Evaluation of the risk factors of radio-dermatitis after breast-conserving surgery

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Research article

Keywords: Breast cancer, post-breast-conserving surgery, radiotherapy, risk factors of radio-dermatitis (RD)

Posted Date: February 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-15417/v1

Abstract

Background

The morbidity of breast cancer has been ranked first among female cancers worldwide and increased by 2% each year in these ten years [1]. Although China as a country with a relatively low incidence of breast cancer compares to other countries, the rapid growth rate of breast cancer is still worth noticing [2].

Method

A total of 521 patients with breast cancer diagnosed in the Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology and underwent breast conserving surgery (lumpectomy plus local radiotherapy) were selected, to investigate demographic data, disease data, treatment data and behavior data. Using univariate and multivariate logistic regression method to analyze the risk factors of RD after radiotherapy.

Results

The variable factors of age ≤40 years old, whiter skin, treatment time in summer, BMI≥25, local thermal therapy, sun exposure, skin scratching and bra wearing are the risk factors of radio-dermatitis, while the affected limb akimbo in daytime and elevating the affected limb in sleep are the protective factors of radio-dermatitis.

Conclusion

This study aims to observe the situation of post-radiotherapy RD after breast-conserving surgery in patients with breast cancer, analyze the risk factors related to patients and treatment, and provide the relevant clinical basis for reducing and preventing the occurrence of RD after breast-conserving surgery.

1. Introduction

At present, except a small number of advanced breast cancer is still using the traditional radical or extended radical surgery, improved surgery such as breast-conserving surgery has been the major surgery treatment of breast cancer in China. On the other hand, radiotherapy as one of the indispensable treatment methods for breast cancer, which can eliminate the subclinical carcinogenesis, and local recurrence can be significantly reduced by adding radiation therapy after breast-conserving surgery. In the course of radiotherapy, while inhibiting or killing the tumour cells, it also has some adverse impact on body tissues, thus causing different levels of radiation damage to normal tissues. It can cause both local and systemic reactions, among which the most common is skin damage, namely radiodermatitis (RD), manifested as varying degrees of erythema, dry, wet peeling, ulcers and other skin damage [3]. Patients with severe RD usually need to suspend radiotherapy and wait for skin repair, which causes the patient to suffer and also causes certain economic losses [4]. Therefore, to find out the risk factors and their corresponding prevention of RD has always been the particular concern of the medical care personnel.

Breast conserving surgery is suitable for T1, T2 and partial T3 stages of breast cancer. Nevertheless, due to the limitation of Chinese national conditions, the proportion of breast conserving surgery in China is far from in United States, France and other western countries [5]. With the enhancement of early diagnosis, the development of comprehensive systemic treatment, popularity of technology and advanced radiotherapy equipment, and the improvement of post-operative quality of life for breast cancer patients, laid the foundation for breast conserving surgery that make it to be the inevitable trend of breast cancer [6]. On the other hand, radiotherapy as one of the indispensable treatment methods for breast cancer, which can eliminate the subclinical carcinogenesis. Local recurrence can be significantly reduced by adding radiation therapy after breast conserving surgery. In addition, as the development of conformal strength modulation technology, the radiation dose is more reasonable, and the chest radiation injury has significantly reduced. Thus, the radiation therapy is as a routine treatment nowadays [7].

In terms of RD is an adverse cutaneous reaction that occurs during or after radiotherapy or interventional radiology. There are two major factors that affect RD, which are internal factors (patient's own factors affecting wound healing) and external factors (radiation dose, energy and segmentation method). Due to the external factors are controllable, however, the internal factors are determined by the combination of immutable innate genetic factors and intervening acquired personal factors [8]. Thus, based on the theoretical basis above, this study divides these two factors into three parts. Firstly, radiation factors, including radiation dose, energy, location, and so on; Secondly, genetic factors, including gender, size of breast, co-existing radiosensitive diseases, cancer susceptibility family, hereditary cancer, family history of cancer, and so on. Thirdly, personal factors, including age, and with basic diseases, such as diabetes, chemotherapy, nutrition level, smoking, infection, UV exposure, etc.

2. Method

From January 2018 to December 2019, a total of 521 patients with breast cancer diagnosed in the Union Hospital affiliated to Tongji Medical College of Huazhong University of Science and Technology and underwent breast conserving surgery (lumpectomy plus local radiotherapy) were selected, to investigate demographic data, disease data, treatment data and behavior data. Using univariate and multivariate logistic regression method to analyze the risk factors of RD after radiotherapy.

2.1 Radiotherapy

2.1.1 Patients with fixed

The patient lies supine on a special breast bracket. According to the bodily form of the patient to determine the position of head pillow, the surface of breast bracket inclination, the fixed location of upper limbs and hips, let the affected side of chest wall at a horizontal level, and make sure the upper arm is fully raised.

2.2.2 CT simulation orientation

Determining the laser alignment point on the patient body surface. Spiral CT was used to scan the calm breathing state, and the scanning layer was 5mm. The scan covers the entire mammary gland and extents at least 3mm away from the upper and lower boundary, where including all the adjacent tissues and organs, such as bilateral lungs and breasts, heart, and so on. The CT images were obtained and transmitted over a private network to the 3D radiotherapy planning system (3D-TPS).

2.2.3 Target area delineation and definition

The CT simulated positioning image with 3D-TPS will be transferred for 3D reconstruction. The affected breast is the clinical target volume (CTV). The upper boundary is the level of the thoracic entrance or the lower margin of the clavicle head, the lower boundary is 2cm below the breast fold; While the inner boundary is the ipsilateral sternocostal joint, and the outer boundary is the midaxillary line or the posterior axillary line; The anterior boundary is 5mm below the thoracic epidermis, and the posterior boundary is close to the chest wall. The planned target volume (PTV) is obtained by extending 5mm of the CVT.

2.2.4 Treatment plan design

Intensity modulated radiotherapy (IMRT) plan was designed by using 3D-TPS, IMRT was beneficial to evenly distribute the radiation dose in the breast target area, that effectively reduce the skin damage level during radiotherapy [9]. The radiation source is 6mv-X-ray, and 5–7 coplanar conformal fields were set, to optimize the bed angle, frame angle and each field dose weight. Using MLC to form 25–40 subfields for distribution irradiation. The prescription dose for whole breast is 50Gy/25times. Then 8mv-E electron wire is used to supplement the tumor bed with 10Gy daily, 5 days a week.

2.2.5 Use of skin compensation film on the chest wall

In this study, 0.5–1cm thick compensation film was used to increase the skin dose of chest wall when the radiotherapy treatment dose of enrolled patients reached 0–36Gy.

3. Evaluation Tool

The first time of skin observation of this study was the 30 days after the start of the radiotherapy, and the changes of chest wall were not recorded after 300 days. The second observation end point was when the patient's skin symptoms were first assessed as radioactive dermatitis. The severity of radiodermatitis was determined on the basis of the clinical manifestations of grade 1–3 radiodermatitis which were defined in the Common terminology criteria for adverse events (CTCAE) version 4.0, which has been designed by the National Cancer Institute (NCI) of the National Institutes of Health (NIH), to evaluate the

severity of organ or tissue toxicity or damage for patients receiving cancer therapy [10]. Before radiotherapy, the patients were informed with the information about potential skin damage during the radiotherapy by their attending physician, and to be asked to report the skin changes in a timely manner without self-treatment. Skin changes were evaluated by an experienced nursing care team at least once a week.

3.1 Statistical approach

Statistic package for social science (SPSS) 24.0 software was used for statistical analysis. The incidence of radiodermatitis is calculated by Kaplan-Meier method. Kaplan-Meier method is used to estimate the survival function from lifetime data. In medical research, it frequently be used to measure the fraction of patients living for a certain duration of time after a certain treatment [11]. Risk factors of radiodermatitis after radiotherapy are analyze by stepwise logistic regression with single and multiple factors. $P < 0.05$ is considered as statistically significant.

3.2 Results

3.2.1 Results: Clinical characteristics of patients

These results include all the 521 patients who had completed radiotherapy and skin compensation membrane (See table 1). The results showed that there were statistically significant differences between the two groups in age, BMI, skin type, season, local hyperthermia, sun exposure, skin scratching, bra wearing, limb akimbo during the day, and limb elevation during sleep ($P<0.05$). However, there were no significant differences in the factors which include hypertension, diabetes, T stage, grade, occurrence time and adjuvant chemotherapy between the two groups ($P>0.05$).

3.2.2 Results: Incidence and occurrence time of radiodermatitis

In this study, the incidence of radiodermatitis after radiotherapy in breast cancer patients undergoing breast conserving surgery was 10.39%. The severity was mainly second degree that at a proportion of 76.11%, and the median time of occurrence was within two weeks after the end of radiotherapy (See table 2). The dependent variable was radiodermatitis, and the independent variables were age, BMI, skin type, summer, local hyperthermia, sun exposure, skin scratching, bra wearing, akimbo the affected limb in the daytime and elevation of the affected limb while sleeping. Logistic regression analysis has performed as in table 2.

The regression results in the table 3 has shown that the age, skin type, the affected limb akimbo in daytime and elevation of limb while sleeping had a negative effect on the presence or absence of radiodermatitis (P<0.05). On the other hand, the variable factors of BMI, summer, local hyperthermia, sun exposure, skin scratching and bra wearing had positive effects on the presence or absence of radiodermatitis (P>0.05). Through the results, it suggested that the variable factors of age ≤40 years old, whiter skin, treatment time in summer, BMI≥25, local thermal therapy, sun exposure, skin scratching and bra wearing are the risk factors of radiodermatitis, while the affected limb akimbo in daytime and elevating the affected limb in sleep are the protective factors of radiodermatitis (see table 3).

4. Discussion

In this retrospective study, relevant data were collected to evaluate the incidence and risk factors of radiodermatitis after radiotherapy after breast conserving surgery in female breast cancer patients. Reasonable study design was adopted to collect and evaluate patients' symptoms every week during and after radiotherapy, so as to ensure timely and accurate data collection and objectivity. However, the main defect of this study is that the data comes from a single medical center, which may affect the results of the factor analysis and lead to biased results.

Among the factors that affect radiodermatitis, clinical radiologists paying more attention on radiation factors than genetic factors, as the genetic factors are harder to intervene than the radiation factors. In nursing aspect, by contrast, the part that allows for early intervention is the individual factors. At present, the empirical data of individual factors are very limited, but they are the most concerned and interested part of clinical radiology nurses. In the risk factors which related to radiodermatitis, the study controlled for radiotherapy factor related variables, by focusing on individual variables such as individual factors and genetic factors related to the partial treatment, and combining relevant literature, to expend corresponding nursing measures.

Under normal circumstance, the skin is in a continuous process of metabolism, the surface cells shed, the basal cells divide and multiply, migrate toward epidermis, keratinization. However, radiotherapy can lead to irreversible double-strand breaks in DNA of basal keratinocytes, stem cells in the hair follicles and increased melanocytes production. The migration of immune cells such as leukocytes to from circulation toward to irradiated skin area is the significant hallmark of radiodermatitis. Thereafter, the death of epidermal cells, biochemical changes in endothelia cells and DNA destruction, as well as inflammatory reactions that can cause skin damage [12].

In the existing studies on risk factors of radiodermatitis, empirical evidence shows that age, skin characteristics, nutritional status, basic diseases, race, smoking, genetic factors, radiation dose, concurrent chemotherapy and irradiation site are closely related to radiodermatitis [13]. In this study, according to logistic regression analysis that age below 35 years, fair skin, treatment time in summer, BMI above 25, local thermotherapy, sun exposure, hot water bath, skin scratch and bra wearing were risk

factors for radiodermatitis in patients. The protected factors of the affected limb were akimbo in day time and elevation of the affected limb before bedtime ($P<0.05$, $P<0.01$).

Body weight/ BMI/ smoking/ diabetes

Body weight, BMI, smoking, diabetes which are metabolic diseases are different from some foreign studies in multivariate analysis of patient own factors, which did not exclude the limitations caused by monocentric study and ethnic differences. According to Beamer (2019) [14], body weight and BMI can be seen as an evaluative parameter to predict the degree of radiodermatitis, as the data has shown that more dermatitis responses in heavier patients than in lighter patients, whilst age and height had no effect on radiodermatitis. In this study, we obey the BMI standard which seen BMI>25 as overweight and BMI>30 as obese, while the results have been showed that in the radiodermatitis group in table 1, there are 55 out of 57 of patients whose BMI ≥25; This means BMI significantly can be a risk factor of developing radiodermatitis.

Furthermore, Marinello et al. (2016) [15] noted that smoking history has been included as a risk factor for radiodermatitis, as smoking aggravates the microcirculation abnormality that caused by radiotherapy. Due to the low proportion of smoking history in the enrolled patients in this study, they were not included in the study scope. Further relevant studies are needed to determine whether metabolic abnormalities such as obesity and diabetes that affect the repair mechanism of radiological damage to the skin.

Adjuvant radiotherapy

Adjuvant radiotherapy after breast conserving radical surgery can reduce the local recurrence rate of breast cancer, among which patients with high risk factors that need adjuvant chemotherapy to improve their survival rate. Although radiotherapy combined with adjuvant chemotherapy can exacerbate adverse reactions, but generally for most patients with good tolerability, postoperative radiotherapy and adjuvant chemotherapy are safe and feasible. Radiotherapy combined with adjuvant chemotherapy also demonstrated improved rates of breast conservation and reduced risk of locoregional recurrence, which are safe and feasible [16]. In this study, the factor of concurrent chemotherapy was taken into consideration to analyze whether it aggravates the incidence of radiodermatitis.

Patient age ≤ 40 years

Age ≤ 40 years for the viewpoint that the prognosis of young women with breast cancer is worse than that of elderly women, relevant western studies define the range of young women as ≤ 40 years, while the Chinese domestic literatures classified the age as ≤ 40 years as well [17–18]. In terms of this study, age ≤ 40 years was considered as one of the risk factors for the occurrence of radiodermatitis, and statistical analysis was conducted.

Skin color and sun exposure

The grating characteristics of Chinese women's skin color were evaluated in this study. The effect of X-ray radiation on the skin during radiotherapy depends on how sensitive the skin towards to the radiation [19]. Considering that the principle of the action of rays on the skin is similar to the reaction of the skin caused by solar irradiation, this study suggests that the sunlight reaction can be related to dermatitis reaction of patients. In this study, the skin color of patients was evaluated and the degree of sunlight exposure of patients to their skin color and daily activities were also evaluated. From level 1 (always exposure to the sun, rarely tanned) to level 4 (rarely exposure to the sun, but easily tanned), in order to reflect the sensitivity of the patients to radiation, and thus to infer the possibility of radiodermatitis. According to the study of Yamazaki et al. (2011) [20], skin pigmentation of patients after radiotherapy was predicted by skin color changes that caused by sun exposure; This study believed that the degree of sun exposure and skin color of patients could be used as criteria to judge whether patients were at high risk of radiodermatitis.

Treatment time

When the treatment time is summer, the climate is hot and humid, the capillary diastole and the blood circulation is rich. Increased sensitivity of vascular endothelia cell to the radiation, coupled with more local skin sweating, thus increase the chance of wet dermatitis. There are few research data and references in this filed. Combined with the experience of a large number of clinical nurses, it is considered that the admission time of patients with radiodermatitis is concentrated in summer. Therefore, the correlation between seasonal factors and the incidence of radiodermatitis was statistically analyzed.

Local thermal therapy

Local thermal therapy is an advanced and effective method to treat tumor. The clinical trial has shown that the combination of thermal therapy and radiotherapy can significantly improve the local control rate of tumors and the survival rate of patients [21]. Lilla et al. (2007) [22] reported that the radiotherapy circumstance of 416 cases of breast cancer patients after breast conserving surgery, and analyzed the significant relationship between radioactive dermatitis and telangiectasia, this allowed for local hyperthermia to cause telangiectasia at the site of radiotherapy. At the same time, combined with relevant studies and analysis, it was found that although adverse reactions to thermal therapy were relatively mild, it can still cause blisters, subcutaneous indentation, subcutaneous pain, and even more serious skin damage such as radiodermatitis [23]. Therefore, local thermal therapy was included in this study.

A hot bath/ scratching the skin/ Wearing a bra/ exposure to the sun

After the patients with a diagnosis of breast cancer have had radiotherapy, the skin tissue where has been accepted radiation became thinner than before, particularly prone to skin reactions. Relevant evidence-based nursing studies show that in order to reduce reaction after radiotherapy, relevant skin care measures include: 1) Educating patients to wear cotton underwear to avoid skin friction in and around the radiotherapy area. 2) Local soap scrubbing or hot water bath and sun exposure are prohibited to avoid skin irritation in the radiotherapy area. 3) When the skin in the radiotherapy area is itchy and unbearable, gently pat the local skin with their hand, cannot scratch the skin [24]. Although such nursing education is conducted by nurses to patients in daily clinical care, the effects of activities such as hot baths, scratching of skin, wearing of bras and exposure to the sun on radiodermatitis are still discussed and analyzed in consideration of the differences in patient compliance.

5. Conclusion

This retrospective study is based on the observation and statistics of the relevant clinical characteristics and incidence of chest wall radiodermatitis of 521 female breast cancer patients treated with radiotherapy after breast conserving surgery. It was found that age ≤ 40 years, fair skin, treatment time is in summer, BMI ≥ 25, local hyperthermia, sun exposure, hot water bath, skin scratching and bra wearing significantly increased the risk of radiodermatitis. Given the impact of radiodermatitis, especially grade 2 to 3 radiodermatitis, on permanent damage to the skin, the nursing team needs to carefully assess the patient's risk factors before and after radiotherapy, and carry out targeted nursing for high-risk groups, to reduce the incidence of radiodermatitis, improve the quality of life of patients, maintain the beauty of breast after breast-conserving treatment, and reduce the psychological pressure of patients.

Declarations

- Ethical approval This study has been approved by the Ethics Committee of Drug Clinical Trials of Huazhong University of Science and Technology; It has been carried out in the city of Wuhan, where located in the middle south of China, with the registration number 1900022422. The participants who have been involved in this study has signed the informed consent form before being included in the study.
- Consent for publication Not applicable.
- Availability of data and materials The data be used and analyzed during the current study are available from the corresponding authors on reasonable request.
- Competing interests The authors declare that they have no competing interests.
- Funding The role of 2018 textbook construction project of Huazhong University of Science and Technology in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript that gave much support. The reference number is 02.05.18020018.
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Tables

Table 1 The difference comparison between the two groups of influencing factors [n (%)]

factors		Non-radiodermatitis group (n=464)	Dermatitis group (n=57)	x^2/Z	P
				8.994※	0.003
Age	≤40	228(49.1)	40(70.2)		
	>40	236(50.9)	17(29.8)		
Hypertension				0.204※	0.651
	none	459(98.9)	56(98.2)		
	yes	5(1.1)	1(1.8)		
Diabetes				0.109※	0.741
	none	444(95.7)	54(94.7)		
	yes	20(4.3)	3(5.3)		
BMI(Kg/m^2)				8.649※	0.003
	<25	89(19.2)	2(3.5)		
	≥25	375(80.8)	55(96.5)		
T stage				0.040※	0.842
	stage1-2	275(59.3)	33(57.9)		
	stage3-4	189(40.7)	24(42.1)		
Grade				-0.209△	0.834
	Grade 1	30(6.5)	4(7.0)		
	Grade 2	382(82.3)	47(82.5)		
	Grade 3	52(11.2)	6(10.5)		
Occurrence time				-0.347△	0.729
	<2weeks	259(55.8)	31(54.4)		
	2-4week	145(31.3)	17(29.8)		
	>4	60(12.9)	9(15.8)		
Adjuvant chemotherapy				0.104※	0.747
	no	47(10.1)	5(8.8)		

	yes	417(89.9)	52(91.2)		
Skin type				-3.928△	<0.01
	I	13(2.8)	12(21.1)		
	II	241(51.9)	31(54.4)		
	III	176(37.9)	10(17.5)		
	IV	27(5.8)	3(5.3)		
	V	7(1.5)	1(1.8)		
Season				13.08※	0.004
	Spring	92(19.8)	11(19.3)		
	Summer	147(31.7)	31(54.4)		
	Autumn	150(32.3)	10(17.5)		
	Winter	75(16.2)	5(8.8)		
Local thermal-therapy				9.788※	0.002
	no	232(50.0)	16(28.1)		
	yes	232(50.0)	41(71.9)		
Sun exposure				9.250※	0.002
	no	420(90.5)	44(77.2)		
	yes	44(9.5)	13(22.8)		
Skin scratching				11.25※	0.001
	no	438(94.4)	47(82.5)		
	yes	26(5.6)	10(17.5)		
Bra dressing				10.68※	0.001
	no	418(90.1)	43(75.4)		
	yes	46(9.9)	14(24.6)		
Akimbo the affected limb in the day time				4.182※	0.041
	no	382(82.3)	53(93.0)		

	yes	82(17.7)	4(7.0)		
Raise the affected limb while sleeping				6.218※	0.013
	no	346(74.6)	51(89.5)		
	yes	118(25.4)	6(10.5)		

Note: ※The statistic x^2 value of the chi-square test；△The statistic Z value of the rank sum test.

Table 2 The evaluation of variables

Variable		Value assignment
Dependent variable	Radiodermatitis	0=no，1=yes
Independent variable	Age (year)	1=≤40，2=>40
	BMI	1=<25Kg/m^2，2=≥25Kg/m^2
	Skin type	1= type I，2= type II，3= type III，4= type IV，5= type V
	Summer	0=no，1=yes
	Local thermal therapy	0=no，1=yes
	Sun exposure	0=no，1=yes
	Skin scratching	0=no，1=yes
	Bra dressing	0=no，1=yes
	Akimbo of the affected limb in the daytime	0=no，1=yes
	Elevation of the affected limb while sleeping	0=no，1=yes

Table 3 Logistic regression analysis of the influence of different factors on radiodermatitis

Factors	Regression coefficient	Standard error	Wald	P	OR	95CI	
						Lower limit	Upper limit
age	-0.730	0.332	4.826	0.028	0.482	0.251	0.924
BMI	1.838	0.749	6.017	0.014	6.281	1.447	27.273
Skin type	-0.728	0.249	8.565	0.003	0.483	0.297	0.786
Summer	1.019	0.323	9.973	0.002	2.772	1.472	5.218
Local thermal therapy	0.973	0.341	8.145	0.004	2.645	1.356	5.158
Sun exposure	1.022	0.414	6.077	0.014	2.778	1.233	6.259
Skin scratching	0.962	0.469	4.210	0.040	2.618	1.044	6.566
Bra dressing	1.144	0.418	7.481	0.006	3.140	1.383	7.128
Akimbo the affected limb in the daytime	-1.292	0.580	4.963	0.026	0.275	0.088	0.856
Elevating the affected limb while sleeping	-0.998	0.484	4.241	0.039	0.369	0.143	0.953