parameters, we will be able to prescribe radiotherapy schedules precisely adapted to the risk group. A high-risk morphotype group can be defined, with particular characteristics such as big-breasted females, of Type 1 skin on Fitzpatrick scale, former or active smokers. For this group, a specific radiotherapy protocol should be proposed. According to Moody et al,²⁴ the high skin toxicity risk of big-breasted patients is linked to localized hot spots and dose heterogeneity. This might be avoided with a “field-in-field” technique or with intensity-modulated radiation therapy.^{17,25,26} However, in the present study, homogeneity indexes were excellent and could not be correlated with acute skin toxicity. No hot spots within below the skin surface were reported either. Such results must be taken very cautiously: although dose calculations were performed with two different treatment planning systems, algorithms do not give reliable results within the skin. The hypothesis of dose heterogeneity within the skin cannot be excluded, as intensity-modulated radiation therapy showed interesting clinical results.²⁶ Selecting patients according to the objective and reproducible risk factors is a *sine qua non* condition to individualize treatments in order to minimize acute skin toxicity of radiation. However, risk factors other than

Table 3. Correlation between patient parameters and acute skin toxicity

Correlation to grade ≥ 2 toxicity	Odds ratio	p	95% confidence interval
Former or active smoker	4.09	0.08	0.86–22.89
High blood pressure	0.62	0.58	0.08–3.13
Phototype	0.55	0.49	0.07–2.77
Chemotherapy	1.56	0.61	0.31–11.68
Body mass index	1.91	0.10	0.89–4.53
Breast size	1.10	0.10	0.98–1.25
Bra cup size	3.46	0.02	1.29–11.92
Lymph node treatment	1.69	0.50	0.35–8.31
Skin-to-xiphoid distance	1.02	0.95	0.45–2.18
Nipple-to-pectoral muscle distance on the healthy side (mm)	2.21	0.07	0.97–5.98
Nipple-to-pectoral muscle distance on the treated side	2.07	0.10	0.89–5.38
Skin-to-spinous process distance	1.37	0.42	0.62–8.26
Left axillary fat thickness	2.72	0.04	1.08–8.26
Right axillary fat thickness	2.45	0.05	0.99–7.27

Table 4. Data on dosimetry

Dosimetric characteristics	Mean (range)
PTV	
In overall population (cm ³)	1026.7 (333.0–2178.0)
In patients with skin toxicity (cm ³)	1264.9 (540.5–2106.0)
$D_{\min}$ (Gy) ^a	1.9 (0.0–14.5)
$D_{\max}$ (Gy) ^a	68.8 (66.8–70.6)
D_{mean} (Gy) ^a	49.5 (36.7–56.6)
Homogeneity index ^{a,b}	1.04 (1.01–1.07)
Hot spot within the skin ^a	0 (0–0)

$D_{\min}$, minimum dose; $D_{\max}$, maximum dose; D_{mean} , mean dose; PTV, planning target volume.

^aAmong overall population.

^bCalculated with Radiation Therapy Oncology Group homogeneity index.²²

anthropometric risk factors have been shown to play a leading role in the variability of skin toxicities. Phototype is obviously a major predictive factor of skin radiosensitivity.²⁷ Other factors have been described, such as diabetes, immunodepression, malnutrition, smoking or obesity.¹⁹ If we find tobacco as a predictive factor of skin toxicity, on the contrary, it is not the case of BMI,

probably because of our reduced patient sample. Indeed, it was shown that co-morbidities such as obesity or tobacco act as co-factors which modify radiotoxicity.²⁸ According to the authors,²⁸ this could explain 30% of individual variability to radiations. Moreover, Chang-Claude et al²⁹ showed that the polymorphism of DNA repair genes (*XRCC1* and *APE1*) seems to be a protective factor against acute radiotherapy skin toxicity, but only among normal-weight females. The genotype's protective effect of *XRCC1* and *XPB* is not found among obese or overweight patients. It seems otherwise that diabetes or autoimmune diseases have an influence on radiosensitivity.³⁰

CONCLUSION

The present study shows the close links between various anthropomorphic parameters and increased risk of skin toxicity. Breast volume is not exactly evaluated using bra cup size, whereas it is a major predictive factor of skin toxicity and represents a particular medical interest. The retrospective nature of the study and the small number of patients are limitations, but the present pilot study provides preliminary results and tendencies in order to design a largest prospective study in a near future. The present study describes a standardized and reproducible protocol to measure breast volume, with breast fat mass and nipple-to-pectoral muscle distance.

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