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ORIGINAL ARTICLE

Clinical significance of S100A7 protein in predicting recurrence of breast cancer in patients undergoing breast-conserving surgery with radiotherapy*

Chao Zhang[1], Changyou Li[2], Gaoyang Lin[3], Yao Qi[4], Zhenfeng Li[5], Jing Xu[4], Tianhui Su[5], Xin Liu[5], Xiao Zou[5] (✉)

[1] Department of Medicine, Qingdao University, Qingdao 266003, China
[2] Biotherapy Center, The Second Affiliated Hospital of Qingdao University, Qingdao 266003, China
[3] Department of Thoracic Surgery, The Affiliated Qingdao Hiser Medical Center of Qingdao University, Qingdao 266003, China
[4] Department of Pathology, The Second Affiliated Hospital of Qingdao University, Qingdao 266003, China
[5] Department of Breast Surgery, The Second Affiliated Hospital of Qingdao University, Qingdao 266003, China

Abstract

Objective To investigate the relationship between the expression of S100A7 protein and prediction of recurrence and prognosis of breast cancer in patients undergoing breast-conserving surgery combined with radiotherapy.

Methods 349 samples of carcinoma tissue wax blocks were selected from January 2011 to January 2014 in Qingdao Central Hospital. All the patients had undergone breast-conserving surgery. We analyzed S100A7 expression in tumor tissue by immunohistochemical staining. Using univariate and multivariate analyses, we evaluated the relationship between S100A7 and clinical results, to explore independent risk factors for local regional recurrence (LRR).

Results The positive expression of S100A7 in the recurrence group (66.7%) was significantly higher than in the non-recurrence group (38.4%), $P = 0.025$. A log-rank test showed that high S100A7 expression was significantly correlated with 5-year regional recurrence free survival rate (RFS) (94.9% *vs* 89.5%, $P = 0.0408$), distant metastasis free survival rate (DFS) (95.4% *vs* 83.5%, $P < 0.001$), and overall survival rate (OS) (99.0% *vs* 92.5%, $P = 0.0011$). Histological grade, vessel carcinoma embolus, lymph node metastasis, S100A7 expression, and tumor size were factors that influenced RFS. Multivariate analysis of the Cox proportional hazard model showed that high S100A7 expression was an independent risk factor that affected breast cancer RFS (HR = 6.864, 95 % CI: 1.575 - 29.915, $P = 0.01$).

Conclusion We concluded that high S100A7 expression is associated with increased risk of LRR and distant metastasis of breast cancer after breast-conserving surgery and postoperative radiotherapy. S100A7 can be used as a molecular marker to screen for patients with high recurrence risk after breast-conserving surgery.

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Key words: S100A7; breast-conserving surgery; radiotherapy; locoregional recurrence; prognosis

The high incidence of breast cancer and the associated high death rates are major health problems globally. In 2018, an American Cancer Society study involving data from 185 countries and 36 types of cancer, showed that one of every 4 female patients with cancer had breast cancer, which was the first in both incidence and death rate of female malignant tumors [1]. At present, the diversity of breast cancer treatment methods and the application of new technologies have made the breast-conserving surgery more popular, which can not only guarantee good therapeutic effect, but also does not reduce the quality of life. Breast-conserving surgery combined

✉ Correspondence to: Xiao Zou. Email: 18372704337@163.com
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with radiotherapy has gradually become the standard treatment for patients with early stage breast cancer, and can significantly reduce the risk of local recurrence and distant metastasis [2]. A study from the Chinese Academy of Medical Sciences also confirmed the above view. On the basis of standard treatment, breast-conserving surgery combined with postoperative radiotherapy can reduce the local regional recurrence rate by approximately 10 percent in 5 years [3]. However, recurrence is an important cause of tumor advancement, metastasis, and treatment failure. Multiple studies have shown that local regional recurrence leads to poorer disease-free and overall survival [4, 5]. Therefore, to improve the therapeutic effect and reduce recurrence and metastasis rate, is a major research challenge in the field of breast cancer.

S100 proteins are a family of small acidic calcium ion-binding proteins and their abnormal expression is involved in the development of many tumors. At present, there are at least 20 known S100 protein family members in humans, and are abnormally expressed in many kinds of cancers, such as breast cancer, gastric cancer, skin cancer, and cervical cancer [6]. S100A7 (S100 calcium-binding protein A7 was first implicated in psoriasis and it plays an important role in regulating various cellular functions such as calcium homeostasis, cell proliferation, differentiation, apoptosis, and cell invasion [7]. S100A7 is believed to enhance the growth and invasiveness of breast cancer cells and plays an important role in the progression of breast cancer [8]. The mechanism may be that the immunoglobulin transmembrane receptor family, also known as late glycation end product receptor (RAGE), acts like a cytokine [9]. Many studies have confirmed that high S100A7 expression is closely related to a number of clinicopathological indicators, with differences in the expression of S100A7 in some special types of breast cancer, suggesting that it is a potential molecular marker for predicting the prognosis of recurrence and metastasis of different types of breast cancer [10–11]. Tumor recurrence and metastasis are complex processes and involve many factors; specific mechanisms remain to be clarified. At present, there are only few studies on the relationship between S100A7 and breast cancer recurrence, and on the relationship between S100A7 and the reactivity of postoperative radiotherapy for breast cancer. This study retrospectively investigated the relationship between S100A7 expression levels after breast-conserving surgery and its relationship with radiotherapy reactivity, to find new molecular markers that can effectively predict breast cancer recurrence after breast-conserving surgery and thus, help to formulate rational treatment plans and improve patient prognosis.

Material and methods

Inclusion and exclusion criteria

The inclusion criteria for this study were: (1) Negative pathological cutting margin and invasive carcinoma after breast-conserving surgery, (2) Radiotherapy, neoadjuvant chemotherapy, and endocrine therapy were not performed before the surgery, (3) Availability of complete clinical data and pathological results, and (4) Standardized whole-breast radiotherapy performed postoperatively. Exclusion criteria were: (1) Non-primary breast cancer patients, (2) Bilateral cases, (3) Inflammatory breast cancer, (4) Patients with stage IV breast cancer with distant metastasis before surgery, (5) Patients with serious life-threatening diseases or other malignant tumors, and (6) Patients with incomplete medical records.

Radiotherapy regime and tumor classification

The samples were collected from January 2011 to January 2014 at The Second Affiliated Hospital of Qingdao University, China from 349 patients after breast-conserving surgery and preserved as wax blocks. After the surgery, the patients received standard whole-breast radiation treatment, and the average postoperative adjuvant radiotherapy dose for the whole breast and regional lymph nodes on the affected side was 50 Gy/25 times/5 weeks. During the study period, adjuvant systemic chemotherapy, endocrine therapy, and targeted therapy were also implemented according to the guidelines. All patients were female; the age of onset was determined by the time of definite diagnosis, and the tumor size was determined by the maximum diameter of tumor in the pathological report, referring to the TNM staging criteria published in the 8th edition by the AJCC [12]. Histological grading was performed using the modified Scarff-Bloom-Richardson grading method, with grades 1–3. According to the expression of estrogen receptor ER, Progesterone receptor PR, human epidermal growth factor receptor-2 HER2, and proliferating cell related nuclear antigen (Ki67), the breast cancer was classified into the following types: Luminal A, Luminal B1, LuminalB2, and overexpression of HER2, TNBC type [13].

Clinical outcomes after surgery and radiotherapy

The information on postoperative survival, recurrence and metastasis for all the patients was mainly obtained by consulting the information of hospitalization, case follow-up system, outpatient and imaging system examination, as well as regular emails and telephone calls, to understand and record the prognosis and survival information of patients. The local recurrence free survival (RFS), distant metastasis free survival (DFS) and overall survival (OS) were recorded after the surgery till the final follow-up or

the time of death.

Immunohistochemical staining

The sections (thickness 4 μm) were soaked with fresh xylene, dewaxed and hydrated with ethanol of different concentration gradients, and thoroughly rinsed with PBS. The well-matched EDTA antigen repair solution (Beijing Zhongshan Jinqiao Biotechnology Co. Ltd., China) was heated to boiling to fully expose the epitope (95 °C, 6 min), cooled to room temperature, and then rinsed with PBS. The enzyme was removed by endogenous peroxidase inhibitors, incubated at room temperature for 10 min, and washed with PBS. Goat serum was used to avoid non-specific staining, incubated at room temperature for 15 min, and poured into the serum without washing. Primary antibody against S100A7 was added (dilution 1:200, Santa Cruz Biotechnology Co., Ltd., USA), and the antibody was replaced with PBS buffer in the negative control group, incubated at a constant temperature for 60 min (37 °C), and fully washed with PBS. Goat anti-mouse/rabbit IgG (Beijing Zhongshan Jinqiao Biotechnology Co., Ltd., China) was added and incubated at room temperature for 15 min and rinsed completely with PBS. Horseradish-labeled streptomycin was added, incubated at room temperature for 15 min, and fully washed with PBS. Then the samples were incubated in 3,3'-diaminobenzidine tetrahydrochloride hydrate (DAB) (Beijing Solaibao co., Ltd., China) 5 min, and were re-dyed with hematoxylin. The film was sealed and observed under microscope.

Immunohistochemical results

Results were interpreted by two senior physicians from the Department of Pathology. Immunohistochemical results were analyzed and scored blindly. In case of controversy, multiple-head optical microscopy was used to observe and re-evaluate the results. Each slice was randomly evaluated by 10 high power microscopic field of view (400×). The S100A7 was mainly expressed in the nucleus or the cytoplasm [14]. Immunohistochemical evaluation criteria used were based on a previous study [15]. Positive expression of S100A7 was defined as expression in more than 10% of stained cancer cells. ER was positive when there was more than 1% of the stained cells [16], Setting up Ki67 high expression group with (> 20%) [17], HER2 immunohistochemistry was defined as 3+ positive, but further FISH test was needed for 2+ patients [18].

Statistical analysis

SPSS 23.0 software was used for statistical analysis. Kaplan-Meier survival curve was drawn. Log-Rank method was used to compare the survival rates between two groups. Multivariate COX regression model was used to analyze the independent risk factors of recurrence. The risk ratio was calculated using HR and 95% confidence interval CI. The statistical significance was defined as $P < 0.05$.

Results

S100A7 staining results

The positive staining of S100A7 was mainly in the nucleus or cytoplasm, Under the microscope, it is brown or light yellow. The representative S100A7 immunostaining results are shown in Fig. 1.

Descriptive statistics

The median age of the patients in this study was 49 years old (ranged, 27–89 years), 117 patients (33.5%) were younger than 45 years old at the time of diagnosis, and 137 patients (39.3%) had postoperative pathological lymph node metastasis (lymph node ≥ 1). Seventy-three cases (20.9%) were luminal A type, 115 cases (33.0%) were luminal B1 type, 67 cases (19.2%) were luminal B2 type, 41 cases (11.7%) were overexpression of HER2, 39 cases (11.2%) were triple negative, and 14 cases were indeterminate type. Up to January 2019, the follow-up time was 27–93 months (median: 73 months), and the follow-up rate was 5.7% ($n = 20$).

S100A7 expression

Of the 349 samples, 141 samples showed positive S100A7 expression. S100A7 expression was found to be

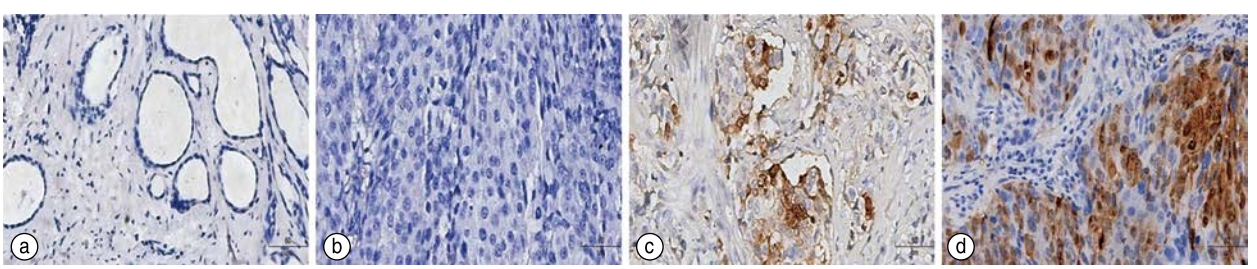

Fig. 1 Expression of S100A7 in breast cancer tissue (SP × 400). (a) Negative expression in normal breast tissue; (b) Negative expression in breast cancer tissue; (c) Positive (predominantly cytoplasmic) expression in breast cancer tissue; (d) Positive (predominantly nuclear) expression in breast cancer tissue

closely correlated with tumor size, histological grade, axillary lymph node metastasis status, ER status, PR status, and breast cancer molecular classification, recurrence status, postoperative distant metastasis, survival status ($P < 0.05$), but had no significant correlation with other clinical data ($P > 0.05$) (Table 1).

Correlation between S100A7 and local regional recurrence and distant metastasis

The Log-rank 5-year survival analysis of the 329 patients showed that the expression of S100A7 protein was significantly correlated with the clinical outcomes of RFS (94.9% *vs.* 89.5% $P = 0.0408$), DFS (95.4% *vs.* 83.5% $P < 0.001$) and OS (99.0% *vs.* 92.5% $P = 0.0011$), as shown in Table 2. Kaplan-Meier survival curves are shown in Fig. 2.

Comparison of clinical characteristics between postoperative recurrence and non-recurrence patients

Twenty patients could not be followed up. Of the remaining 329 patients, 24 (6.9%) had local regional recurrence, 31 (8.9%) had distant metastasis, and 12 (3.4%) died of breast cancer-related complications and secondary malignant tumors. The Log-rank test suggested that histological grade, intravascular thrombolytic tumor, lymph node metastasis, S100A7 expression and tumor size were the factors influencing RFS ($P < 0.05$). COX analysis results showed that S100A7 expression (HR = 6.864, 95% CI: 1.575–29.915, $P = 0.01$), vessel carcinoma embolus (HR = 4.921, 95% CI: 1.072–22.599, $P = 0.04$), age (HR = 0.091, 95% CI: 0.015–0.556, $P = 0.009$), and molecular subtypes of cancer (HR = 0.615, 95% CI: 0.391–0.967 $P = 0.035$) are independent factors affecting local regional recurrence ($P < 0.05$) (Table 3).

Discussion

Breast cancer is the most common malignant tumor among women under 40 years [19]. Several studies have

Table 1 Correlation between clinical pathology features and S100A7 expression in 349 cases of Breast Cancer [*n* (%)]

Clinical pathology feature	*n* (%)	Expression of S100A7		*P* value	Clinical pathology feature	*n* (%)	Expression of S100A7		*P* value
		Negative	Positive				Negative	Positive	
Total	349	208	141		ER Status				0.002[a]
Age (years)				0.528	Negative	84 (24.1)	38	46	
< 45	117 (33.5)	67	50		Positive	265 (75.9)	170	95	
≥ 45	232 (66.5)	139	93		PR Status				0.002[a]
Menopausal				0.941	Negative	84 (24.1)	38	46	
Yes	184 (52.7)	110	74		Positive	265 (75.9)	170	95	
No	165 (47.3)	98	67		HER2 status				0.422
Tumor size (cm)				0.005[a]	Negative	226 (64.8)	137	89	
≤ 2	207 (59.3)	136	71		Positive	109 (31.2)	65	44	
> 2	142 (40.7)	72	70		Unknown	14 (4.0)	6	8	
Location				0.316	Ki67 expression				0.102
Left	192 (55.0)	119	73		Low	142 (40.7)	92	50	
Right	157 (45.0)	89	68		High	207 (59.3)	116	91	
Histological grade				< 0.001[a]	Pathologic types				0.069
I/II	255 (73.1)	168	87		Invasive ductal carcinoma	310 (88.8)	190	120	
III	94 (26.9)	40	54		The other types	39 (11.2)	18	21	
Vessel carcinoma embolus				0.001[a]	Local recurrence				0.025[a]
Negative	284 (81.4)	181	103		No	305 (87.4)	188	117	
Positive	65 (18.6)	27	38		Yes	24 (6.9)	8	16	
Lymph node metastasis				< 0.001[a]	Lost to follow-up	20 (5.7)	12	8	
Negative	212 (60.7)	148	64		Postoperative distant metastasis				< 0.001[a]
Positive	137 (39.3)	60	77		No	298 (85.4)	188	110	
Molecular Subtype				0.012[a]	Yes	31 (8.9)	8	23	
Luminal A	73 (20.9)	47	26		Lost to follow-up	20 (5.7)	12	8	
Luminal B1	115 (33.0)	75	40		Survival status				0.001[a]
Luminal B2	67 (19.2)	44	23		Alive	317 (90.8)	193	124	
HER2-overexpressied	41 (11.7)	22	19		Deceased	12 (3.4)	1	11	
TNBC	39 (11.2)	14	25		Lost to follow-up	20 (5.7)	12	8	
Unclassified	14 (4.0)	6	8						

[a] $P < 0.05$

Table 2 Relationship between S100A7 expression and 5-year clinical outcome

Clinical outcome	S100A7 Expression (%)		*P*-Value
	Negative	Positive	
Local recurrence-free survival	94.9	89.5	0.0408
Distant metastasis-free survival	95.4	83.5	0.0001
Overall survival	99	92.5	0.0011

found that young female patients may have more aggressive tumor molecular characteristics and higher risk of distant and local recurrence than older patients [19–20]. Breast-conserving surgery has the distinct advantages of less trauma, fewer complications, with less impact on women's mental health. Breast-conserving surgery is now the first choice for young patients with early stage breast cancer. There is no statistical difference in the 5-year follow-up between adjuvant whole breast radiotherapy after breast-conserving surgery and modified radical mastectomy [21]. Although breast-conserving surgery and postoperative radiotherapy are the recommended treatment methods for early breast cancer, there is still a high risk of recurrence. The effectiveness of radiotherapy is affected by the inherent biological resistance of the tumor as well as chemotherapy and endocrine therapy, so the recurrence of the tumor cannot be ignored. Studies have shown that some patients fail to benefit from radiotherapy after breast-conserving surgery due to the inherent radiation resistance of the tumor [22]. It is probable that the radiotherapy causes DNA damage repair dysfunction of tumor cells from the ionizing radiation, and some signal transduction pathways affect the expression of one or more genes and proteins, leading to radiotherapy resistance, tumor recurrence, and metastasis. Recurrence is a well-known independent prognostic factor that affects breast cancer mortality [23]. The presence of local recurrence causes patients to undergo reoperation, which increases the risk of distant metastasis even after

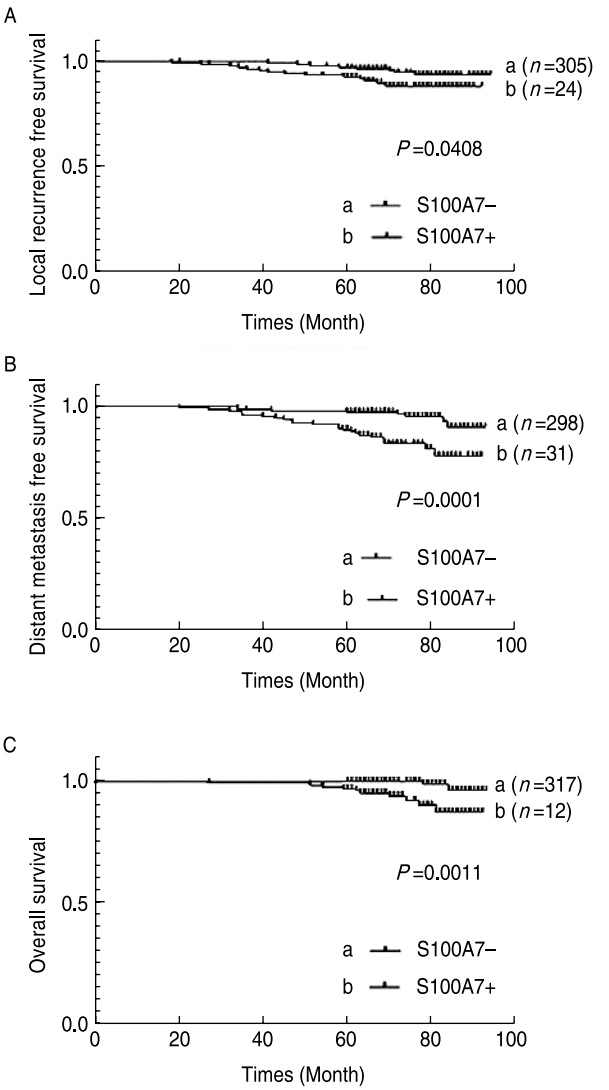

Fig. 2 Kaplan-Meier Survival Curves were drawn according to the expression of S100A7

Table 3 Factors influencing the recurrence free survival rate of Breast Cancer after breast-conserving surgery and postoperative radiotherapy were analyzed by single factor and multi-factor tests

Variable	S100A7 Expression (%)		Multivariate	
	P value	Relative risk (95% CI)	*P* value	Relative risk (95% CI)
Histological grade	0.0045[a]	3.008 (1.193–7.582)	0.12	2.440 (0.794–7.499)
Vessel carcinoma embolus	0.012[a]	2.754 (0.9695–7.821)	0.04[a]	4.921 (1.072–22.599)
Lymph node metastasis	0.0043[a]	3.123 (1.348–7.232)	0.099	0.368 (0.112–1.209)
S100A7 Expression	0.0408[a]	2.276 (0.9985–5.188)	0.01[a]	6.864 (1.575–29.915)
Tumor size	0.0053[a]	3.137 (1.381–7.125)	0.139	0.389 (0.112–1.358)
HER2 status	0.0755		0.416	0.656 (0.237–1.812)
Age	0.669	1.211 (0.5181–2.831)	0.009[a]	0.091 (0.015–0.556)
Molecular subtype	0.125		0.035[a]	0.615 (0.391–0.967)
Ki67 expression	0.5612	1.285 (0.5661–2.917)	0.199	2.391 (0.632–9.048)

Univariate analysis was conducted by log-rank test, and multivariate statistical analysis was conducted by proportional hazard model (Cox). [a]*P* value < 0.05 was considered statistically significant; 95% CI, 95% confidence interval

the second operation, leading to poor prognosis for the patients. Therefore, it is of great significance to screen high-risk breast cancer recurrence patients for various molecular markers through comprehensive assessment of risk factors to improve the treatment plan, the treatment effect, and the prognosis.

Many clinical studies have confirmed many influencing factors for local regional recurrence after breast-conserving surgery, including, lymph node metastasis, tumor stage, histological grade, and ER state [24–25]. In this study, the 5-year follow-up of 349 patients with breast conserving surgery and postoperative radiotherapy showed significant statistical differences between the relapsed group and the non-relapsed group in the indicators of histological grade, intravascular thrombolytic tumor, lymph node metastasis, S100A7 expression, and tumor size. Multivariate COX regression model analysis showed that the age, the histological grade, and the abnormal expression of S100A7 were independent risk factors for postoperative local recurrence of breast cancer. The results of large sample size studies showed that the risk of local regional recurrence was also high after adjuvant radiotherapy after modified radical surgery, suggesting that operative method is not an absolute factor affecting postoperative recurrence, and comprehensive treatment of various schemes is crucial, among which radiotherapy resistance is one of the urgent problems to be solved.

In recent years, research has focused on S100A7 expression in different classification and its association with other proteins, genes, and the influence on distant metastasis and prognosis, more focused on the study of breast cancer recurrence in patients with breast cancer, modified radical is still much research directly confirmed S100A7 with breast cancer confirmed breast surgery acceptance criteria recurrence after radiotherapy, the relationship between the radiation sensitivity and the prognosis. There have been few studies on the mechanisms of S100A7 expression, breast cancer recurrence, and radiation sensitivity relationship. A Japanese study results showed that adipose stromal cells can produce paracrine cytokine by raising S100A7 expression in breast cancer cells to promote the growth of cancer cells and thus, affect the recurrence and metastasis. Kaplan-Meier survival analysis and multivariate analysis showed that S100A7 could be used as an independent risk factor for predicting recurrence of invasive breast cancer [26], However, this study did not further analyze the recurrence rate and risk factors of breast-conserving surgery. Further research has shown that the [27] members of the family S100A, coded by Chromosome 1 q21.3, mainly S100A7, S100A8, S100A9 and IL-1 receptor kinase 1 (IRAK1) make a feedback loop that drives the ball tumor growth and since this feedback loop is an important part of a breast cancer recurrence, it can be used as biomarker for recurrence and can also serve as a therapeutic target. At present, most research on the S100 protein family has focused on studying S100A4. In terms of radiotherapy sensitivity, some studies have confirmed that the up-regulation of S100A4 in breast cancer cells may increase the interaction with mutated p53 gene and enhance the resistance to radiation [28]. As a member of S100A family, other members may share the same regulatory mechanism. The correlation between S100A2 and S100A7 and breast cancer recurrence and radiotherapy sensitivity warrants further research.

To conclude, in this study, the expression and prognosis analysis of S100A7 protein in the recurrence group after breast-conserving surgery and radiotherapy were preliminarily discussed. However, the relatively small sample size was a limitation, and thus, the use of S100A7 as a molecular marker for breast cancer recurrence needs to be verified by a larger sample size study and in vitro cell experiments, to provide stronger theoretical basis for the follow-up study on molecular mechanisms and signaling pathways.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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