

Analysis of factors related systemic recurrence after breast conserving surgery in stage I breast cancer

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Objectives: In these days, patients with stage I breast cancer have increased by regular health examination and diagnostic tool development. The aim of this retrospective study is to identify systemic recurrence related factors after breast conserving surgery (BCS) for stage I breast cancer.

Methods: In this study, we analyzed the correlation between systemic recurrence and pathologic factors. We reviewed 223 patients who underwent BCS for stage I breast cancer. Postoperative pathologic factors, recurrent rates and sites were studied. In addition, preoperative patients' data were also collected. Statistical analysis was done by using PASW 16.0 (SPSS Inc., Chicago, IL, USA).

Results: Systemic recurrence was found in 16 patients (7.17%) within 5 years after primary surgery. 5 patients had lymphatic invasion and 6 patients had vascular invasion. Lymphatic and vascular invasion had statistical correlation with systemic recurrence ($P = 0.004$, $P = 0.001$).

Conclusions: In this retrospective study, we can conclude that vascular invasion and lymphatic invasion are related systemic recurrence after BCS for stage I patients. Further studies with large cohort will be required to fully understand the risk factors of systemic recurrence for stage I breast cancer patients.

Key Words: Breast neoplasms, Recurrence, Risk factors

Breast cancer is the most common form of cancer in the western world, with diverse clinical, pathological and molecular features. With the recent development of health examination and diagnosis tools, the discovery rate of stage I breast cancer is increasing; and as surgical methods are developing, breast conserving surgery, which has a lower frequency of complications and no difference in terms of survival rates compared to mastectomy, is being widely used worldwide.¹⁻³

Therefore, it is an important task for many surgeons to study factors related to recurrence after treating stage I breast cancer with breast conserving surgery.

Accordingly, the author conducted a clinical review of 223 patients diagnosed with stage I breast cancer among those who received surgery for breast cancer from January 2002 to December 2007. The author analyzed the effects of age, ER (estrogen receptor) expression, PR (progesterone

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receptor) expression, HER-2 (human epidermal growth factor receptor-2) expression, blood vessel invasion, lymphovascular invasion, histological grade, p53 mutations, Ki-67, and EIC (extensive intraductal component) on systematic recurrence.

MATERIALS AND METHODS

Subjects

The medical records of patients that received breast conserving surgery for stage I breast cancer from January 2002 to December 2007 were retrospectively analyzed, and the last tracking of the patients was November 2012. Subjects consisted of patients who had a record of at least 5 years of tracking after surgery, and the recurrence rates and parts of recurrence within 5 years of surgery were analyzed. Those who received surgery or chemotherapy due to primary cancers that occurred in organs other than breasts, and those who received neoadjuvant chemotherapy or radiotherapy to lower the stages of breast cancer were excluded. A total of 223 patients were examined as the subjects for this study, and core needle biopsy was used for pre-operative diagnosis. The marginal zones of clinical specimens and sentinel lymph nodes were checked through the frozen section test during surgery. The marginal zones of all clinical specimens and sentinel lymph nodes turned out to have 'no tumor,' which was confirmed through the final post-operative patho-

logical examination. All tumors were found to be 2cm or smaller through the pathological examination. Chemotherapy was omitted for patients aged 35 or above who satisfied the requirements of histological grade 1 and positive hormone receptor, while all other patients received chemotherapy.

Pathological factors of patients were analyzed through ER, PR, HER-2 protein, p53 mutations, Ki-67, histological grade, lymphovascular invasion, blood vessel invasion and EIC analysis with post-operative pathological examination, and pre-operative data of patients were also examined.

Post-operative pathological factors were analyzed through the immunohistochemical (IHC) test, and ER and PR are considered positive when at least 10% is expressed on the IHC test, and HER-2 protein expression was exhibited when it is 3+ on the IHC test or is positive on FISH (fluorescence *in situ* hybridization). EIC is considered positive when at least 25% is expressed, Ki-67 is exhibited when at least 14% is expressed, and p53 mutation occurred when at least 1% is expressed.

Statistical analysis

A chi-squared test through PASW 16.0 (SPSS Inc., Chicago, IL, USA) was used to conduct multivariate analysis, and the results were considered statistically significant if *P*-value was below 0.05.

Table 1. Clinicopathologic characteristics of total patients (n = 223)

	No. of patients	Percentage
Age (year)		
< 40	28	12.6
≥ 40	195	87.4
Estrogen receptor		
(+)	130	58.3
(-)	93	41.7
Progesterone receptor		
(+)	112	50.2
(-)	111	49.8
HER-2		
(+)	103	46.2
(-)	120	53.8
Histologic grade		
I and II	141	63.2
III	82	36.8
Lymphatic invasion		
(+)	17	7.6
(-)	206	92.4
Vascular invasion		
(+)	17	7.6
(-)	206	92.4
p53 mutation		
(+)	76	34.1
(-)	147	65.9
Ki-67		
(+)	162	72.6
(-)	61	27.4
EIC		
(+)	85	38.1
(-)	138	61.9

EIC = extensive intraductal component, HER-2 = human epidermal growth factor receptor-2

RESULTS

Histological characteristics of all patients

Table 1 shows the clinical and pathological characteristics of all patients. All patients were female, and 28 were below age 40 (12.6%) and 195 were age 40 and above (87.4%). 130 patients (58.3%) exhibited ER expression, and 112 (50.2%) exhibited PR expression, while 103 patients (46.2%) exhibited HER-2 protein expression. For histological grade, 141 patients (63.2%) were in Grade I/II, and 82 patients (36.8%) in Grade III.

17 patients (7.6%) exhibited lymphovascular and blood vessel invasion respectively, and 76 patients (34.1%) exhibited p53 mutations. Ki-67 was expressed in 162 patients (72.6%), and EIC was positive in 85 patients (38.1%).

Statistical analysis of post-operative pathological factors and systematic recurrence

Table 2 shows the correlation between post-operative pathological factors and systematic recurrence. 4 patients below age 40 and 12 patients age 40 and above showed recurrences, but

Table 2. Analysis of risk factor for recurrence after partial mastectomy

	Recurrence(+)	Recurrence(-)	<i>P</i> -value
Tota	16	207	
Age(year)			0.124
< 40	4	24	
≥ 40	12	183	
Estrogen receptor			0.293
(+)	7	123	
(-)	9	84	
Progesterone receptor			0.615
(+)	7	105	
(-)	9	102	
HER-2			1.000
(+)	8	95	
(-)	8	112	
p53 mutation			1.000
(+)	5	71	
(-)	11	136	
Ki-67			0.110
(+)	13	149	
(-)	3	58	
Histologic grade			0.566
I and II	7	134	
III	9	73	
Lymphatic invasion			0.004
(+)	5	12	
(-)	11	195	
Vascular invasion			0.001
(+)	6	11	
(-)	10	196	
EIC			1.000
(+)	6	79	
(-)	10	128	

EIC = extensive intraductal component, HER-2 = human epidermal growth factor receptor-2

there was no statistical significance according to age ($P = 0.124$). Moreover, 7 of the patients that showed recurrences also showed ER expression, which had no statistical significance ($P = 0.293$), and the same was true for PR ($P = 0.615$). There were 8 patients who showed HER-2 protein expression, which was not related to recurrence ($P = 0.799$), and p53 mutations and Ki-67 expression were also not related ($P = 1.000$, $P = 0.110$). Histological grade and EIC also did not indicate any relevance to systematic recurrence ($P = 0.566$, $P = 1.000$). Of all the patients that showed recur-

rences, 5 exhibited lymphovascular invasion and 6 exhibited blood vessel invasion, which were related to systematic recurrence ($P = 0.004$, $P = 0.001$).

Analysis on parts of recurrence and recurrence rates

Table 3 shows parts of post-operative recurrence and recurrence rates. The average observation period of all patients was 82.3 months. Systematic recurrence was found in 16 patients (7.17%), with the liver was the organ were recurrences most frequently occurred (5 patients). Of

Table 3. Postoperative recurrent site and rate

	No. of population	Percentage (%)
Recurrence	16	100
Recurrent site		
Liver	5	31.3
Bone	4	25.0
Brain	2	12.5
Contralateral breast	1	6.3
Contralateral breast and lung	1	6.3
Lung and liver	1	6.3
Brain and liver	1	6.3
Bone and brain	1	6.3

the remaining patients with recurrences, 4 showed recurrences in bones and 2 in the brain. There was also one case each for the contralateral breast, contralateral breast and lung, lung and liver, brain and liver, and bone and brain simultaneously.

DISCUSSION

Surgical treatment of breast cancer began when William Halsted performed radical mastectomy in 1894. Due to recent changes in the basic concept of breast cancer, efforts are being made to minimize the extent of surgery including the breast conserving surgery procedure. In 1990, breast conserving surgery was acknowledged to reveal “no difference in terms of survival rates compared to mastectomy for patients with stages 1 and 2.” In addition, with its associated aesthetic and psychological benefits, breast conserving surgery is

positioning itself as a universal treatment for breast cancer.⁴⁻⁸

With the recent development of health examination and diagnosis technology, the number of stage I breast cancer patients is increasing. The rate of early breast cancer in Korea was 23.8% in 1996, but it increased to 24.5% in 2004. Breast cancer patients may show a favorable prognosis if there is no axillary lymph node metastasis, but there are recurrences in 20-30% of all breast cancer patients during the survival period.^{8,9}

Well-known prognostic factors related to breast cancer include the state of surgical resection margin, EIC, patient age, tumor size, lymph node metastasis, HR expression, histological grade, tumor marker, DNA proliferation marker (Ki-67, S demarcation, mitotic index), lymphovascular and blood vessel invasion.¹⁰⁻¹³

Many studies have revealed that patient age below 35 or 40 is a risk factor for recurrence.^{5,6,8,11,13-20} Kim et al. stated that the difference in recurrence

rates among age groups originates from the tumor-biological difference. However, the present study did not reveal any relevance between age and systematic recurrence.¹³ Whether HR is expressed or not is also known to be a factor related to prognosis of patients.²⁰⁻²² However, a few studies have claimed that the state of HR has no relation to local or systematic recurrence, and this study also corroborated this.^{8,14} In general, overexpression of HER-2 protein is known to be a factor that has negative effects on prognosis regarding histological nuclear grade, lymph node metastasis, recurrence and survival rates.¹⁴ Albert et al. argued that patients who show no HR expression but overexpression of HER-2 protein are more vulnerable to local-systematic recurrence for 8 years.²¹ However, this study indicated that HER-2 expression has no relation to systematic recurrence, which is consistent with the study by Lee et al.⁵ p53 is a tumor suppressor gene located on the chromosome p17, and is related to cell cycle and DNA restoration; and the mutation of this gene is correlated with genetic instability.¹⁴ The relevance with regard to p53 mutations, Ki-67, histological grade and lymph node metastasis or survival rates has been reported by many studies, but the results have been conflicting, and this study revealed that there is no relation to systematic recurrence.^{10,19,23,24} Blood vessel and lymphovascular invasion of breast cancer has been shown to be related to recurrence in multiple studies.^{8,19,24} Previous studies revealed that lymphovascular and blood vessel invasion is related to the total or

disease-free survival period, and this study also indicated that lymphovascular and blood vessel invasion is a factor related to systematic recurrence.^{11,25}

EIC, which looks like normal tissues around an infiltrative mass, is also known to be a risk factor with regard to local recurrence, but its relevance to local recurrence is unclear and its pathological physiology is also not widely known. A few studies have claimed that EIC is related to systematic or local recurrence, but this study revealed no relation to systematic recurrence.

This study found that among patients that received breast conserving surgery for stage I breast cancer, blood vessel and lymphovascular invasion in post-operative pathological examination is related to systematic recurrence. Therefore, patients exhibiting lymphovascular and blood vessel invasion in post-operative pathological examination require more active treatment and should be subject to more rigorous tracking. However, this study featured a limited number of patients and therefore general principles cannot be extrapolated; thus, it is necessary to conduct a large-scale study on a greater number of patients.

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