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Original Article

Combination impact of axillary lymph node status and biological subtypes on prognosis and breast conserving surgery in locally-invasive breast cancer: a real-world study of a Chinese population

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Abstract: The combination impact of axillary lymph node status and biological subtypes on prognosis of locally-invasive breast cancer and feasibility levels of breast conserving surgery have not been thoroughly examined. The current study collected 3,302 patients with histologically-confirmed primary invasive breast cancer undergoing curative surgery. Expression statuses of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2), along with axillary lymph nodes status and follow-up information, were collected for all patients. Patients were divided into six subgroups, according to immunohistochemical results and axillary lymph nodes status, including G1-G6: G1 (LN+/luminal-like), G2 (LN+/basal-like), G3 (LN+/HER2+HR-), G4 (LN-/luminal-like), G5 (LN+/basal-like), and G6 (LN+/HER2+HR-) groups. Prognostic effects of the G subgroup were detected and its association with the feasibility of breast conserving surgery was explored. A total of 2,031 patients underwent mastectomy procedures (61.5%), while 1,271 (38.5%) underwent breast conserving surgery. There were 1,016 (30.8%), 223 (6.8%), 457 (13.8%), 1,002 (30.3%), 257 (7.8%), and 457 (10.5%) patients in G1 to G6 subgroups, respectively. The median follow-up time was 92 months (ranging from 3 to 187), while disease recurred in 387 patients (11.7%). The G subgroup was an independent factor for DDFS and DFS (both P<0.001) and the only independent factor for LRFS (P<0.001). The G subgroup was also significantly correlated with surgery type (P<0.001). Combination of axillary lymph node status and biological subtype was associated with multiple prognosis of primary breast cancer. Thus, it is a potential indicator for feasibility of breast conserving surgery.

Keywords: Breast cancer, biological subtype, axillary lymph node status, prognosis, breast conserving surgery

Introduction

Breast cancer is the most common cancer in Chinese women, with approximately 272.4 thousand new cases and 70.7 deaths, annually [1]. Prognosis for breast cancer patients is generally favorable and mortality rates have declined, due to early detection and improved adjuvant therapies [2, 3]. However, recurrence is not uncommon. Women with recurrence still experience poor survival outcomes and declined quality of life. The annualized hazard of recurrence has been reported as 10.4% during the first 5 years and 4.5% during the following 5 years [4].

Existence of metastatic axillary lymph nodes has been proven to be associated with high risk for distant recurrence [5]. Adjuvant therapies have been assigned to control the disease and improve survival. Besides host factors, breast cancer patients present with divergent local recurrence and distant metastasis, mostly depending on biological subtypes [6, 7], frequently defined as HR+/HER2-, HR-/HER2+, and HR-/HER2- [8]. These biological subtypes may also be associated with efficacy levels of systemic cancer therapies [9, 10]. However, few studies have explored the combination effects of axillary lymph node status and biological subtypes on breast cancer prognosis.

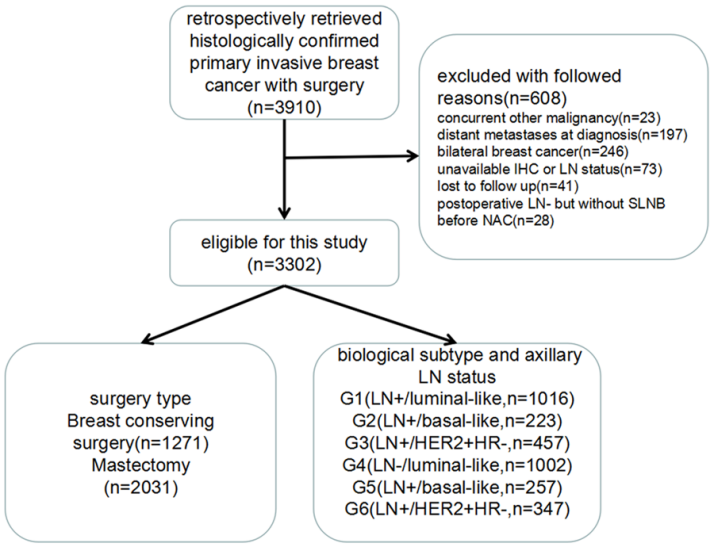

Figure 1. Flow chart of patient enrollment.

Lymph node biopsies, followed by breast conserving surgeries, have become the preferred operations for early breast cancer [11]. These have been accompanied by the recognized effectiveness of neoadjuvant therapies, significantly increasing the chances for breast conserving surgery [12, 13]. However, the impact of biological subtypes on the feasibility of breast conserving surgery has not been thoroughly examined.

Therefore, the purpose of this study was to detect the combination impact of axillary lymph node status and biological subtypes on prognosis of locally-invasive breast cancer and feasibility levels of breast conserving surgery.

Methods

Study population

The protocol of this retrospective study was approved by the Institutional Review Board. Informed consent was waived due to the retrospective nature of the study. Patient records were extracted from a prospective database including all consecutive breast cancer cases at the hospital since January 2002. Eligible participants were female patients with histologically-confirmed primary invasive breast cancer undergoing curative surgery. Exclusion criteria: Concurrent with other malignancies, distant metastases at the time of diagnosis, bilateral breast cancer, unavailable information of immunohistochemical results or axillary lymph nodes status, and a follow-up time less than 3 months after surgery (lost since the first outpatient interview); Patients that underwent neoadjuvant therapy and obtained a negative result of postoperative axillary lymph node dissection (ALND). A total of 3,302 patients from January 2002 to December 2011 (**Figure 1**) were finally included. The mean age at confirmed diagnosis was 50.9 ± 11.2 years (ranging from 21 to 92 years).

Information regarding adjuvant therapies used was obtained from patient medical records. A total of 1,987 patients received preoperative chemotherapy and 1,318 patients received postoperative chemotherapy. A total of 2,425 patients received adjuvant chemotherapy. Adjuvant chemotherapy consisted of CEF (epirubicin, cyclophosphamide, fluorouracil), T (paclitaxel), TC (paclitaxel, cyclophosphamide), EC (epirubicin, cyclophosphamide), TP (paclitaxel, carboplatin), CAF (cyclophosphamide, doxorubicin, fluorouracil), CMF (cyclophosphamide, methotrexate, fluorouracil), CTF (cyclophosphamide, pirarubicin, fluorouracil), AC (doxorubicin, cyclophosphamide), AC-T (doxorubicin, cyclophosphamide, paclitaxel), Capecitabine, NVB (vinorelbine), NF (vinorelbine, fluorouracil), NP (vinorelbine, paclitaxel), and NPF (vinorelbine, paclitaxel, fluorouracil). Hormone receptor (HR)-positive breast cancer patients were all treated with endocrine therapy (anastrozole, exemestane, or letrozole for postmenopausal women and tamoxifen or tamoxifen plus aromatase inhibitors for premenopausal women). Patients with breast conserving surgery, ≥ T3-staged tumors, ≥ 4 metastatic axillary lymph nodes, or metastatic axillary lymph nodes existing after neoadjuvant therapies were treated with radiotherapy.

Clinical-pathologic evaluations

Tumor sizes, histologic types, and tumor staging were determined with reference to surgically excised specimens. Histologic tumor staging was performed according to the 7th edition of AJCC (American Joint Committee on Cancer) TNM staging system [14]. Expression statuses

of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2) were determined with reference to biopsy specimens or surgically excised specimens. ER and PR levels were evaluated by the percentages of stained tumors [15], with the positivity for ER or PR defined as ≥ 10% stained tumor cells and either ER or PR positive regarded as HR positive. HER2 status was scored by the American Society of Clinical Oncology and the College of American Pathologists (ASCO/CAP) criteria. This assess the intensity and completeness of membrane staining [15]. A score of 0/+ indicates negative and 3+ indicates positive. A score of 2+ was further evaluated with fluorescence *in situ* hybridization (FISH) to determine HER2 status. If the ratio of HER2 gene signals to the chromosome 17 probe signal was greater than 2.2, the tumor was classified as HER2 positive. Cancers were classified into three biological subtypes, including the basal-like subtype (ER-, PR-, and HER2-), HER2+/HR- subtype (ER-, PR-, and HER2+), and luminal-like subtype (HR+, regardless of other characteristics) [9].

Positive axillary lymph nodes (LN+) were determined at the existence of at least one positive result of axillary puncture cytology (FNA), SLNB, and postoperative ALND. Negative axillary lymph nodes (LN-) were determined when at least one negative result of SLNB and ALND.

Considering both biological subtypes and axillary lymph node statuses, patients were divided into six subgroups, including G1-G6: G1 (LN+/luminal-like), G2 (LN+/basal-like), G3 (LN+/HER2+HR-), G4 (LN-/luminal-like), G5 (LN+/basal-like), and G6 (LN+/HER2+HR-).

Statistical analysis

Statistical analysis was conducted using SPSS 22.0. Two-tailed $P<0.05$ indicates statistical significance. Continuous variables are described as mean ± standard deviation, while categorical variables are described in terms of percentages. Frequency tables were analyzed using Chi-squared tests. Bonferroni's correction was used for multiple comparisons.

Patients were followed up until death. Postoperative follow-ups included telephone inperson interviews at 6-month intervals, outpatient interviews at 3-month intervals for 2 years, and 6-month intervals until death. Local recurrence-free survival (LRFS) was calculated from surgery to the first event, including ipsilateral breast tumor recurrence, ipsilateral chest wall recurrence, or ipsilateral skin and surgical scar recurrence. Distant disease-free survival (DDFS) was calculated as the time from surgery to the time of recurrence at a distant site (bone, liver, lung, or central nervous system) or death from breast cancer. Disease-free survival (DFS) was calculated from surgery to the first event, including local or regional recurrence, distant metastases, contralateral breast cancer, or death from any cause. Patients without recurrence were censored at the last follow-up. The cut-off date was December 31, 2017. Univariate Kaplan-Meier analysis, along with log-rank estimates, was conducted to produce survival curves and compare survival outcomes among different conditions of patients. Cox's proportional hazards model was used to obtain hazard ratios (HR) for each clinical-pathologic variables. Independent prognostic factors were selected with a backward stepwise selection procedure.

Results

Patient characteristics and recurrence outcomes

Mastectomies (n = 2031) or breast conserving surgeries (n = 1271) were performed for all patients. Histologic types of invasive breast cancers were as follows: Invasive ductal carcinoma (IDC, n = 2963, 89.7%); Invasive lobular carcinoma (ILC, n = 145, 4.4%); Other types (n = 194, 5.9%). Histologic tumor staging results showed 1,504 T1 tumors (46.6%), 1,559 T2 tumors (47.2%), 123 T3 tumors (3.7%), and 116 T4 tumors (3.5%). Biological subtypes were as follows: Basal-like subtype (n = 480, 14.5%); HER2+/HR- subtype (n = 804, 24.3%); Luminal-like subtype (n = 2018, 61.2%). There were 1,696 (51.4%) patients with positive axillary lymph nodes and 1,606 (48.6%) patients with negative lymph nodes. The six subgroups, G1-G6, contained 1,016 (30.8%), 223 (6.8%), 457 (13.8%), 1,002 (30.3%), 257 (7.8%), and 347 (10.5%) patients, respectively.

The median follow-up time was 92 months (ranging from 3 to 187). A total of 173 patients

Table 1. Patient characteristics according to recurrence status

Variables	All patients (n = 3302)	Nonrecurrence (n = 2915)	Recurrence (n = 387)	*P* value
Patient age (y)*	50.98 ± 11.22 (50.00)	51.00 ± 11.18 (50.00)	49.79 ± 11.42 (50.00)	0.047
Tumor size (cm)*	2.42 ± 1.28 (2.10)	2.35 ± 1.19 (2.10)	2.93 ± 1.69 (2.55)	<0.001
Histologic type				0.001
IDC	2963 (89.7)	2607 (89.4)	356 (92.0)	
ILC	145 (4.4)	122 (4.2)	23 (5.9)	
Other	194 (5.9)	186 (6.4)	8 (2.1)	
Histologic tumor staging				<0.001
T1	1504 (46.6)	1389 (47.7)	115 (29.7)	
T2	1559 (47.2)	1343 (46.0)	216 (55.8)	
T3	123 (3.7)	96 (3.3)	27 (7.0)	
T4	116 (3.5)	87 (3.0)	29 (7.5)	
Surgery type				<0.001
Breast conserving surgery	1271 (38.5)	1172 (40.2)	99 (25.6)	
Mastectomy	2031 (61.5)	1743 (59.8)	288 (74.4)	
Adjuvant chemotherapy				<0.001
No	877 (26.6)	822 (28.2)	55 (14.2)	
Yes	2425 (73.4)	2093 (71.8)	332 (85.8)	
Subgroups				<0.001
G1 (LN+/luminal-like)	1016 (30.8)	850 (29.1)	166 (42.9)	
G2 (LN+/basal-like)	223 (6.8)	180 (6.2)	43 (11.1)	
G3 (LN+/HER2+HR-)	457 (13.8)	367 (12.6)	90 (23.2)	
G4 (LN-/luminal-like)	1002 (30.3)	953 (32.7)	49 (12.7)	
G5 (LN-/basal-like)	257 (7.8)	242 (8.3)	15 (3.9)	
G6 (LN-/HER2+HR-)	347 (10.5)	323 (11.1)	24 (6.2)	

Note-Unless otherwise noted, data are numbers of patients, with percentages in parentheses. *Data are means ± standard deviations, with medians in parentheses.

(5.2%) were lost to follow-up. Disease recurred in 387 of the 3,302 patients (11.7%) at a median of 38 months (ranging from 3 to 166 months). Of these 387 patients, 71 (18.3%) had local or regional recurrence, 336 (86.8%) had distant recurrence, 32 (8.3%) had both local and distant recurrence, and 12 (3.1%) had contralateral breast cancer (**Table 1**). The mean tumor size was significantly larger in patients with recurrence than in those without recurrence (P<0.001). Compared with the nonrecurrent group, the recurrence group had more cases of IDC (89.4% vs 92.0%, P = .001) and higher histologic tumor stages (P<0.001). More non-recurrent patients underwent breast-conserving surgery than recurrent patients (40.2% vs 25.6%, P<0.001) and less non-recurrent patients underwent adjuvant chemotherapy than recurrent patients (71.8% vs 85.8%, P<0.001). The non-recurrent group contained less cases of G1-G3 (positive axillary lymph nodes) than the recurrence group (47.9% vs 77.2%, Bonferroni's adjusted P<0.001).

Univariate and multivariate survival analysis

Univariate cox survival analysis (**Table 2**) demonstrated that larger tumor sizes and higher histologic grades were associated with poorer LRFS, DDFS, and DFS. Mastectomies and adjuvant chemotherapy were associated with poorer DDFS and DFS. IDC demonstrated poorer DDFS and DFS, compared with other histologic types. Younger women were associated with poorer LRFS. G4-G6 subgroups (LN- tumors) demonstrated better DDFS and DFS than G1-G3 subgroups (LN+ tumors). G2 and G3 had worse LRFS and DFS than G1, but the three subgroups (G1-G3) showed comparable DDFS levels. G1 yield comparable LRFS with G4-G6 subgroups. Survival curves are demonstrated in **Figure 2**.

Multivariate cox analysis demonstrated that the G subgroup was the only independent factor for LRFS (P<0.001, **Table 3**). The G subgroup also stayed significant for DDFS and DFS.

Table 2. Univariate cox analysis results according to LRFS, DDFS, and DFS

Variables	LRFS			DDFS			DFS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Patient age	0.951	0.941, 0.961	<0.001	0.993	0.983-1.003	0.167	0.992	0.983, 1.001	0.081
Tumor size	4.63	3.657, 5.861	<0.001	1.326	1.254-1.402	<0.001	1.296	1.227, 1.369	<0.001
Histologic type			0.982			0.004			0.006
IDC	1			1			1		
ILC	0.911	0.286, 2.900		1.219	0.775, 1.917		1.22	0.800, 1.861	
Other	0.944	0.344, 2.593		0.24	0.099, 0.582		0.336	0.167, 0.678	
Histologic tumor staging			<0.001			<0.001			<0.001
T1	1			1			1		
T2	1.731	1.013, 2.958		1.945	1.517, 2.493		1.850	1.473, 2.323	
T3	2.050	0.611, 6.873		3.929	2.527, 6.109		3.384	2.209, 5.183	
T4	8.358	3.933, 17.760		4.922	3.183, 7.609		4.387	2.898, 6.642	
Surgery type			0.239			<0.001			<0.001
Breast conserving surgery	1			1			1		
Mastectomy	1.359	0.816, 2.263		2.317	1.790-2.998		2.012	1.594, 2.940	
Adjuvant chemotherapy			0.217			<0.001			<0.001
No	1			1			1		
Yes	1.446	0.805, 2.595		2.404	1.745, 3.312		2.122	1.594, 2.824	
G Subgroups			<0.001			<0.001			<0.001
G1	1			1			1		
G2	3.142	1.582, 6.239		1.352	0.954-1.916		1.349	0.964, 1.887	
G3	2.300	1.265, 4.184		1.206	0.916, 1.588		1.328	1.027, 1.716	
G4	0.318	0.136, 0.745		0.238	0.166-0.342		0.292	0.212, 0.402	
G5	0.741	0.255, 2.150		0.290	0.157-0.534		0.366	0.216, 0.621	
G6	0.534	0.184, 1.548		0.359	0.223-0.579		0.421	0.274, 0.646	

Abbreviations: LRFS: local recurrence-free survival; DDFS: distant disease-free survival; DFS: disease-free survival; HR: hazard ratio. G subgroup: G1 (LN+/luminal-like), G2 (LN+/basal-like), G3 (LN+/HER2+HR-), G4 (LN-/luminal-like), G5 (LN+/basal-like), G6 (LN+/HER2+HR-).

Multivariate analysis results were in accordance with univariate analysis. It was observed that G2 and G3 demonstrated worse DFS than G1 (HR = 2.022, 95% CI, 1.487 to 2.750 for G2, and HR = 1.363, 95% CI, 1.044 to 1.781 for G3), although the three showed similar risks for distant metastasis (**Table 3**).

Association between surgery type, biological subtype, and axillary lymph node status

Association analysis demonstrated that surgery type was significantly correlated with biological subtype and axillary lymph node status, P<0.001. In the same biological subtype, LN (+) patients had significantly less breast conserving surgery (G1 vs G4, 27.5% vs 56.6%; G2 vs G5, 30.5% vs 47.1%; G3 vs G6, 23.2% vs 37.5%, Bonferroni's adjusted P<0.05). In LN (-) patients, luminal-like (G4) yielded more breast conserving surgery than basal-like (G5) (Bonferroni's adjusted P = 0.012) or HER2+HR-(G6) (Bonferroni's adjusted P<0.001). However, in LN (+) patients, luminal-like (G1), basal-like (G2), and HER2+HR-(G3) yielded similar results for breast conserving surgery (P = 0.104) (**Table 4**).

Discussion

The current study found that the combination of biological subtypes and axillary lymph node status could predict risk for local and distant recurrence. LN- tumors have a lower risk for distant recurrence than LN+ tumors but have similar risk for local recurrence with LN+/luminal-like tumors. LN+ tumors have comparable risks for distant recurrence, regardless of biological subtype, but luminal-like tumors present lower risks for local recurrence and better disease-free survival. To the best of our knowledge, there have been no other reports concerning the prevalence of biological subtypes and axillary LN status of breast cancer based on a big data of Chinese population. There is also a lack of big data on local recurrence and distant metastasis for breast cancer patients with different combinations of axillary LN status and

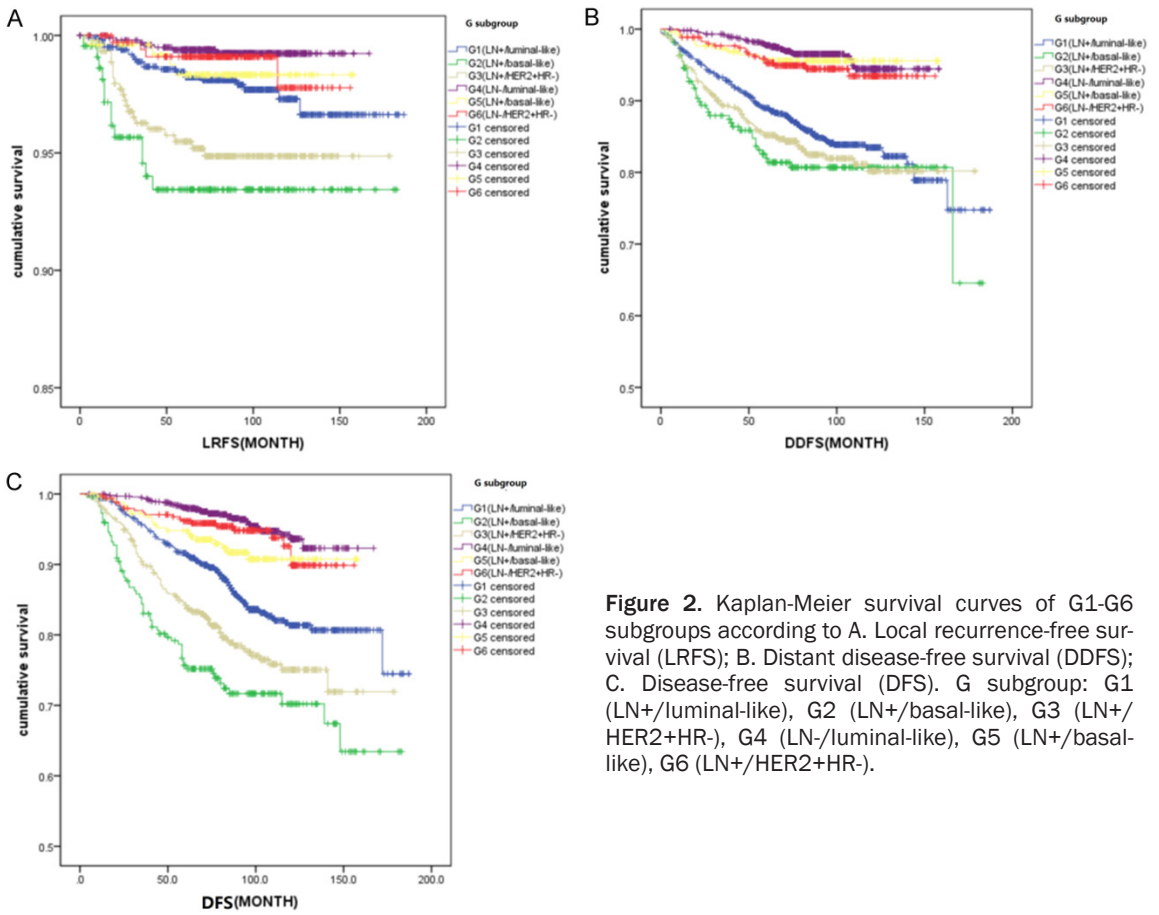

Figure 2. Kaplan-Meier survival curves of G1-G6 subgroups according to A. Local recurrence-free survival (LRFS); B. Distant disease-free survival (DDFS); C. Disease-free survival (DFS). G subgroup: G1 (LN+/luminal-like), G2 (LN+/basal-like), G3 (LN+/HER2+HR-), G4 (LN-/luminal-like), G5 (LN+/basal-like), G6 (LN+/HER2+HR-).

biological subtype. This study first demonstrated predictive roles of the combination of biological subtypes and axillary lymph nodes in evaluating multiple survival outcomes before surgery. Results suggest that patients with poor survival outcomes should be paid more attention or assigned with timely regimen adjustment.

Results showed that metastasis axillary LN is the most important factor associated with higher risks for distant recurrence, as LN- tumors presented lower risks for distant recurrence than LN+ tumors, regardless of biological subtype. However, local recurrence was significantly influenced by biological subtypes, with luminal-like tumors yielding the minimum risk for local recurrence.

The current study also discussed the relationship between surgery type and combination of biological subtypes and axillary LN status. For LN (-) tumors, luminal-like means a larger chance for breast conserving surgery than basal-like or HER2+HR-. For LN (+) tumors, the three biological types have a similar chance for breast conserving surgery. All were significantly lower than LN (-) tumors. Mastectomies, including complete excision of the breasts and cleaning axillary lymph nodes, often induce parts of upper limb edema, paresthesia, and upper limb dysfunction [16]. These inevitably lower life quality. With the improvement of renewed ideas and treatment technology, breast cancer surgery has become the first choice for early breast cancer in Western countries. However, breast conserving surgery accounts for only 10% to 20% in China [17], compared with about 50% in Western countries [18, 19]. A major reason is the misjudgment for the feasibility of breast conserving surgery. Thus, it is of clinical value in identifying indicators for breast conserving surgery. Accurate judgment for surgery type does not only avoid secondary operations but promotes more choices for breast conserving surgery.

This retrospective study had several limitations, however. First, this study was conducted at a single hospital and was subjected to poor representativity. However, this hospital is a

Table 3. Multivariate cox analysis results according to LRFS, DDFS, and DFS

Independent factor	Adjusted HR	95% CI of HR	P
LRFS			
G Subgroup			<0.001
G1	1	/	
G2	3.142	1.582, 6.239	
G3	2.300	1.265, 4.184	
G4	0.318	0.136, 0.745	
G5	0.741	0.255, 2.150	
G6	0.534	0.184, 1.548	
DDFS			
Tumor size	1.163	1.059-1.277	0.002
T staging	1.237	1.028-1.489	0.025
Surgery type (0, breast conserving; 1, mastectomy)	1.52	1.161-1.989	0.002
Adjuvant chemotherapy (0, no; 1, yes)	1.536	1.085-2.173	0.015
G subgroup			<0.001
G1	1	/	/
G2	1.307	0.917-1.863	0.138
G3	1.000	0.75-1.332	0.998
G4	0.348	0.237-0.511	<0.001
G5	0.337	0.177-0.642	0.001
G6	0.406	0.248-0.663	<0.001
DFS			
Age	1.024	1.015-1.034	<0.001
Tumor size	1.187	1.091-1.291	<0.001
T staging	1.363	1.247-1.716	<0.001
G subgroup			<0.001
G1	1	/	/
G2	2.022	1.487-2.75	0.001
G3	1.363	1.044-1.781	0.023
G4	0.323	0.224-0.465	<0.001
G5	0.612	0.375-1.001	0.05
G6	0.415	0.281-0.734	0.001

Abbreviations: LRFS: local recurrence-free survival; DDFS: distant disease-free survival; DFS: disease-free survival; HR: hazard ratio. G subgroup: G1 (LN+/luminal-like), G2 (LN+/basal-like), G3 (LN+/HER2+HR-), G4 (LN-/luminal-like), G5 (LN+/basal-like), G6 (LN+/HER2+HR-).

well-known cancer hospital which accept patients from all over the country. The 3,302 patients included in this study came from 16 provinces. Thus, they were representative of the Chinese breast cancer population. Second, this study did not conduct analysis to test the impact of adjuvant therapy regimens on survival outcomes. This study collected patients over a span of more than ten years, during which treatment has greatly improved and several new drugs have appeared. Thus, it was hard to evaluate whether the optimal regimen was assigned for each patient. This study respectively reviewed all adjuvant therapies to avoid obviously inappropriate regimens. Third, many factors, including tumor location, treatment response, and patients, influenced the feasibility of breast conserving surgery. Significant association between G subgroups and surgery type did not indicate definite causal correlation. Due to these limitations and confounders, present study results should be viewed with some caution. However, most findings were well in line with prior clinical studies or with experimental data. Efforts to determine preoperative risk stratification of recurrence and feasibility of breast conserving surgery are warranted and ongoing.

Table 4. Association between surgery type and combination of biological subtypes and axillary lymph node status (G subgroup)

			G subgroup						
			G1 (LN+/luminal-like)	G2 (LN+/basal-like)	G3 (LN+/HER2+HR-)	G4 (LN-/luminal-like)	G5 (LN+/basal-like)	G6 (LN-/HER2+HR-)	Total
Surgery type	Breast conserving surgery	No.	280	67	106	567	121	130	1271
		Percentage%	27.5%	30.0%	23.2%	56.6%	47.1%	37.5%	38.5%
	Mastectomy	No.	736	156	351	435	136	217	2031
		Percentage%	72.5%	70.0%	76.8%	43.4%	52.9%	62.5%	61.5%
Total		No.	1016	223	457	1002	257	347	3302

Conclusion

The current study concludes that the combination of axillary lymph node status and biological subtypes is associated with multiple prognosis of primary breast cancer and is the only independent predictor for local recurrence. This combination of axillary lymph node status and biological subtype is also a potential indicator for the feasibility of breast conserving surgery.

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Disclosure of conflict of interest

None.

Abbreviations

ER, expression statuses of estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor type 2; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; LN, lymph node; LN+, positive axillary lymph node; LN-, negative axillary lymph node; LRFS, local recurrence-free survival; DDFS, distant disease-free survival; DFS, disease-free survival; HR: hazard ratio.

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