·Clinical Research·

Clinical characteristics and prognosis of very young patients with breast cancer in the southern of China

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[Abstract] Background and Objective: Even though most breast cancers occur in postmenopausal women in western countries, age <35 is one of the prognostic factors. This study was to compare the clinicopathologic characteristics and prognosis between premenopausal breast cancer patients aged of <35 and ⩾35 in south China, and to explore the prognostic factors. **Methods:** A total of 905 consecutive premenopausal patients were evaluated, with first diagnosis of breast cancer referred to surgery at the Sun Yat-sen University Cancer Center from October 2003 to December 2006. The clinicopathologic factors and the survival rates between the very young group(aged of <35 at diagnosis) and the non-young group(aged of ⩾35 at diagnosis) were retrospectively compared. **Results:** The overall median follow-up time was 27.77 months. The 3-year disease-free survival rate was significantly lower (78.0% vs. 89.1%, P<0.001) and the 3-year survival rate relatively lower (94.3% vs. 96.8%, P=0.10) in the very young group than in the non-young group. In addition, the 3-year survival and disease-free survival rates were significantly lower in the very young group with HR (hormone receptor)-positive than in the non-young group (P<0.05). The univariate and multivariate analysis of clinicopathologic characteristics between two groups showed that age <35 at diagnosis, axillary lymph node involvement, presence of vascular invasion, and high expression of Ki67 were risk factors for recurrence. **Conclusions:** Compared with non-young premenopausal patients, very young breast patients with HR-positive cancer have a worse outcome.

Key words: very young patient, breast cancer, clinical characteristic, prognosis factor

From a global perspective, most breast cancers occur in postmenopausal women, but quite a number of young women also suffer from this disease. Currently, the age of less than 35 years is a cut-off for defining young-aged breast cancer in international multi-center clinical trials.[1] In the US, breast cancer patients aged less than 35 years account for about 2.5% of the total; similarly in Europe, the proportion of young breast cancers in newly-diagnosed cases in each year is about 3.5%; however, in Korea, this proportion is about 9.5%.[2-4] In China, the proportion is 10%–15%,[5,6] much higher than those reported in the US and Europe, which still shows an increasing tendency. Though this proportion is not high, the absolute number of young patients is large. In addition, the reason for its relatively poor prognosis is worth further study. Hence, we conducted a retrospective study on clinical characteristics and prognosis of young-aged breast cancer to provide new ideas about more effective treatments for young breast cancer patients.

Clinical Data and Methods

Clinical data

We collected the data of 1377 operable breast cancer patients in South China treated at Sun Yat-Sen University Cancer Center (SYSUCC) from October 2003 to December 2006, of whom 905 cases were included for analyses according to the following inclusion and exclusion criteria. Inclusion criteria were as follows: 1) with complete clinical data, including general status, pathologic diagnosis, tumor stage, treatment and survival; 2) with complete follow-up data, including the time and location of metastasis; 3) with detection results of six tumor markers, including estrogen receptor (ER), progesterone receptor (PR), HER2/neu, Ki67, P53 and vascular endothelial growth factor

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(VEGF). Exclusion criteria were as follows: 1) postmenopausal or perimenopausal patients (in case that those physiological conditions influenced the analysis); 2) unknown ovarian hormone levels after hysterectomy; 3) recurrent metastatic breast cancers that only underwent palliative resection; 4) those only received chemotherapy in SYSUCC and without complete information of tumor specimens; 5) those with other malignant tumors were excluded in survival analysis; 6) those with non-invasive carcinoma were excluded in the evaluation of tumor size.

According to the criteria set by SYSUCC, the interpretation of the pathologic immunohistochemical (IHC) indices were as followed: ER-, PR-, P53- and VEGF-positive cases all referred to > 10% of the cells being positive; HER2/neu-negative, positive and marginally positive cases referred to 0–25%, > 50% and 26%–50% of the cells being positive, respectively; high expression of Ki67 referred to > 25% of the cells being positive.

All the 905 patients included were premenopausal women, and they were divided according to diagnostic age into study group (189 patients aged < 35 years, with a median of 32 years) and control group (716 patients aged ⩾ 35 years, with a median of 44 years). The study group accounted for 13.7% (189/1377) of all patients and 20.9% (189/905) of premenopausal patients.

Treatments

Each patient had received corresponding local treatments (surgery plus radiotherapy) and systemic treatments (mainly adjuvant chemotherapy and endocrine therapy). The main surgical operations included radical mastectomy, modified radical mastectomy and breast-conserving surgery. The indications of adjuvant radiotherapy set by SYSUCC were as follows: primary tumor > 5 cm in size, invasion of the pectoral fascia, more than four metastatic axillary lymph nodes, and positive surgical margin. .60Co or linear accelerator was used for radiotherapy, and the target volume mainly included the chest wall and supraclavicular region. The general dose was 50 Gy, while 60 Gy was for the whole-breast radiotherapy after breast-conserving surgery. Anthracycline-containing regimens were mainly used for adjuvant chemotherapy, while CMF regimen (CTX, MTX, and 5-FU) was administrated instead in some minor cases. The main drug used in endocrine therapy was tamoxifen (TAM).

Follow-up

All patients were followed up till January 2008. Locoregional recurrence meant the recurrence in ipsilateral mammary glands, chest wall, or regional lymph nodes identified clinically or histologically, while distant metastasis referred to the metastatic carcinoma detected by clinical examination or imaging. Locally advanced breast cancer (LABC) referred to stage III breast cancer. Disease-free survival (DFS) was calculated from the first day after operation to the first time of recurrence or metastasis. Overall survival (OS) was defined as the interval from the first day after operation to death or last contact.

Statistical analysis

SPSS13.0 software was used for statistical analysis. Descriptives of clinical data were expressed in percentage or median. Univariate analysis of clinicopathologic indices (including age, tumor size, number of axillary lymph nodes, pathologic type, treatment, local or distant metastasis, and so on) was performed by the χ^2 test and Fisher exact test, and multivariate analysis by the Cox regression. Survival was analyzed by the Kaplan-Meier method, and compared by the log-rank test. Odds ratio (OR) and 95% confidence interval (CI) were analyzed by the logistic regression. A value of $P<0.05$ was considered significant.

Results

Clinical characteristics of the included cases

As shown in Table 1, the proportion of LABC was significantly larger in study group than in control group (32.3% vs. 24.9%, $P=0.040$), and the node-positive rate was also significantly higher in study group than in control group (57.7% vs. 43.5%, $P=0.007$). The difference in tumor stage between the two groups was not significant ($P=0.369$). Among the 644 detectable pathologic specimens, the occurrence rate of vascular cancer embolism was significantly higher in study group than in the control group ($P=0.022$). In addition, among the cases with complete pathologic data, no significant difference was observed between the two groups in the positive rates of ER, PR, HER2, Ki-67, P53 and VEGF ($P>0.05$).

Differences in treatment methods between the two groups

As shown in Table 2, no significant difference in endocrine therapy was observed between the study group and the control group, where TAM was mainly used and ovariectomy plus aromatase inhibitors were applied to a few patients with TAM contraindication [3 (1.59%) in the study group and 4 (0.56%) in the control group]. Compared with the control group, the study group showed a preference for breast-conserving surgery alone or plus adjuvant radiotherapy. Almost all patients had received standard chemotherapy with anthracycline-containing regimen; however, more patients in the study group had received paclitaxel-containing adjuvant chemotheray.

Recurrence and metastasis of breast cancer in young patients

By the end of follow-up, 98 patients had disease progression, of whom 14 received further treatments in other hospitals had been followed up via telephone, 84 had received further treatments in SYSUCC, and 13 of them died. The recurrence/metastasis rate of the study group was significantly higher than that of the control group (16.4% vs. 7.4%, OR = 2.122, 95% CI = 1.399–3.218, $P<0.001$). Based on the data of initial failure of the 84 progressed cases further treated at SYSUCC, comparing with the control group, the study group showed a higher locoregional recurrence rate (5.91% vs. 2.70%, $P=0.039$) and a higher distant metastasis rate (10.75% vs. 4.82%, $P=0.003$), with significant differences. By the end of follow-up, 27 patients died, 9 (4.8%) in the study group and 18 (2.5%) in the control group, without significant difference ($P=0.145$).

Survival of young breast cancer patients

By the end, the median follow-ups were 27.77 months for all patients, 27.20 months for the study group, and 27.85 months for the control group. The median DFS was significantly longer in the

Table 1 Comparison of clinicopathological characteristics between two groups of patients with breast cancer

Characteristic	Item	Very young patients [number (%)]	Non-young patients [number (%)]	*P*
ER[a]	Total	187	700	0.609
	Positive rate <10%	85(45.5)	295(42.1)	
PR[a]	Total	187	701	0.863
	Positive rate <10%	68(36.4)	248(35.4)	
HER2[a]	Total	187	696	0.290
	++-+++	70(37.4)	220(31.6)	
Ki67[a]	Total	178	671	0.221
	Positive rate ⩾25%	71(39.9)	302(45.0)	
P53[a]	Total	180	663	0.341
	P53 mutation	117(65.0)	489(73.8)	
VEGF[a]	Total	179	670	0.513
	Positive rate >10%	104(58.1)	426(63.6)	
Grade[a]	Total	131	375	0.369
	G1	7 (5.3)	22 (5.9)	
	G2	75(57.3)	188(50.1)	
	G3	49(37.4)	165(44.0)	
VI[a]	Total	176	468	0.022
	VI presented	23(13.1)	32 (6.8)	
pT stage	Total	187	714	0.141
	pT0	2 (1.1)	5 (0.7)	
	pT1	53(28.3)	230(32.2)	
	pT2	101(54.0)	390(54.6)	
	pT3	14 (7.5)	57 (8.0)	
	pT4	17 (9.1)	32 (4.5)	
Tumor size[a]	Total	185	710	0.346
	⩽2 cm	54(29.2)	233(32.8)	
	>2 cm	131(70.8)	477(67.2)	
LN status	Total	189	716	0.005
	pN0/sentinel node negative	80(42.3)	405(56.6)	
	pN1	58(30.7)	162(22.6)	
	pN2	25(13.2)	82(11.4)	
	pN3	26(13.8)	67 (9.4)	
Positive LN[a]	Total	186	714	0.007
	0	80(43.0)	405(56.7)	
	1-3	56(30.1)	164(23.0)	
	4-9	24(12.9)	81(11.3)	
	⩾10	26(14.0)	64 (9.0)	
AJCC stage	Total	189	716	0.040
	0	2 (1.0)	5 (0.6)	
	Ⅰ	28(14.8)	161(22.5)	
	Ⅱ	98(51.9)	372(52.0)	
	Ⅲ	61(32.3)	178(24.9)	

[a]The data of some patients are incomplete. ER, estrogen receptor; PR, progestrone receptor; VI, vascular invasion; LN, lymph node; VEGF, vascular endothelial growth factor.

study group than in the control group (43.24 months vs. 28.12 months, $P<0.05$) (Fig. 1). The median OS was slightly shorter in the study group than in the control group (49.32 months vs. 51.25 months, $P=0.10$). The 1-, 2-, and 3-year DFS rates were all significantly higher in the study group than in the control group ($P<0.001$). The 3-year OS rates of the study group and the control group were similar ($P=0.10$).

Stratified analyses showed that the 3-year DFS and OS rates of lymph node-negative patients were significantly lower in the study group than in the control group, the 3-year DFS rate of lymph node-positive patients was also significantly lower in the study group than in the control group, but their 3-year OS rates had no significant difference; among ER- or PR-negative patients, no significant difference was observed in either 3-year DFS rate or 3-year OS rate between the two groups, while among ER- or PR-positive patients, the prognosis of the study group was significantly worse than that of the control group ($P<0.001$) (Table 3).

Table 2 Comparison of treatments between two groups of patients with breast cancer

Treatment	Very young patients [number(%)]	Non-young patients [number(%)]	*P*
Surgery			0.002
Mastectomy	166(87.8)	675(94.3)	
Breast conservation	23(12.2)	41 (5.7)	
Paclitaxel-based chemotherapy			0.009
Yes	71(37.5)	199(27.8)	
No	118(62.5)	517(72.2)	
Anthracycline-based chemotherapy			0.549
Yes	177(93.6)	666(93.1)	
No	12 (6.4)	50 (6.9)	
Radiotherapy			0.005
Yes	50(26.5)	125(17.5)	
No	139(73.5)	591(82.5)	
Hormonal therapy			0.843
Yes	105(55.6)	392(54.7)	
No	84(44.4)	324(45.3)	

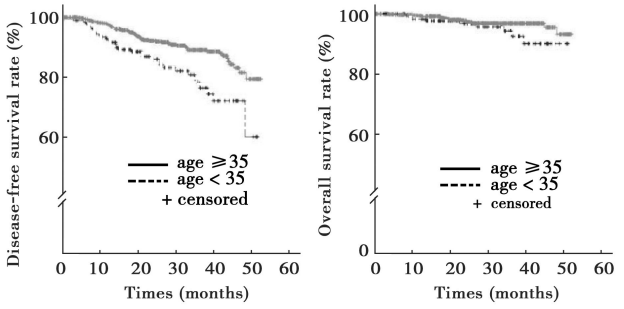

Figure 1 Disease-free survival and overall survival curves of patients with breast cancer

Univariate and multivariate analyses of the recurrent factors

Univariate analysis indicated that age of < 35 years, lymph node-positive, vascular cancer embolism, the greatest diameter of tumor > 2 cm, and high expression of Ki67 were all risk factors of recurrence. Multivariate analysis showed that only age of < 35 years, lymph node-positive, vascular cancer embolism, and high expression of Ki67 were risk factors of recurrence (Table 4).

Table 3 Subgroup survival rates of two groups of patients with different hormone receptor status and nodal status

Receptor/Nodal status	3-year survival rate (%)			3-year disease-free survival rate (%)		
	Very young patients	Non-young patients	*P*	Very young patients	Non-young patients	*P*
ER negative	96.2	94.9	0.964	80.9	87.2	0.197
ER positive	92.8	98.0	0.020	75.1	90.3	<0.001
PR negative	98.5	95.2	0.608	88.7	86.3	0.856
PR positive	92.0	97.6	0.012	72.0	90.6	<0.001
LN negative	94.3	99.2	<0.001	89.6	94.8	0.006
LN positive	94.4	93.9	0.671	69.2	81.9	0.047

Abbreviations as in Table 1.

Discussion

In our study, young breast cancer patients accounted for 13.7% of all breast cancer patients, similar to the incidence in other areas of China,[5, 6] suggesting a homogeneous age distribution of breast cancer onset without significant regional variation in China. Nab *et al.*[7] reported that the median age of 2052 breast cancer patients was 56.5, while the data of SYSUCC was 47,[8] indicating a timing advance of about 10 years in China. According to a similar treatment guideline, the data of SYSUCC showed that the 5-year survival rate of operable breast cancer patients was 75.2%,[8] similar to those reported in the US and Europe.[9] The current study indicated that the recurrence/metastasis rate of young breast cancer patients was significantly higher than that of the control group (P<0.001), and their DFS was also significantly shorter than that of the control group (P< 0.001). No significant difference in OS was observed between the two groups despite the relatively worse situation of the study group. Hence, we suppose that diagnostic age of < 35 years might be an independent prognostic factor of breast cancer recurrence, though it could not be used as a prognostic factor of OS currently.

According to a number of international clinical studies, comparing with the breast cancers in aged patients, those in young patients are more invasive biologically (for example, higher proportion of cells in S phase, higher ER-negative rate, higher histological stage, and more lymphovascular invasion),[1,10-15] with relatively worse prognosis.[16,17] However, in the current study, the situation was somehow different from those reported in other countries, where there were neither higher ER- or PR-negative rate, nor more histological stage Ⅲ cases, nor more P35-positive cases, but was similar in terms of lymphovascular invasion. In China, there is no significant difference in most clinicopathologic

Table 4 Univariate and multivariate analysis of clinicopathologic variables

Variable	Hazard ratio	95% CI	*P*
Univariate analysis			
Age <35 years	2.122	1.399–3.218	<0.001
LN positive	3.539	2.247–5.574	<0.001
VI presented	3.464	1.973–6.081	<0.001
Histologic Grade 3	1.501	0.936–2.407	0.092
Tumor size >2 cm	1.740	1.063–2.849	0.028
Family histoty	1.308	0.524–2.992	0.524
Premature menarche	1.080	0.804–1.451	0.609
ER-negative	1.110	0.737–1.672	0.618
PR-negative	1.140	0.756–1.720	0.532
HER2 ++–+++	1.358	0.902–2.043	0.143
Ki67⩾25%	1.525	1.017–2.287	0.041
P53 mutation	1.218	0.771–1.924	0.398
VEGF positive	1.093	0.724–1.652	0.671
Multivariate analysis			
Age <35 years	1.769	1.073–2.916	0.025
LN positive	2.868	1.592–5.167	<0.001
VI presented	2.079	1.153–3.749	0.015
Tumor size >2 cm	1.146	0.613–2.143	0.669
Ki67⩾25%	2.169	1.289–3.651	0.004

CI, confidence interval. Other abbreviations as in Table 1.

indices between the young breast cancer p atients and the premenopausal control group, which is also different from the situations in the US and Europe. This provides some clues on why the prognosis of the premenopausal patients are better in China than in the US and Europe.

Generally, young breast cancer patients show rapid disease progression, with a higher rate of lymph node metastasis and a worse prognosis, which are opposite to the situations in old patients. Colleoni *et al.*[1] and Kothari *et al.*[18] independently compared the prognosis between the patients aged ⩽ 35 years and those aged > 35 years, and found that the prognosis of the study group was significantly worse than that of control group. Zhou *et al.*[19] reported that the local recurrence rates of breast cancer patients aged <35, 35-50 and >50 years were 12%, 5.6% and 6.9% , respectively. In our current study, for the young patients, the median OS was 49.32 months, and the 1-, 2-, and 3-year OS rates were 98.3%, 96.8%, and 94.3%, respectively. A trend was also observed that the3-year FDS and OS rates of young breast cancer patients were lower than those of the control group, but without significant difference. This agrees with the findings in other countries.

In our study, further stratified analyses showed that the prognosis of ER/PR-positive young patients was worse than that of ER/PR-negative old patients. A study in Korea[15] got a similar result that among Korean patients, the prognosis of HR-positive (especially PR-positive) young patients was worse than that of the control group. It is a consensus that HR is a favorable prognostic factor of breast cancer after operation, that is, the prognosis of HR-positive patients is better than HR-negative patients. However, in our study, comparing with the control group, HR-positive young patients had worse OS and DFS, while HR-negative ones showed no significant differences. This result is the same as those in other studies abroad.[15,20,21] What's more, we discovered that, comparing with the control group, HR-positive young patients had a higher vascular cancer embolism rate, larger tumor size and higher LABC rate, which might be the reasons for the poor prognosis. In terms of treatment method, the therapeutic outcome in the study group should have been better since they had received a more active treatment with adjuvant radiotherapy and chemotherapy and more young patients had received TAM endocrine therapy; however, it turned out opposite. This is probably because the HR-positive patients aged <35 years benefit much less from chemotherapy than the HR-negative ones, 22and the onset rate of amenorrhea induced by chemotherapy is also lower in those aged < 35 years than in those aged ⩾35 years.[23] According to a meta-analysis on the adjuvant treatment with LHRHa for HR-positive premenopausal breast cancer patients,[24] only those who are ⩽ 40-year-old can benefit from ovariectomic treatment. Therefore, in our opinion, we should apply a more active treatment with ovariectomy to the young patients to improve their therapeutic outcome. Yet, no consensus has been established on whether we should apply ovariectomy in combination with TAM or aromatase inhibitors. Some international studies, such as SOFT, TEXT and PERCHE, are now under way, and the results will further answer the question which kind of postoperative endocrine therapy is better for HR-positive young patients.

Our study also showed that the node-negative young patients had worse DFS and OS than the control group; however, among the node-positive patients, although young patients had a worse DFS than the control group, there was no significant difference in OS between the two groups, which may be attributed to the improvement of rescue and treatment methods. But this phenomenon may also be due to short follow-up. A Korean study[15] showed that among patients with lymph node metastasis, young patients had worse DFS and OS than old patients, while among node-negative patients, no significant difference existed between the study group and the control group. Some studies in the US and Europe also support this viewpoint.[21,25,26] In fact, no agreement has ever been reached on whether age is a risk factor of node-negative breast cancer patients. In the 1998 and 2001 St. Gallen consensus meetings,[27,28] it was recommended that age < 35 years be a risk factor for the recurrence of node-negative breast cancer. Some other studies also considered age < 35 years to be an independent factor for predicting DFS and OS of node-negative breast cancer patients.[14, 29, 30]

Comparing the clinicopathologic features and treatments between the two groups, no difference in clinicopathologic features among node-negative patients was found between the two groups, and as for treatments, we merely found that more young patients had received breast-conserving surgery. Till now,

there is still no final conclusion about whether age is a risk factor of local recurrence in breast-conserved cases, and there are still inconsistent findings in previous clinical studies. But it was reported in most studies that among those who received breast-conserving surgery, young patients had a higher local recurrence rate.[12,19,31-35] However, this difference was not manifested in the current study. Of course, this may be due to the small sample size of breast-conserving patients and the short follow-up in our study. In the stratified analysis on node-negative patients who received breast-conserving surgery, there was only one recurrent case in the control group, which was not adequate for the analysis of the impact of breast-conserving surgery on the prognosis of node-negative young patients.

Conclusion

Our study showed that the prognosis of young breast cancer patients was worse than that of the premenopausal non-young patients in South China. HR-positive young patients benefited much less than HR-negative patients from postoperative chemotherapy, and their DFS was significantly shorter than that of HR-positive patients in the control group. Hence, a more active adjuvant endocrine therapy should be adopted to enhance the therapeutic effect on HR-positive young breast cancer patients. Compared with the simple endocrine therapy using TAM, TAM combined with ovariectomy might be more effective, but this needs to be proved by further studies.

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