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RESEARCH

Trends and Present Treatment Patterns of Early Breast Cancer in Southwest China

Qiancheng Hu · Ting Luo · Ping He · Xiaorong Zhong · Tinglun Tian · Qing Lv · Xi Yan · Hong Zheng

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Abstract To analyze the changing patterns of treatment and to explore the current treatment approaches for breast cancer in Southwest China, we conducted a population-based retrospective cohort study of early breast cancer cases. The data of patients who registered in the information management system for breast cancer in Huaxi Hospital, Sichuan University from 1989 to 2012 were extracted. Nearly all patients underwent surgery, among whom radical mastectomy was the predominant option. Chemotherapy (88.7 %) was the most predominant adjuvant therapy approach. The percentage of patients receiving radiation therapy displayed fluctuant increase, which was 37.1 % in 2001 and reached up to 67.6 % in 2011. Besides, the endocrinetherapy became more and more popular in the hormone-receptor positive patients and the percentage of endocrinetherapy was increased from 54.1 at 2001 to 85.6 % at 2011. However, more than 10 % of hormone-receptor positive patients still did not receive endocrinetherapy annually. The hormone-receptor positive patients who received endocrinetherapy had better 5-year disease free survival (DFS) and overall survival (OS) compared to those without endocrinetherapy (5-y DFS: 88.4 % vs. 75.1 %, $P<0.001$; 5-y OS: 95.7 % vs. 88.4 %, $P<0.001$). N stage appeared to have greater impact on the 5-year DFS and OS than molecular subtyping. The treatment for breast cancer in China has been significantly improved but more attentions should be paid to radiotherapy and endocrine therapy. In addition, the value of N stage in the prognosis of breast cancer should not be ignored when the molecular typing draws more and more attentions.

Keywords Early breast cancer · Southwest China · Trends · Present treatment

Introduction

Breast cancer is one of the most common cancers worldwide today and the most frequently diagnosed cancer in women [1]. More than one million new cases are diagnosed, resulting in > 400,000 deaths annually [1, 2]. Both the incidence and mortality rates are increasing in developing countries though decreasing or stable during the past 2 to 3 decades in western countries [3] . A rapid increased incidence, more than twice as fast as the global rate, has been documented in China, a developing country, over the past decade [4] .

Breast cancer is a complex disease, characterized by heterogeneity of clinical features, genetic alterations, sensitivity to treatment and prognosis. Good clinical outcomes and prognosis depend on early diagnosis and appropriate therapeutic strategy. The developing adjuvant therapy has obviously improved the prognosis of breast cancer patients. Adjuvant chemotherapy for early breast cancer, which experienced an evolution from CMF (cyclophosphamide, methotrexate, fluorouracil) to anthracycline and taxane, could reduce the risk of death by 8–8 % [5] . After breast-conserving surgery, the local recurrence rate of patients receiving radiotherapy was 14.3 % compared to 39.2 % of the patients not receiving radiotherapy ($p<0.001$) [6] . Adjuvant endocrine therapy by tamoxifen was responsible for 39 % reduction of recurrence rate and 31 % reduction of mortality rate [7] . Aromatase inhibitor (AI) was

Co first author: Qiancheng Hu and Ting Luo

Q. Hu · T. Luo · P. He · X. Zhong · T. Tian · X. Yan · H. Zheng (✉)
Department of Head & Neck and Mammary Oncology and Department of Medical Oncology, Cancer Center and State Key Laboratory of Biotherapy, Laboratory of Molecular Diagnosis of Cancer, West China Hospital, Sichuan University, No.37 Guo Xue Xiang, Chengdu 610041, China
e-mail: hongzheng11@gmail.com

Q. Lv
Department of Thyroid and Breast Surgery, West China Hospital, Sichuan University, Chengdu 610041, China

the preferred option among postmenopausal patients with primary breast cancer [8–10] . The overall survival in male patients with HER2 (human epidermal growth factor receptor) positive cancer was significantly better after adjuvant treatment with tamoxifen compared to AI [11] . HER2 positive patients seem to benefit from trastuzumab therapy [12, 13] . Therefore, treatment approaches are varied upon the different features of patients. Furthermore, the differences in the accessible resources and economic status among the patients make things more complex. By far, data on treatment patterns for breast cancer in China is unavailable.

In current study, we analyzed the treatment patterns of breast cancer, in addition to the profiles, from 1989 to 2012 in Southwest China to investigate the changing of treatment patterns for breast cancer and to provide direction for treatment of this disease.

Methods

Study Design

This study was a population-based retrospective cohort study which enrolled all the patients with early breast cancer registered in the information management system for breast cancer in Huaxi Hospital, Sichuan University from 1989 to 2012. This study was approved by the ethics committee of Huaxi hospital, Sichuan University.

Population-Based Data

As described previously [4], China is stratified into 7 geographic regions according to the traditional administrative district definition which are Northeastern China, North China, East China, Middle China, South China, Northwestern China and Southwestern China. Huaxi Hospital, the largest integrated hospital of China, is located in Southwestern China. In 2007, the departments of Medical Oncology, Breast Surgery, Radiation Oncology, Pathology and Radiology of Huaxi Hospital were joined together to form a multidisciplinary breast center (MDT) and an information management system for breast cancer was establish at the same time. In current study, the required data was collected from this information management system. The diagnosis and therapy of breast cancer are followed the NCCN guidelines (http://www.nccn.org) and St Gallen International Expert Consensus [14–19]. A combination of prospective and retrospective methods is applied by the medical secretaries to collect and record the basic characteristics, medical history, diagnosis, laboratory examinations, treatment and follow-up data of the patients. Follow-up was carried out for all patients by outpatient visit, telephone or e-mail, which was performed at least once every 3–6 months within 1–2 years after diagnosis, once every 6–12 months within 3–5 years, and once every 1 year after 5 years. Loss of follow-up was defined as that more than twice the indicated time, no any updated information was recorded at the information management system for breast cancer. The 5-year follow-up rate was 93.0 % (6730/7234). There was 7.0 % of patients was lost to follow-up due to the changes of contact (5.4 %, n=388), explicit refusal (1.1 %, n=79) or unable connection by phone (0.5 %, n=37).

Immunohistochemical assays data of estrogen receptor (ER), progesterone receptor (PR), Human Epidermal Growth Factor receptor (HER2) and KI-67 were available. The expression of ER and PR was recorded as negative or positive. Before 2010, ER and PR positive was defined as that the immunoperoxidase staining of tumor cell nuclei was not less than 10 %. After 2010, when the American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer [20] was reported, ER and PR positive was defined as that the immunoperoxidase staining of tumor cell nuclei was not less than 1 %.. Negative HER2 was defined as 0 or +, while positive HER2 was defined as +++. Partial samples with + or ++ HER2 expression were subjected to fluorescence in situ hybridization (FISH) assay to determine whether the HER was amplified. According to their expression, the patients were divided into 5 groups [21] . Luminal A: ER or PR positive, HER2 negative and low Ki-67 (<14 %); Luminal B: ER or PR positive, HER2 negative and high Ki-67 (≥14 %)/ER or PR positive and HER2 positive; HER2/neu+: ER negative, PR negative and HER2 positive; Triple negative breast cancer (TNBC): ER negative, PR negative and HER2 negative; uncertain: pathological information cannot meet the above requirements.

Statistical Analysis

All data and information derived from the information management system for breast cancer were reviewed and organized by two independent researchers. Disease-free survival (DFS) is defined as the time from the pathological confirmation of breast cancer to the first recurrence of cancer (local-regional recurrence, distant metastasis, and contralateral breast cancer), death of any cause or the end point of follow-up. Local-regional recurrence was defined as recurrence at the ipsilateral breast or any regions of the lymph drainage area (armpits, internal mammary or intercostal lymph node). Overall survival (OS) is defined as the time from the pathological confirmation of breast cancer to the death of any cause or the end point of follow-up. In current study, the follow-up was continued up to March 13, 2013.

Kaplan-Meier curve was applied to analyze the cumulative survival rate. The difference between groups was evaluated by log-rank test. A two-tailed $P < 0.05$ was defined as statistic significant. All statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Basic Characteristics

A total of 7234 early breast cancer cases were registered in the information management system for breast cancer from 1989 to 2012 (Table 1). The median age at diagnosis was 47 years with most patients aged more than 30 years, especially 41–50 years. The majority of breast cancer patients were female, accounting for 99.5 % (7,201 cases) of all cases, and only 33 cases were male (0.5 %). Among the female patients with the median menopause age of 49 years, 58.7 % were diagnosed before menopause and 41.3 % after menopause. At the end of the follow-up, 42.1 % (3035 cases) patients were at premenstrual status, 47.6 % (3,426 cases) at postmenopausal status, and the menopausal status of 10.3 % (740 cases) patients could not be confirmed.

Pathological Characteristics

Invasive ductal carcinoma is the main pathological type of breast cancer, accounting for about 84.7 % of all breast cancers (Table 1). Other types including ductal carcinoma in situ (2.7 %), microinvasion (0.2 %), mucinous (1.9 %), lobular (1.2 %) and invasive carcinoma (4.6 %) together accounted for a small percentage. According to the TNM staging, most cancers were diagnosed at early to middle T stage and N stage. There were 78.8 % patients with Tis, T0, T1 or T2 stage cancers at diagnosis. The percentage of cases diagnosed at N0, N1, N2 and N3 stage were 50.8, 26.2, 11.5 and 10.6 %, respectively. More than half of the patients were ER positive (55.6 %), and the same was true on PR expression that 53.7 % patients were PR positive. With regard to Ki-67 index, most cases (62.8 %) were greater than or equal to 14 %. Immunohistochemical analysis showed that 45.1 % patients were HER2 (human epidermal growth factor receptor) positive and 41.6 % were HER2 negative. Among the HER2 positive cases, there were 12.2 HER2+++, 12.0 HER2++ and 20.9 % HER2+ ones. FISH detection was performed for 33 %(785/2378)of patients with HER2++ or HER2+ cancers and the results revealed that 10 HER2+ and 26.3 % HER2+ patients were diagnosed with gene amplification (Table 2). Fig. 1 shows the proportion of HER2++ patients who underwent FISH detection in each year. The rate was increased with time, which was only 5.6 % before 2009 and reached up to 77.8 % at 2012.

Treatment Patterns

Most of the patients underwent surgery procedures and radical mastectomy was the predominant option (85.1 %). A minority of cases received breast conservative surgery (4.8 %) or extensive radical mastectomy (6.8 %). With respect to adjuvant therapy, chemotherapy was the most widely used strategy

Table 1 Basic characteristics of the included patients

Characteristic	Number of cases (n=7,234)	Percentage (%)
Sex		
Male	33	0.5
Female	7,201	99.5
Age, years		
16–30	193	2.7
31–40	1,498	20.7
41–50	2,842	39.3
51–60	1,724	23.8
61–89	976	13.5
Unknown	1	0.0
Menopause status[#]		
Premenopause (Diagnosis)	4,229	58.7
Postmenopause (Diagnosis)	2,971	41.3
Unknown	1	0.0
Premenopause (Follow-up)	3,035	42.1
Postmenopause (Follow-up)	3,426	47.6
Unknown	740	10.3
Histopathologic type		
Ductal carcinoma in situ	195	2.7
Microinvasion	18	0.2
Invasive ductal carcinoma	6,126	84.7
Mucinous	136	1.9
Medullary	47	0.6
Lobular	88	1.2
Invasive carcinoma	333	4.6
Others	298	4.1
Tumor (T)		
Tis	199	2.8
T0	221	3.1
T1	1,893	26.2
T2	3,390	46.9
T3	540	7.5
T4	275	3.8
Tx	716	9.9
Lymph node status (N)		
N0	3,676	50.8
N1	1,895	26.2
N2	831	11.5
N3	767	10.6
Nx	65	0.9
Estrogen receptor		
−	2,413	33.4
+	2,510	34.7
++	365	5.0
+++	1,149	15.9
±	94	1.3
Unknown	703	9.7

Table 1 (continued)

Characteristic	Number of cases (n=7,234)	Percentage (%)
Progesterone receptor		
−	2,499	34.5
+	2,609	36.1
++	415	5.7
+++	863	11.9
±	112	1.5
Unknown	736	10.2
Ki-67		
<14 %	851	11.8
≥14 %	4,545	62.8
Unknown	1,838	25.4
Human epidermal growth factor receptor-2		
−	3,008	41.6
+	1,511	20.9
++	867	12.0
+++	883	12.2
±	88	1.2
Unknown	877	12.1
Histologic grade		
I	156	2.2
II	1,214	16.8
III	2,321	32.1
Unknown	3,543	49.0
Primary surgery		
Radical mastectomy	6,155	85.1
BCS	347	4.8
Extensive radical mastectomy	493	6.8
Others	67	0.9
Unknown	172	2.4
Adjuvant chemotherapy		
Yes	6,418	88.7 %
No	818	11.3
Adjuvant endocrine therapy		
Yes	3,937	54.4
No	3,297	45.6
Adjuvant radiotherapy		
Yes	2,033	28.1
No	5,201	71.9

#, Excluding 36 male breast cancer; ±, under more than 5 microscopic fields (total 10 fields), there was no stained tumor cell nuclei. Tis refers to carcinoma in situ; Txrefers toprimary tumor thatcannot be assessed or missing data; Nxrefers to regional lymph nodes that cannot be assessed or missing data; Unknown includes no surgery and missing data; BCS, breast-conserving surgery,SERM, selective estrogen receptor modulator; AI, aromatase inhibitor

(88.7 %) compared to radiotherapy (28.1 %) and endocrine therapy (54.4 %) for breast cancer patients in China (Table 1).

Table 2 FISH detection and IHC assay for HER2 gene among included patients

IHC	FISH			
	Negative	Amplification	Borderline	Total
−(%)	34(94.4)	0(0)	2(5.6)	36
+ (%)	321(82.3)	39(10.0)	30(7.7)	390
++ (%)	250(63.3)	104(26.3)	41(10.4)	395
+++ (%)#	6(8.8)	57(83.8)	5(7.4)	68
±(%)	5(55.6)	0(0)	4(44.4)	9
Total	616	200	82	898

IHC, immunohistochemistry; *FISH*, fluorescence in situ hybridization; After 2009, amplification was defined as HER2gene/chromosome 17 ratio >2.2; Borderline was defined as HER2 gene/chromosome 17 ratio between 1.8–2.2; Negative was defined as HER2 gene/chromosome 17 ratio <1.8; #,+++ means borderline overexpression by IHC

Chemotherapy regimen, messy due to lack of specification before 2007, was designed after operation according to the guidelines of NCCN [22] and St Gallen after 2007 [23] . Anthracycline and/or taxane chemotherapy was the preferred adjuvant chemotherapy for breast cancer though the specified regimens were different under different clinical stage (Table 3). The percentage of patients with N1, N2 or N3 stage cancer receiving adjuvant chemotherapy was little more than that of patients with N0 stage cancer. FEC (fluorouracil + epirubicin + cyclophosphamide amide) chemotherapy was the most important treatment option for N0 (30.4 %) and N1 (26.2 %) stage cancers and was the secondary option for N2-N3 stage cancers (20.8 %), among which TEC (taxane + epirubicin + cyclophosphamide) chemotherapy was the main regimen (25.7 %).

Endocrine therapy became more and more popular among patients with hormone receptor-positive (HR+) breast cancer (Fig. 2a). The percentage was increased from 54.1 % at 2001

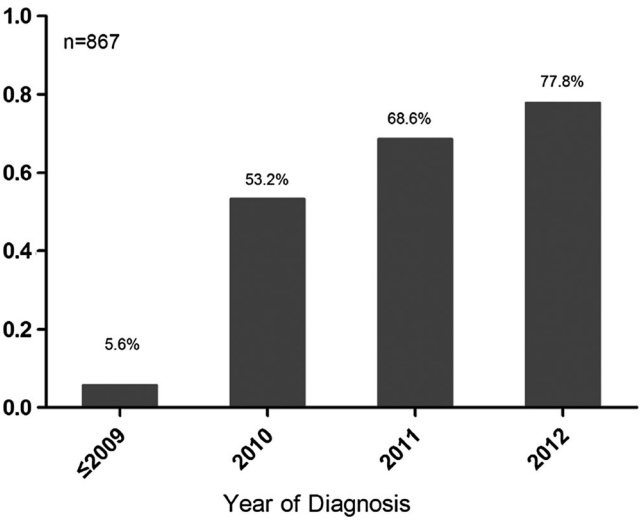

Fig. 1 The trend of fluorescence in situ hybridization detection among HER2++ patients

Table 3 Chemotherapy regimens for patients with different N stage cancer

	N0(n=3,676)	N1(n=1,895)	N2-N3(n=1,598)
CMF	7.1 %	5.6 %	5.8 %
TC	8.3 %	2.7 %	2.3 %
EC	1.7 %	1.1 %	0 %
FEC	30.4 %	26.2 %	20.8 %
FEC-T	5.5 %	10.9 %	0.9 %
TEC	3.3 %	10.0 %	25.7 %
AC-T	4.7 %	10.1 %	4.7 %
TE	5.9 %	11.3 %	16.6 %
None	14.9 %	7.1 %	7.4 %
Other	18.2 %	15.0 %	15.8 %

C, cyclophosphamide; *M*, methotrexate; *F*, fluorouracil; *T*, Taxanes; *E*, antharcycline

to 85.6 % at 2011. Since endocrine therapy has not yet been started for some patients at 2012, the percentage was lower than 2011. Among the premenopausal patients, endocrine therapy with selective estrogen receptor modulator (SERM) was absolute dominant compared to aromatase inhibitors (AI) (Fig. 2b). When it comes to postmenopausal patients, things were totally changed that neither SERM nor AI was absolute dominant (Fig. 2c). The proportion of AI therapy was increased from 20.0 % in 2002 to 73.2 % in 2012 while SERM was decreased from 78 % to 26.5 %. It should be noted that the proportion was low in 2006 when compared to the adjacent years, 2005 and 2007. But the detail reason is not clear and needs further investigation. In current study, a total of 3848 cases with HR + cancers received adjuvant endocrine therapy. At the end point of follow-up, 48.7 % (1,875 cases) still adhered to endocrine therapy but 30.1 % (1,158 cases) discontinued. Analysis of the 1158 cases revealed that the

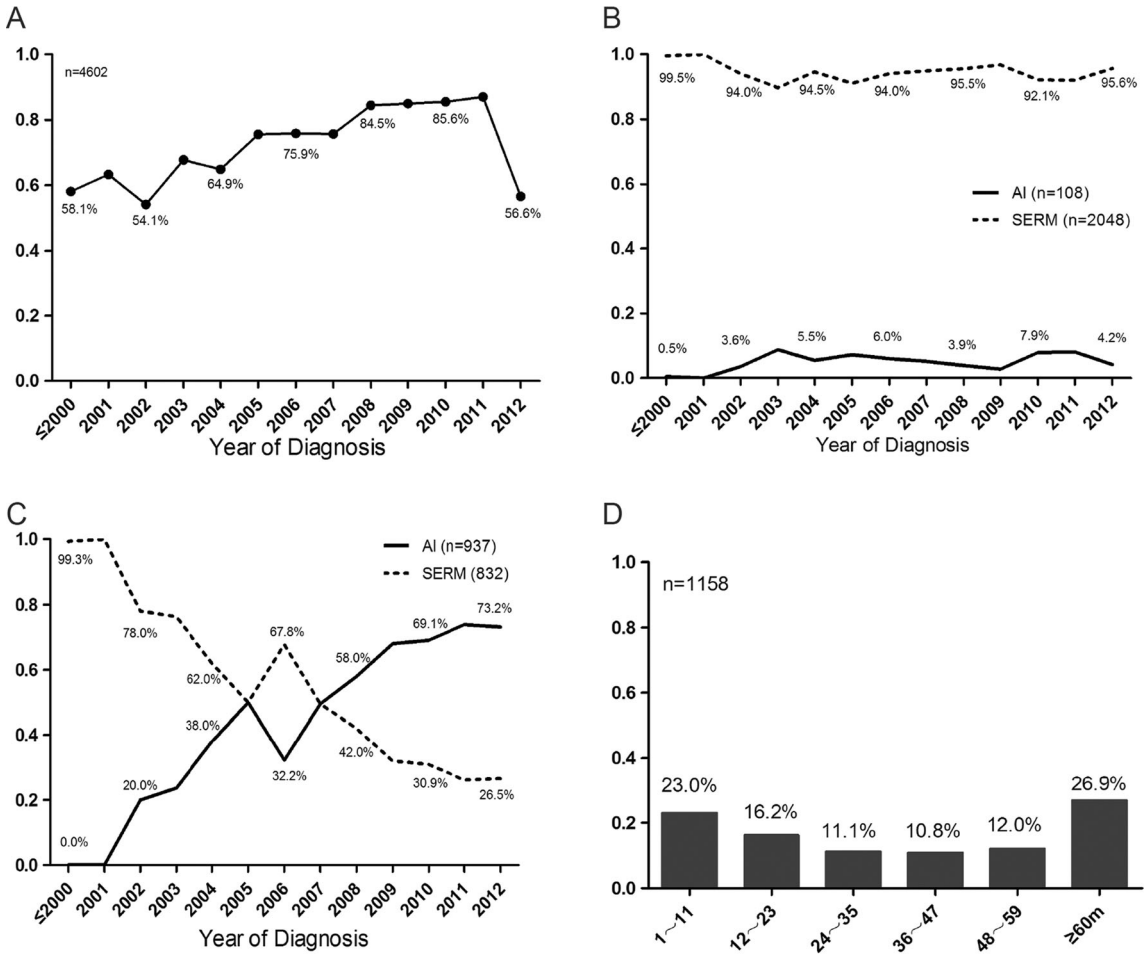

Fig. 2 The endocrine treatment patterns for hormone-receptor positive breast cancer. **a**. The trend of endocrine therapy among patients with hormone-receptor positive breast cancer; The percentage of endocrine therapy was very low at 2012 since many patients were undergoing chemotherapy and have not yet started to receive endocrine therapy; **b**. The trend of endocrine therapy using selective estrogen receptor modulator or aromatase inhibitors among premenopausal patients with hormone-receptor positive breast cancer; The patients receiving aromatase inhibitors therapy underwent ovariectomy; **c**. The trend of endocrine therapy using selective estrogen receptor modulator or aromatase inhibitors among postmenopausal patients with hormone-receptor positive breast cancer; **d**, The duration time of endocrine therapy among patients with hormone-receptor positive breast cancer

rates of discontinuance were 23.0, 16.2, 11.1, 10.9 and 12.0 % at the first, second, third, fourth and fifth years, respectively (Fig. 2d). There were 26.9 % cases continuing to receive endocrine therapy more than 5 years. The patients with T3-T4, N2-N3 stage cancer or receiving breast conserving surgery should be subjected to adjuvant radiation therapy. But, only 51.7 % (1150/2226) of them received adjuvant radiation therapy. At 2001, the percentage of patients receiving radiation therapy was 37.1 %, which was fluctuant increased and reached up to 67.6 % in 2011 (Fig. 3). The percentage was very low at 2012 since many patients have not yet started to receive radiation therapy. In the 1015 cases diagnosed with HER2-positive cancer by immunohistochemistry and FISH assay, 254 ones (25 %) received a targeted therapy using trastuzumab.

The survival Rate

The 5-year DFS of HR + patients who received endocrine therapy were obviously better than those not receiving endocrine therapy (88.4 % vs. 75.1 %, $p<0.001$, Fig. 4a). Similarly, the overall survival (OS) of HR + patients receiving endocrine therapy was 95.7 %, which is higher than that of HR + patients not receiving endocrine therapy (83.8 %, $p<0.001$, Fig. 4b).

According to the expression of ER, PR, HER2 and Ki-67, the patients with breast cancer were divided into 5 groups: Luminal A, Luminal B, TNBC, Her2/neu and uncertainty. Among them, patients with Luminal A type cancer have the best 5-year DFS rate, which was 90.6 % compared to 84.9 % ($p<0.001$), 80.4 % ($p<0.001$), 77.4 % ($p<0.001$) and 75.1 % of patients with Luminal B, TNBC Her2/neu and uncertainty cancers, respectively (Fig. 5a). Clear difference was observed

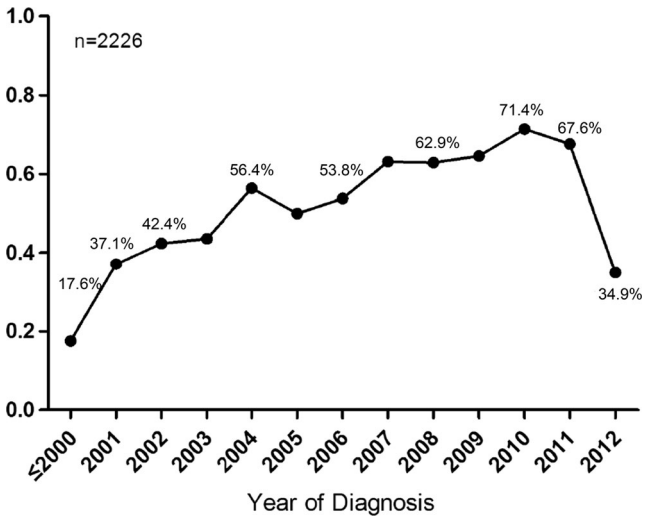

Fig. 3 The trend of radiotherapy endocrine therapy treatment patterns among breast cancer patients recommended to receive radiotherapy. The percentage of radiotherapy was very low at 2012 since many patients were undergoing chemotherapy and have not yet started to receive radiotherapy

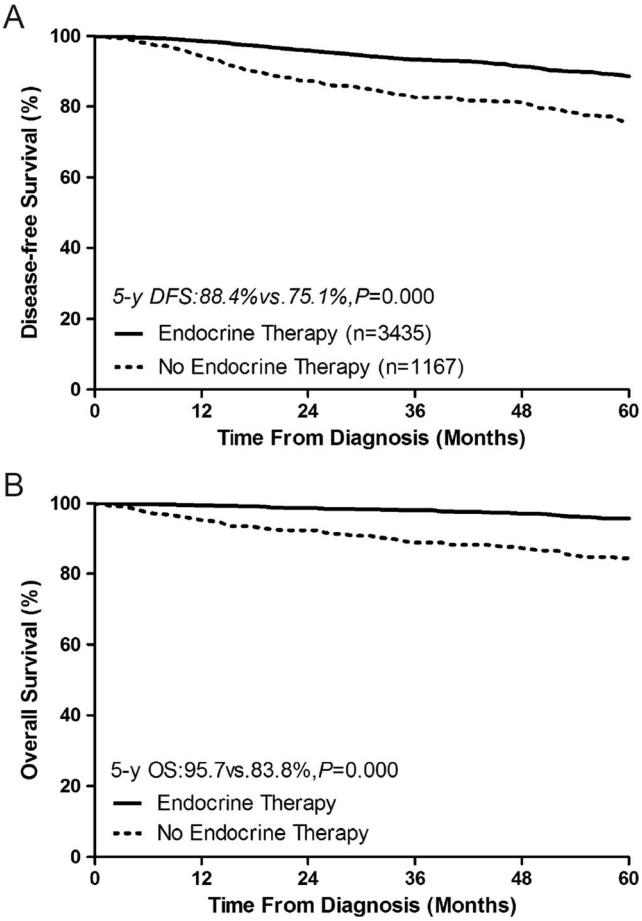

Fig. 4 The 5-year DFS (**a**) and OS (**b**) of hormone-receptor positive patients with or without endocrine therapy. Patients with endocrine therapy were defined as the ones received endocrine therapy more than 1 day

in 5-year DFS rate between patients with Luminal B and TNBC cancers (84.9 % vs. 80.4 %, $p=0.013$), as well as patients with Luminal B and TNBC cancers (84.9 % vs. 77.4 %, $p=0.017$). There was no significant difference in 5-year DFS rate between patients with TNBC cancer and Her2/neu cancer (80.4 % vs. 77.4 %, $p=0.815$). The 5-year OS rate of patients with Luminal A cancers was also the highest (95.5 %), followed by patients with Luminal B (92.8 %), TNBC (87.7 %), Her2/neu cancers (85.2 %). There was obvious difference when compared the 5-year OS rate of Luminal A patients to Luminal B ($p=0.04$), TNBC ($p<0.001$), and Her2/neu patients ($p<0.001$). Additionally, Luminal B patients had significant higher 5-year OS rate compared to TNBC ($p<0.001$) (Fig. 5b).

The 5-year DFS rate of patients with stage N0, N1, N2, N3 and Nx cancers was 90.9, 87.1, 74.9, 58.5 and 77.0 %, respectively. Significant difference in 5-year DFS rate was observed between stage N0 and N1 patients ($p<0.001$), N1 and N2 patients ($p<0.001$), as well as N2 and N3 patients ($p<0.001$) (Fig. 5c). The same was true when it comes to 5-year OS rate that patients with stage N0 cancers had the

highest 5-year OS rate followed by patients with stage N1, N2 and N3 cancers. Significant difference was observed between any two N stage cancer (Fig. 5d).

Further, we analyzed the effect of molecular subtyping on 5-year DFS and OS rate among patients with same N stage cancers or the effect of N stage among patients with same molecular subtyping cancers. There was no significant different in 5-year DFS rate between different subtyping cancers among patients with stage N0 cancers except Luminal A and TNBC patients (93.5 % vs. 87.4 %, $P<0.001$, Fig. 6a). Both Luminal A and B patients had higher 5-year OS rate than TNBC patients ($P=0.004$ and $P=0.020$, respectively, Fig. 6b). With respect to stage N1 cancers, things were different that, whatever 5-year DFS or OS, both Luminal A and B patients displayed higher rate than TNBC patients and Her2/neu patients ($p<0.05$), but no difference was found between Luminal A and B patients as well as between TNBC patients and Her2/neu patients (Fig. 6c and d). Among patients with stage N2 cancer, only the 5-year OS rate of Luminal A and B patients were different from TNBC patients (both $P=0.001$) (Fig. 6e and f). There was no significant difference in either 5-year DFS or OS rate among stage N3 patients with different molecular subtyping cancers (Fig. 6g and h).

The N staging presented distinct effects on the 5-year DFS (or OS) rate of patients with different molecular subtyping cancers. Among Luminal A patients, statistically significant difference in 5-year DFS and OS rate mainly appeared between stage N3 and other stage (N0, N1 and N2) patients though the 5-year DFS rate of stage N0 patients was also higher than N2 stage patients ($P=0.004$) (Fig. 7a and b), while difference was found between any N stage patients with Luminal B cancers ($P<0.01$) (Fig. 7c and d). As for TNBC patients, whatever 5-year DFS or OS rate, there was significant difference between any N stage patients except between stage N2 and stage N3 patients (Fig. 7e and f). Statistically significant difference in 5-year DFS and OS rate mainly appeared between stage N0 and stage N1, N2 and N3 patients with HER2/neu positive cancer ($p<0.001$ for DFS; $P=0.010$, $P=0.003$ and $P<0.001$ for OS, respectively) (Fig. 7g and h).

Discussion

The incidence rate of breast cancer is increasing in China and it remains a leading public health burden today. In this study, we analyzed the profiles and the treatment patterns of breast

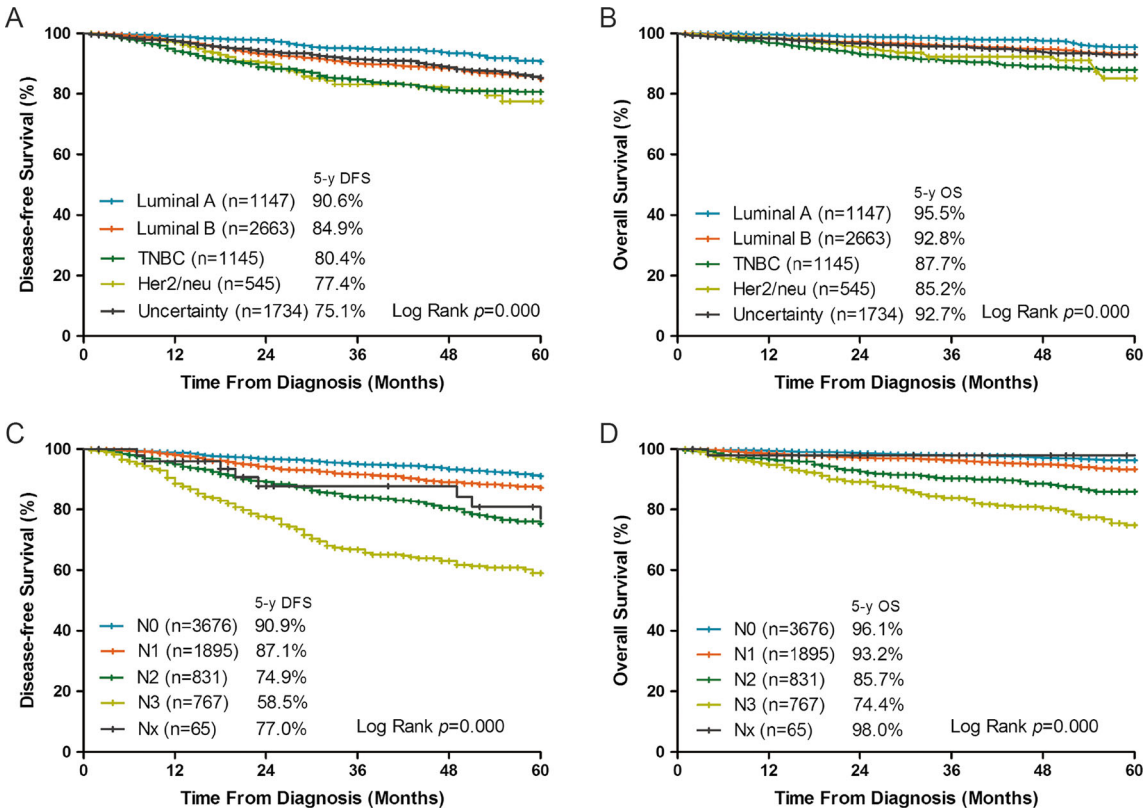

Fig. 5 The 5-year DFS and OS of patients with different subtypes of breast cancer. **a** and **b**. 5-year DFS (**a**) and OS (**b**) rates of patients with luminal A, luminal B, triple negative, Her2/neu and uncertainty breast cancer; **c** and **d**. 5-year DFS (**c**) and OS (**d**) rates of patients with stage N0, N1, N2, N3 and Nx breast cancer

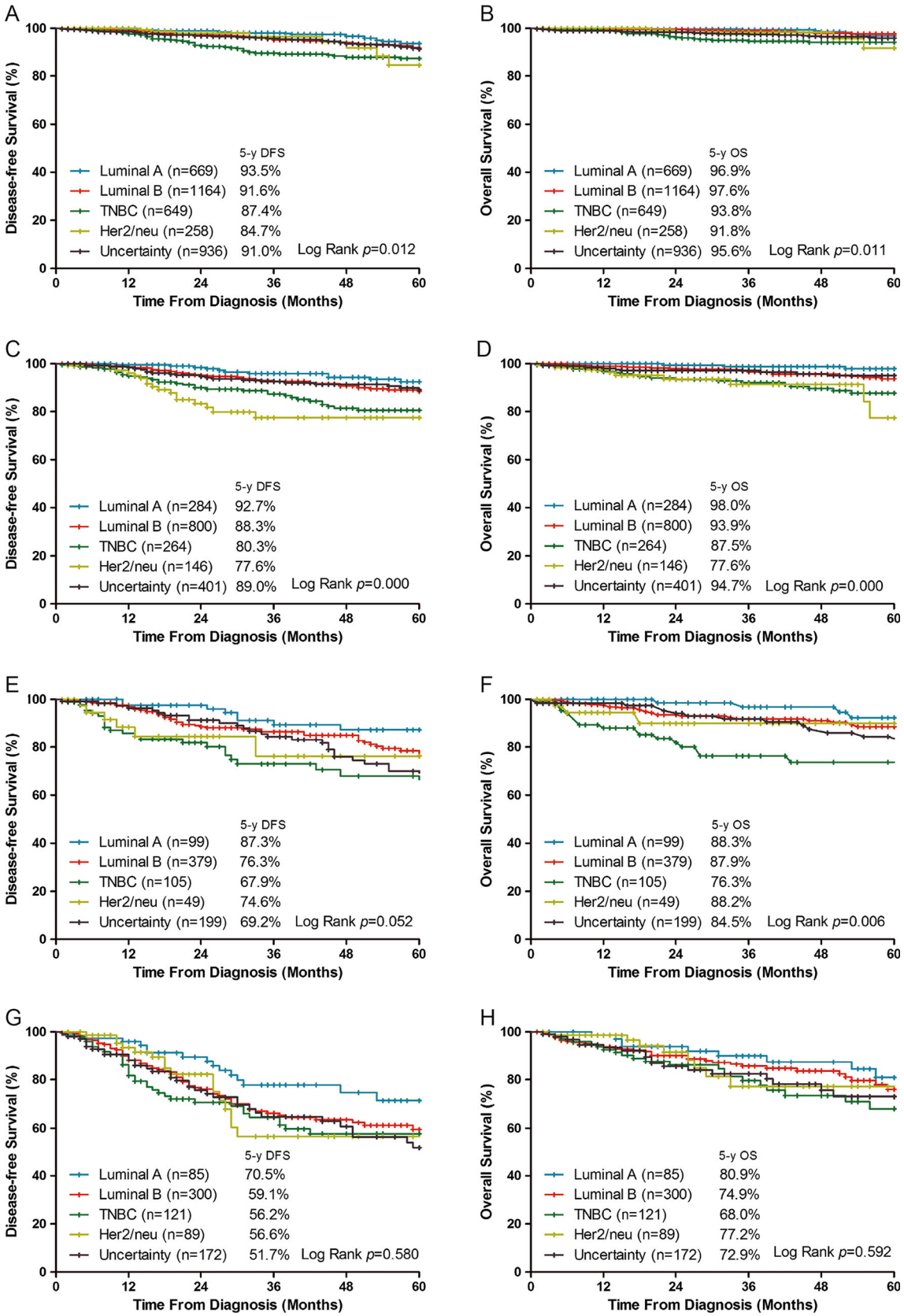

Fig. 6 The effect of molecular subtyping on 5-year DFS and OS among patients with same N stage cancers. **a**, **c**, **e** and **g**. The 5-year DFS of patients with stage N0 **a**, N1 **c**, N2 **e** and N3(**g**) breast cancer; **b**, **d**, **f** and **h**. The 5-year OS of patients with stage N0 **b**, N1 **d**, N2 **f** and N3 **h** breast cancer

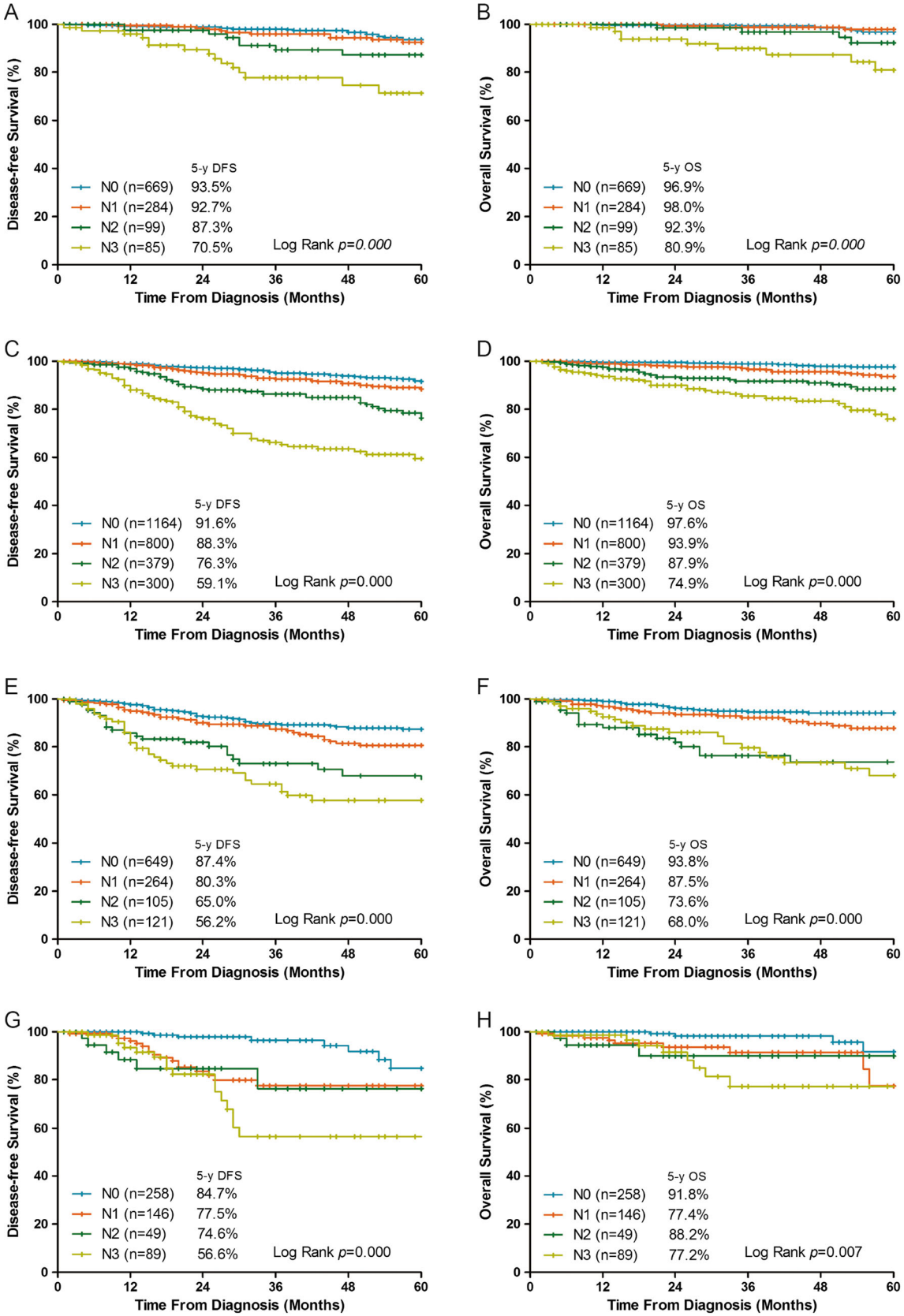

Fig. 7 The effect of N staging on 5-year DFS and OS among patients with same molecular subtyping cancers. The 5-year DFS of patients with stage luminal **a** (**a**), luminal **B** (**c**), triple negative (**e**) and Her2/neu (**g**) breast cancer; **b**, **d**, **f** and **h**. The 5-year OS of patients with stage luminal **a** (**b**), luminal **b** (**d**), triple negative (**f**) and Her2/neu (**h**) breast cancer

cancer from 1989 to 2012 in Southwest China to present the actuality and the advance of the treatment for breast cancer.

The median age at diagnosis was 47 years in current study, which was similar to the previous studies within China but earlier than that reported for Western Caucasian [24] . The main subtype of breast cancer was Luminal type and more than half of patients (52.5 %) were diagnosed with Luminal type cancer in this study, which was lower compared to 67 % reported in United States [25] and 74.6 % in Guangzhou, China [26] . The proportion of patients with triple-negative breast cancer was reported to be varied from 10.2 to 30.6 % [25, 27–30] and about 18.5 % of patients in China were diagnosed with this subtype [31], which was similar to that reported in current study (15.8 %). More than half of HER2++ patients did not undergo further FISH detection in this study, resulting in a low proportion of HER2 positive cancer and a high proportion of uncertain cancer at the same time. FISH detection was available in our hospital in 2010, and since then it became more and more popular among HER2 positive patients. About 10 % HER2+ patients were diagnosed with gene amplification through FISH detection, in agreement with previous reports (7.4–12.2 %) [32, 33] . Besides to lack of FISH detection, the high proportion of uncertain cancer was caused by that the system we used was established in 2007 and prior to this the data of patients were collected by the assistants from the medical record department that some data were lost and these patients were recorded as uncertain cases.

Modified radical mastectomy surgery was still the main approach for early breast cancer and only 4.8 % of patients received breast-conserving surgery, lower than that reported in Shanghai, China (13.8 %) [34] and largely lower than that reported in United State (59 %) [35] . With regard to the adjuvant treatment, chemotherapy was the predominant option, conformed with previous report within China [36] . In this study, the mainstream program of chemotherapy for different N stage cancers had a clear tendency that higher intensity chemotherapy regimen was carried out for patients with higher N stage cancers. However, despite the tendentious chemotherapy strategy, patients with stage N2 or N3 cancer still had worse 5-year DFS and OS rate. The proportion of radiotherapy among patients recommended to receive this was increased year by year which indicated that the more and more attention was paid on radiotherapy. But there was about half patients still did not undergo radiotherapy due to various reasons, such as the lack of sufficient understanding on radiotherapy and the blocked transform from chemotherapy to radiotherapy, such as missing the time of out-patient radiotherapy (the patients who didn't stay in the hospital received regular radiotherapy by outpatient visit), unable to reimburse the expense of out-patient radiotherapy and so on. This issue is expected to be resolved through regular education and optimization of the transform from chemotherapy to radiotherapy. Additionally, only 25 % of the patients with HER2 positive cancer received targeted therapy with trastuzumab, which may be one of the reasons of the low 5-year DFS and OS rate in HER2 positive patients when considered the fact that adjuvant trastuzumab significantly improved disease-free and overall survival among women with HER2-positive breast cancer [37]. The high cost of adjuvant trastuzumab was largely responsible for the low adoption rate. Huaxi Hospital, located in Chengdu, Sichuan Province in southwest China, belongs to a second-tier city relative to Beijing and Shanghai and accordingly, the economic development is relatively backward. Moreover, many patients of Huaxi Hospital are from Sichuan Province. In 2012, the per capita GDP was 21,013 Yuan in Sichuan, approximately equal to $ 3,104, while the annual cost of trastuzumab treatment was about 320,000 Yuan, approximately equal to $ 47,000. More than 15-fold difference between the drugs expense paying by the patients themselves and the per capita GDP is the main cause of low utilization of targeted therapy.

It is should be discussed the endocrine therapy situations among patients with hormone-receptor positive cancers. Previous studies have shown that hormone therapy can obviously reduce the recurrence rate and mortality of patients with hormone-receptor-sensitive breast cancer [7, 8, 21] . In current study, we also found the improved 5-year DFS (88.4 % vs. 75.1 %, $P<0.001$) and OS (95.7 % vs. 88.4 %, $P<0.001$) in hormone-receptor-positive patients with endocrine therapy compared to that without endocrine therapy. However, there were still some hormone-receptor-positive patients who did not undergo endocrine therapy or discontinued at an early course. It seems that discontinuation is common during the endocrine therapy course. Hershman et al. [38] showed that only 49 % of patients completed the endocrine therapy while 31 % discontinued early and the survival rate was significantly higher in patients with sustained endocrine therapy than the ones with early discontinuation (10-year OS: 80.7 % vs. 73.6 %, $P<0.001$). Barron et al. [39] conducted a cohort study and found that the cumulative tamoxifen nonpersistence rate was 22.1 % within 1 year, 28.4 % within 2 years and increased to 35.2 % by the end of follow-up at 3.5 years. In present study, the discontinuation rate at 1 2 and 3 years was 23.0, 39.2 and 50.3 %, respectively. Only 26.9 % of patients adhered to the endocrine therapy for 5 years. Even to 2011, there were still 12.9 % patients who had not received endocrine therapy. High rate of discontinuation was observed that new strategies should be developed to improve the persistence among HR positive patients, especially when considering the survival benefit from endocrine therapy. Tamoxifen remained to be the predominant options for premenopausal patients but not always for the postmenopausal patients. From the early 21st century, some studies have showed the preliminary evidence that AIs (anastrozole or letrozole) were superior to tamoxifen for postmenopausal patients [40–42]. However, the 2003 St. Gallen guidelines recommend that anastrozole should be used only for patients by whom tamoxifen is

contraindicated or not tolerated [17]. Until to the ninth St Gallen (Switzerland) expert consensus meeting in 2005, no definitive conclusion was made on the usage of tamoxifen or AIs for endocrine therapy (Meeting Highlights: International Expert Consensus on the Primary Therapy of Early Breast Cancer 2005. But most experts recommend AIs as the standard endocrine therapy method in the St Gallen International Breast Cancer Conference at 2009 [19] . So, AIs are becoming more widely accepted. Our findings is parallel to this that the utilization rate of aromatase inhibitors in postmenopausal patients was increased year by year and reached to 73.2 % in 2012. However, the situation was changed in 2011 St Gallen conference, in which the experts suggested that both tamoxifen and AI are accepted options for the postmenopausal setting but in the presence of involved lymph nodes, the majority supported AI (2011). Also, in 2013 St Gallen conference, the Panel didn't thought that AIs were necessary for postmenopausal patients although a combination of AIs and tamoxifen was recommended. In contrast, the Panel strongly believed that some postmenopausal patients could be treated with tamoxifen alone. More studies are needed to explore the association of AIs and tamoxifen for endocrine therapy.

Recently, molecular typing appeared to play key roles in the prognosis of breast cancer. A body of evidences showed that Luminal A patients have the best prognosis, followed by the Luminal B, triple negative and HER2/neu positive patients [21, 26], in accordance with our research. The lymph node status is also one predictor for prognosis of breast cancer. In current study, the survival rate became worse with the higher N stage. Most present studies [43, 44] only centered on the single prognostic value of lymph node status or molecular typing in breast cancer patients but few explored the value of lymph node status upon molecular typing or in turn. We made a primary attempt on this but more prospective studies are needed to confirm our results. Interestingly, the effects of N staging on the 5-year DFS and OS rate for different molecular type cancers were not the same The effect of the molecular typing on the survival of patients with stage N2 cancer, especially the stage N3 cancer, was weakened. The prognosis of stage N3 patients was independent of the molecular typing. Therefore, though the molecular typing draws more and more attentions on the prognosis of breast cancer, the value of N stage should not be ignored.

In summary, the data in our study revealed that the therapy for breast cancer in China has been significantly improved though a gap still exists between the current treatment situation in China and the guidelines for breast cancer. Sufficient understanding of the importance of adjuvant therapy by patients may enhance the treatment compliance of them and consequently improve the survival of breast cancer patients in China. In addition, the value of N stage for prognosis of breast cancer should not be ignored when the molecular typing draws more and more attentions.

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References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
2. Huang X-E, Hirose K, Wakai K et al (2004) Comparison of lifestyle risk factors by family history for gastric, breast, lung and colorectal cancer. Asian Pac J Cancer Prev 5:419–427
3. Jemal A, Center MM, Desantis C, Ward EM (2010) Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 19:1893–1907
4. Fan L, Zheng Y, Yu KD et al (2009) Breast cancer in a transitional society over 18 years: trends and present status in Shanghai, China. Breast Cancer Res Treat 117:409–416
5. Berry DA, Cronin KA, Plevritis SK et al (2005) Effect of screening and adjuvant therapy on mortality from breast cancer. N Engl J Med 353:1784–1792
6. Fisher B, Anderson S, Bryant J et al (2002) Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 347:1233–1241
7. Ctsu RI (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717
8. Howell A, Cuzick J, Baum M et al (2005) Results of the ATAC (Arimidex, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365:60–62
9. Thürlimann B, Keshaviah A, Coates AS et al (2005) A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 353:2747–2757
10. Coombes RC, Hall E, Gibson LJ et al (2004) A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 350:1081–1092
11. Eggemann H, Ignatov A, Smith BJ et al (2013) Adjuvant therapy with tamoxifen compared to aromatase inhibitors for 257 male breast cancer patients. Breast Cancer Res Treat 137:465–470
12. Perez EA, Romond EH, Suman VJ et al (2011) Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2–positive breast cancer: Joint analysis of data from NCCTG N9831 and NSABP B-31. J Clin Oncol 29:3366–3373
13. Welslau M, Dieras V, Sohn JH et al (2014) Patient-reported outcomes from EMILIA, a randomized phase 3 study of Trastuzumab Emtansine (T-DM1) versus capecitabine and lapatinib in human epidermal growth factor receptor 2-positive locally advanced or metastatic breast cancer. Cancer-Am Cancer Soc 120:642–651
14. Goldhirsch A, Wood WC, Senn HJ, Glick JH, Gelber RD (1995) Meeting highlights: international consensus panel on the treatment of primary breast cancer. J Natl Cancer Inst 87:1441–1445
15. Goldhirsch A, Glick JH, Gelber RD, Senn HJ (1998) Meeting highlights: international consensus panel on the treatment of primary breast cancer. J Natl Cancer Inst 90:1601–1608
16. Goldhirsch A, Glick JH, Gelber RD, Coates AS, Senn HJ (2001) Meeting highlights: international consensus panel on the treatment of primary breast cancer. Seventh international conference on adjuvant therapy of primary breast cancer. J Clin Oncol 19:3817–3827
17. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thurlimann B, Senn HJ (2003) Meeting highlights: updated international expert

consensus on the primary therapy of early breast cancer. J Clin Oncol 21:3357–3365
18. Goldhirsch A, Glick JH, Gelber RD et al (2005) Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. Ann Oncol 16:1569–1583
19. Goldhirsch A, Ingle JN, Gelber RD et al (2009) Thresholds for therapies: highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2009. Ann Oncol 20: 1319–1329
20. Hammond ME, Hayes DF, Dowsett M et al (2010) American society of clinical oncology/College of American pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). Arch Pathol Lab Med 134:e48–72
21. Goldhirsch A, Wood WC, Coates AS et al (2011) Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol 22:1736–1747
22. Network NCC, NCCN clinical practice guidelines in oncology: breast cancer (2007) National comprehensive cancer network
23. Harbeck N, Jakesz R (2007) St. Gallen 2007: breast cancer treatment consensus report. Breast Care 2:130–134
24. Parkin DM, Fernández LM (2006) Use of statistics to assess the global burden of breast cancer. Breast J 12:S70–S80
25. Carey LA, Perou CM, Livasy CA et al (2006) Race, breast cancer subtypes, and survival in the Carolina breast cancer study. JAMA 295:2492–2502
26. Xue C, Wang X, Peng R et al (2012) Distribution, clinicopathologic features and survival of breast cancer subtypes in Southern China. Cancer Sci 103:1679–1687
27. Sørlie T, Perou CM, Tibshirani R et al (2001) Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 98:10869–10874
28. Kurebayashi J, Moriya T, Ishida T et al (2007) The prevalence of intrinsic subtypes and prognosis in breast cancer patients of different races. The Breast 16:72–77
29. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V (2007) Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype. Cancer 109:1721–1728
30. Haffty BG, Yang Q, Reiss M et al (2006) Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 24:5652–5657
31. Zhao J, Liu H, Wang M et al (2009) Characteristics and prognosis for molecular breast cancer subtypes in Chinese women. J Clin Oncol 100:89–94
32. Panjwani P, Epari S, Karpate A et al. (2010) Assessment of HER-2/neu status in breast cancer using fluorescence in situ hybridization & immunohistochemistry: experience of a tertiary cancer referral centre in India
33. Press MF, Sauter G, Bernstein L et al (2005) Diagnostic evaluation of HER-2 as a molecular target: an assessment of accuracy and reproducibility of laboratory testing in large, prospective, randomized clinical trials. Clin Cancer Res 11:6598–6607
34. Yu K-D, Li S, Shao Z-M (2011) Different annual recurrence pattern between lumpectomy and mastectomy: implication for breast cancer surveillance after breast-conserving surgery. Oncologist 16:1101–1110
35. Smith GL, Xu Y, Shih Y-CT et al (2009) Breast-conserving surgery in older patients with invasive breast cancer: current patterns of treatment across the United States. J Am Coll Surg 209:425–433. e422
36. Li J, Zhang B-N, Fan J-H et al (2011) A Nation-Wide multicenter 10-year (1999-2008) retrospective clinical epidemiological study of female breast cancer in china. BMC Cancer 11:364
37. Slamon D, Eiermann W, Robert N et al (2011) Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365:1273–1283
38. Hershman DL, Shao T, Kushi LH et al (2011) Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 126:529–537
39. Barron TI, Connolly R, Bennett K, Feely J, Kennedy MJ (2007) Early discontinuation of tamoxifen. Cancer 109:832–839
40. Baum M, Budzar A, Cuzick J et al (2002) Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 359:2131–2139
41. Ellis MJ, Coop A, Singh B et al (2001) Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: Evidence from a phase III randomized trial. J Clin Oncol 19:3808–3816
42. Dixon JM, Jackson J, Hills M et al (2004) Anastrozole demonstrates clinical and biological effectiveness in oestrogen receptor-positive breast cancers, irrespective of the erbB2 status. Eur J Cancer 40: 2742–2747
43. Ihemelandu CU, Leffall LD Jr, Dewitty RL et al (2007) Molecular breast cancer subtypes in premenopausal and postmenopausal African-American women: age-specific prevalence and survival. J Surg Oncol 143:109–118
44. Wang GS, Zhu H, Bi SJ (2012) Pathological features and prognosis of different molecular subtypes of breast cancer. Mol Med Report 6: 779–782