Biologic subtype is a more important prognostic factor than nodal involvement in patients with stages I and II breast carcinoma

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Purpose: Nodal infiltration has been one of the most important prognostic factors in breast cancer. In recent decades, risk stratification has greatly changed, and is applied in accordance with hormone receptor and human epidermal growth factor receptor 2 (HER2) status. We compared the prognostic power of tumor subtype to nodal involvement in early breast cancer.
Methods: We reviewed the medical records of 505 patients who had curative surgery for stage I or II breast cancer. We analyzed clinicopathologic factors according to tumor subtype and nodal involvement. Tumors were classified into 4 subtypes according to immunohistochemical status of estrogen receptor, progesterone receptor, HER2, and Ki67 labeling index. Disease-free survival (DFS) and overall survival were analyzed.
Results: There were 363 node-negative patients (71.9%) and 142 node-positive patients (28.1%). Luminal A, Luminal B, HER2, and triple-negative breast cancer subtypes were composed of 207 (41.0%), 147 (29.1%), 42 (8.3%), and 109 patients (21.6%), respectively. The median follow-up period was 89.5 months. Node negative-luminal A subtype showed the best prognosis with regard to 5-year DFS, and the pN1-triple negative subtype was associated with the shortest DFS (95.1% *vs.* 67.8%; hazard ratio, 9.554; P < 0.001). However, the node negative-triple negative subtype was associated with a worse 5-year DFS than the pN1-luminal A subtype ([86.4%; hazard ratio, 2.647; P = 0.048] *vs.* [93.2%; hazard ratio, 2.061; P = 0.194]).
Conclusion: Node negative-triple negative breast cancer was associated with a poorer prognosis than pN1-luminal A subtype. Tumor subtype has greater prognostic power compared to nodal status in early breast cancer.
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Key Words: Breast neoplasms, Lymphatic metastasis, Prognosis, Triple negative breast neoplasms

INTRODUCTION

Breast cancer has been shown to be a heterogeneous group of diseases at the molecular, pathological, and clinical level. Intrinsic subtypes of breast cancer, according to gene expression profiling, were first recognized by Perou et al. [1]. Many studies have shown that each subtype has different histopathological presentations and prognostic outcomes [2-4]. However, gene expression profiling to identify breast cancer subtypes is not routinely used in the clinical setting due to its high cost. Each subtype has been revealed to have characteristic immunohistochemical (IHC) profiles according to estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67 expression status. Guidelines recommend treatment of breast cancer patients according to intrinsic subtype, as diagnosed by IHC staining of these surrogate markers [5,6].

Nonetheless, axillary lymph node metastasis remains a powerful prognostic factor that affects decision-making regarding the use of adjuvant chemotherapy in early breast cancer.

Tamoxifen and trastuzumab have contributed to decreased recurrence and mortality in hormone receptor-positive and HER2-positive breast cancer patients. However, cytotoxic chemotherapy remains the mainstay of treatment for many early breast cancer patients, especially node-positive or ER and HER2-negative patients. In these cases, it is not clear which patients will benefit more from chemotherapy: node-positive early breast cancer or node-negative patients with a poor prognostic subtype. In this study, we compared the recurrence rates in early breast cancer patients from two groups of patients with extremely different subtypes and nodal status, luminal A-node positive (pN1) type and triple negative breast cancer (TNBC)-node negative (pN0) type, which are usually treated with chemotherapy and/or endocrine treatment.

METHODS

Patients

We retrospectively reviewed the medical records of 945 breast cancer patients who had curative surgery at our institution between 2003 and 2009. Of these patients, we excluded those with bilateral breast cancer, neoadjuvant chemotherapy, *in situ* carcinoma, tumor size less than 0.5 cm, stage III or IV breast cancer, metastatic carcinoma from other origin, and tumors of nonepithelial origin. Finally, 505 patients were included (Fig. 1). All pathologic records included primary tumor characteristics, such as tumor size, stage, tumor grade, ER, PR, and HER2 status, and Ki67 labeling index. Systemic adjuvant chemotherapy, endocrine treatment, and radiotherapy were performed in accordance with clinical guidelines. Pathologic staging was based on the 7th American Joint Committee on Cancer criteria
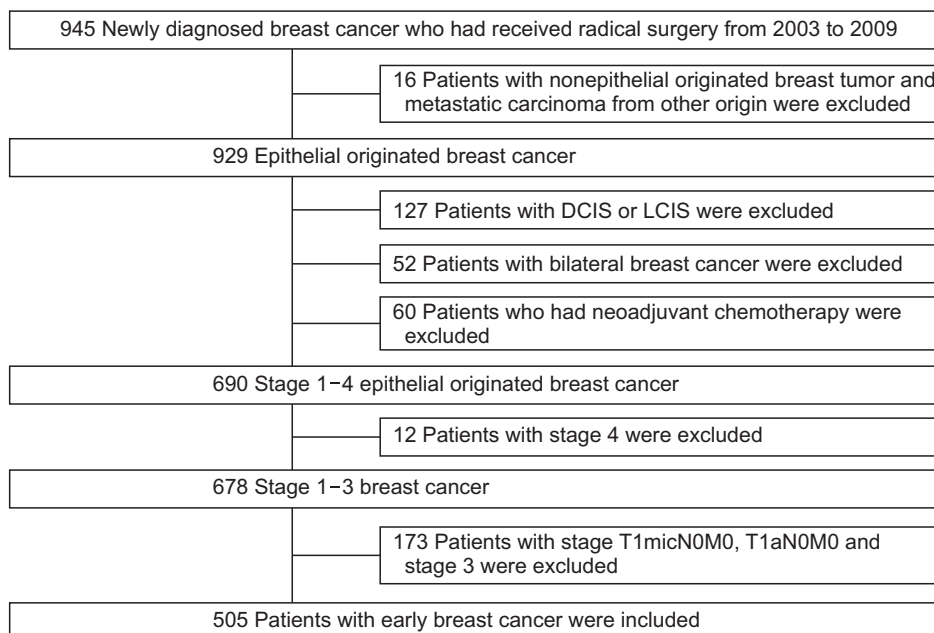
[7]. Following surgery, patients underwent regular follow-ups at 6-month intervals during the first 5 years, followed by annual follow-up. Types of recurrence included local and regional recurrence, and distant metastasis.

Immunohistochemistry for surrogate markers

Tissue samples were fixed in neutral buffered formalin and embedded in paraffin. Four-micrometer-thick sections were immunostained for ER, PR, HER2, and Ki67. IHC was performed, following epitope retrieval, using a polymer detection system with antibodies against ER (clone SP1, Neomarkers, Lab Vision Co., Fremont, CA, USA; 1:500 dilution), PR (clone SP2, Neomarkers, Lab Vision Co.; 1:400 dilution), HER2 (clone CB11, Novocastra, Newcastle upon Tyne, UK; 1:500 dilution), and Ki67 (clone MIB-1, Dako, Glastrup, Denmark; 1:1000 dilution) according to manufacturers' recommendations. Hormone receptors were defined as positive when ≥10% of nuclei showed positive staining. For HER2 staining, intense staining (3+) or amplification of the *her-2/neu* gene using fluorescence *in situ* hybridization was regarded as positive. Ki67 was scored as the percentage of positively stained nuclei out of 1,000 cells counted. Breast cancers were divided into four subtypes, as per recommendations from the 13th International Breast Cancer Conference held at St Gallen, Switzerland in 2013: luminal A (ER positive, PR positive, Ki67 < 20%, HER2 negative), luminal B (ER positive, PR negative or Ki67 > 20% or HER2 positive), HER2 (ER negative, PR negative, HER2 positive), and TNBC (ER negative, PR negative, HER2 negative) [5].

Statistical analysis

The patients were divided into two groups according to

945 Newly diagnosed breast cancer who had received radical surgery from 2003 to 2009

→ 16 Patients with nonepithelial originated breast tumor and metastatic carcinoma from other origin were excluded

929 Epithelial originated breast cancer

→ 127 Patients with DCIS or LCIS were excluded

→ 52 Patients with bilateral breast cancer were excluded

→ 60 Patients who had neoadjuvant chemotherapy were excluded

690 Stage 1–4 epithelial originated breast cancer

→ 12 Patients with stage 4 were excluded

678 Stage 1–3 breast cancer

→ 173 Patients with stage T1micN0M0, T1aN0M0 and stage 3 were excluded

505 Patients with early breast cancer were included

Fig. 1. Description of study population. DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

nodal involvement, and independent t-test, Pearson chi-square test, and Fisher exact test were used to analyze the differences between the node-negative and node-positive groups. Disease-free survival (DFS) and overall survival (OS) were analyzed for all patients; DFS was defined as the time period from the date of first diagnosis to the date when a recurrence was diagnosed by radiologic imaging or pathological confirmation. OS was defined as the period from the date of diagnosis with breast cancer to the date of death. The Kaplan-Meier method, with log rank test, was used to analyze the DFS and OS, and the Cox proportional hazard regression model was used to compare the prognostic power of nodal status and subtype using PASW Statistics ver. 18.0 (SPSS Inc., Chicago, IL, USA). To compare the time-dependent risk of recurrence, the hazard function ratios of the different subtypes were analyzed during the observed follow-up period using STATA 13 (StataCorp LP., College Station, TX, USA). Values of $P \leq 0.05$ were considered as statistically significant.

RESULTS

Clinicopathologic characteristics are described in Table 1. Mean patient age was 51.6 years (range, 26–84 years). Pathologically node-negative patients comprised 71.9% of the total number of patients, and node positivity was seen in 28.1% of patients. Of the 505 patients included in the study, 44.6% had stage I breast cancer and 55.4% had stage II breast cancer. Hormone receptor positivity was seen in 70.1% of patients, and HER2 was positive in 20.4% of cases. Luminal A, luminal B, HER2, and triple negative subtypes, as defined using surrogate markers, accounted for 41%, 29.1%, 8.3%, and 21.6% of breast tumors, respectively.

Adjuvant chemotherapy was administered to 67.9% of patients. Chemotherapy regimens used included cyclophosphamide-methotrexate-fluorouracil (CMF), adriamycin-based regimens, and adriamycin plus taxane regimens. Adjuvant endocrine treatment was performed to 98% of hormone receptor-positive patients with tamoxifen or aromatase inhibitor. Adjuvant radiotherapy, including post-mastectomy radiotherapy, was administered to 212 patients (42.0%), and nine patients with HER2 overexpression were treated with adjuvant trastuzumab for 1 year. The median follow-up duration for all patients was 89.5 months (range, 2–136 months). The 5-year and 10-year DFS for all cases were 90.6% and 86.3%, respectively.

Comparative analysis showed that there were more mastectomies performed in the node-positive group than in pathologic node-negative patients (P = 0.006). Ductal carcinoma as histologic type was more frequently found in node-positive group than node-negative group. Hormone receptor positivity was more prominent in node-positive group (P = 0.041), however HER2 status and distribution of subtypes

Table 1. Clinicopathologic characteristics

Characteristic	Value
Age (yr)	51.59 ± 11.1 (26–84)
≤40	71 (14.1)
>40	434 (85.9)
Sex	
Female	501 (99.2)
Male	4 (0.8)
Operation method	
Breast conserving surgery	256 (50.7)
Mastectomy	249 (49.3)
Tumor size (cm)	1.976 ± 1.0 (0.1–10.0)
≤2	305 (60.4)
>2	200 (39.6)
Histologic type	
Ductal	439 (86.9)
Lobular	18 (3.6)
Others[a]	48 (9.5)
Histologic grade	
1 and 2	209 (41.4)
3	263 (52.1)
Unknown	33 (6.5)
Stage	
IA	225 (44.6)
IIA	212 (42.0)
IIB	68 (13.4)
Nodal status	
pN0	363 (71.9)
pN1	142 (28.1)
Hormone receptor	
Positive	354 (70.1)
Negative	151 (29.9)
HER2	
Positive	103 (20.4)
Negative	402 (79.6)
Intrinsic subtype	
Luminal A	207 (41.0)
Luminal B	147 (29.1)
HER2	42 (8.3)
Triple negative	109 (21.6)
Adjuvant chemotherapy	
Yes	343 (67.9)
CMF	84 (16.6)
Adriamycin based[b]	147 (29.1)
Adriamyin with taxane[c]	112 (22.2)
No	162 (32.1)
Adjuvant endocrine therapy	
Yes	361 (71.5)
SERM	186 (36.8)
SERM with LHRHa	13 (2.6)
SERM, LHRHa followed by AI	2 (0.4)
AI	90 (17.8)
SERM followed by or after AI	70 (13.9)
No	144 (28.5)

Table 1. Continued

Characteristic	Value
Adjuvant radiotherapy	
Yes	212 (42.0)
Whole breast	203 (40.2)
Whole breast with regional node	7 (1.4)
Postmastectomy radiotherapy	2 (0.4)
No	293 (58.0)
Recurrence	
Yes	51 (10.1)
Locoregional only	17 (3.4)
Distant metastasis only	21 (4.2)
Locoregional and distant	13 (2.6)
No	454 (89.9)
Survival	
Yes	481 (95.2)
No	24 (4.8)

Values are presented as mean ± standard deviation (range) or number (%).
HER2, human epidermal growth factor receptor 2; CMF, cyclophosphamaide + methotrexate + 5-fluorouracil; SERM, selective estrogen receptor modulator; LHRHa, luteinizing hormone-releasing hormone analogue; AI, aromatase inhibitor.
[a]Histology of "Others" includes papillary, mixed, tubular, metaplastic, adenoid cystic, adenosquamous, apocrine, cribriform, medullary, squamous, poorly differentiated carcinoma. [b]Adriamycin based regimen includes adriamycin + cyclophosphamide, 5-fluorouracil + adriamycin + cyclophosphamide and 5-fluorouracil + epirubicin + cyclophosphamide. [c]Adriamycin with taxane regimen includes adriamycin + paclitaxel and adriamycin + doxetaxel.

were not statistically different between two groups. Adjuvant chemotherapy was predominantly performed more in node-positive group (P < 0.001). Adjuvant radiotherapy was performed more in node-negative group (P < 0.001), because more breast conserving surgeries was done in node-negative group. Other factors, such as age, tumor size, histologic grade, or adjuvant endocrine treatment did not show statistical differences (Table 2).

The node-positive group was associated with significantly worse 5-year and 10-year DFS compared to the node-negative group (87% vs. 92.4%, 79.3% vs. 85.1%, P = 0.005) (Fig. 2A); the TNBC subtype showed the worst 5-year and 10-year DFS when compared to the luminal A subtype (82.4% vs. 94.1%, 79.9% vs. 92.9%, P = 0.010) (Fig. 2B).

In luminal A and B disease, there were no statistically significant differences in DFS between the pN0 and pN1 groups. However, in the HER2 and TNBC types, there were evident statistical differences in DFS between the pN0 and pN1 groups (Fig. 3A–D). Analysis of hazard ratios for all 505 patients showed that the pN1 group was associated with 2.81-fold increase in DFS compared to the pN0 group, and the TNBC subtype was associated with a 2.58-fold increase in DFS compared to the

Table 2. Clinicopathologic factors according to nodal status

| Characteristic	pN0 (n = 363)	pN1 (n = 142)	P-value[a]
Age (yr)			0.992
≤40	51 (14.0)	20 (14.1)	
>40	312 (86.0)	122 (85.9)	
Operation method			0.006
Breast conserving surgery	198 (54.5)	58 (40.8)	
Mastectomy	165 (45.5)	84 (59.2)	
Tumor size (cm)			0.116
≤2	227 (62.5)	78 (54.9)	
>2	136 (37.5)	64 (45.1)	
Histologic type			0.016
Ductal	308 (84.8)	131 (92.3)	
Lobular	12 (3.3)	6 (4.2)	
Others	43 (11.8)	5 (3.5)	
Histologic grade			0.999
1 and 2	151 (44.3)	58 (44.3)	
3	190 (55.7)	73 (55.7)	
Hormone receptor			0.041
Positive	245 (67.5)	109 (76.8)	
Negative	118 (32.5)	33 (23.2)	
HER2			0.813
Positive	75 (20.7)	28 (19.7)	
Negative	288 (79.3)	114 (80.3)	
Intrinsic subtype			0.184
Luminal A	146 (40.2)	61 (43.0)	
Luminal B	99 (27.3)	48 (33.8)	
HER2	34 (9.4)	8 (5.6)	
Triple negative	84 (23.1)	25 (17.6)	
Adjuvant chemotherapy			<0.001
Yes	214 (59)	129 (90.8)	
CMF	79 (21.8)	5 (3.5)	
Adriamycin based[b]	131 (36.1)	16 (11.3)	
Adriamyin with taxane[c]	4 (1.1)	108 (29.8)	
No	149 (41)	13 (9.2)	
Adjuvant endocrine therapy			0.101
Yes	252 (69.4)	109 (76.8)	
No	111 (30.6)	33 (23.2)	
Adjuvant radiotherapy			<0.001
Yes	170 (46.8)	42 (29.6)	
No	193 (53.2)	100 (70.4)	
Recurrence			0.004
Yes	28 (7.7)	23 (16.2)	
Locoregional only	11 (3.0)	6 (4.2)	
Distant metastasis only	9 (2.5)	12 (8.5)	
Locoregional and distant	8 (2.2)	5 (3.5)	
No	335 (92.3)	119 (83.8)	
Survival			0.295
Yes	348 (95.9)	133 (93.7)	
No	15 (4.1)	9 (6.3)	

Values are presented as number (%).
HER2, human epidermal growth factor receptor 2; CMF, cyclophosphamaide + methotrexate + 5-fluorouracil (5-FU).
[a]The chi-square test was used to identify the differences in variables between groups according to nodal status. [b]Adriamycin based regimen includes adriamycin + cyclophosphamide, 5-FU + adriamycin + cyclophosphamide and 5-FU + epirubicin + cyclophosphamide. [c]Adriamycin with taxane regimen includes adriamycin + paclitaxel and adriamycin + doxetaxel.
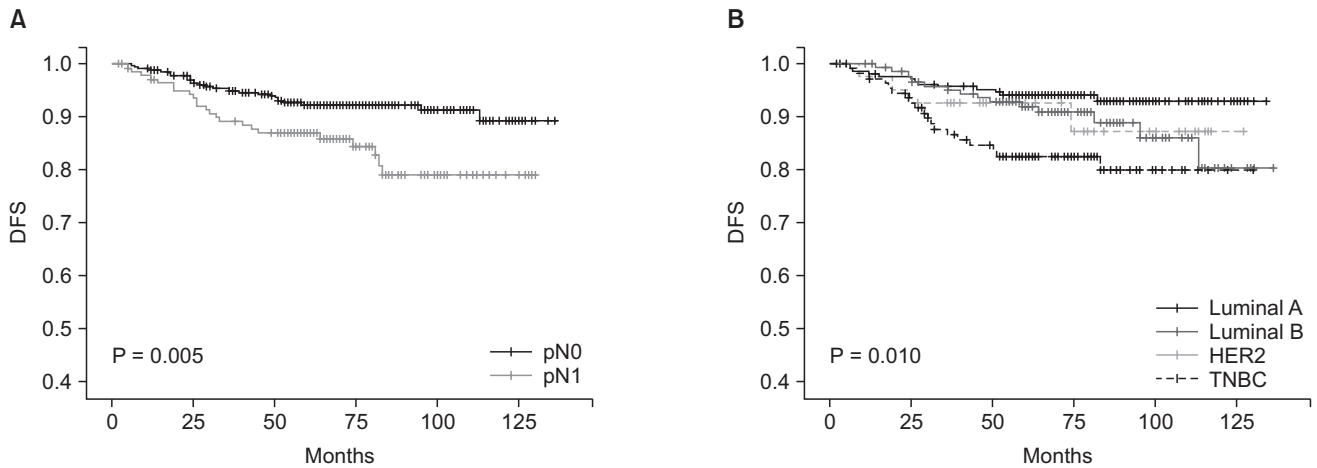
Fig. 2. Disease-free survival (DFS) of total patients according to nodal status (A) and intrinsic subtype (B). HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.
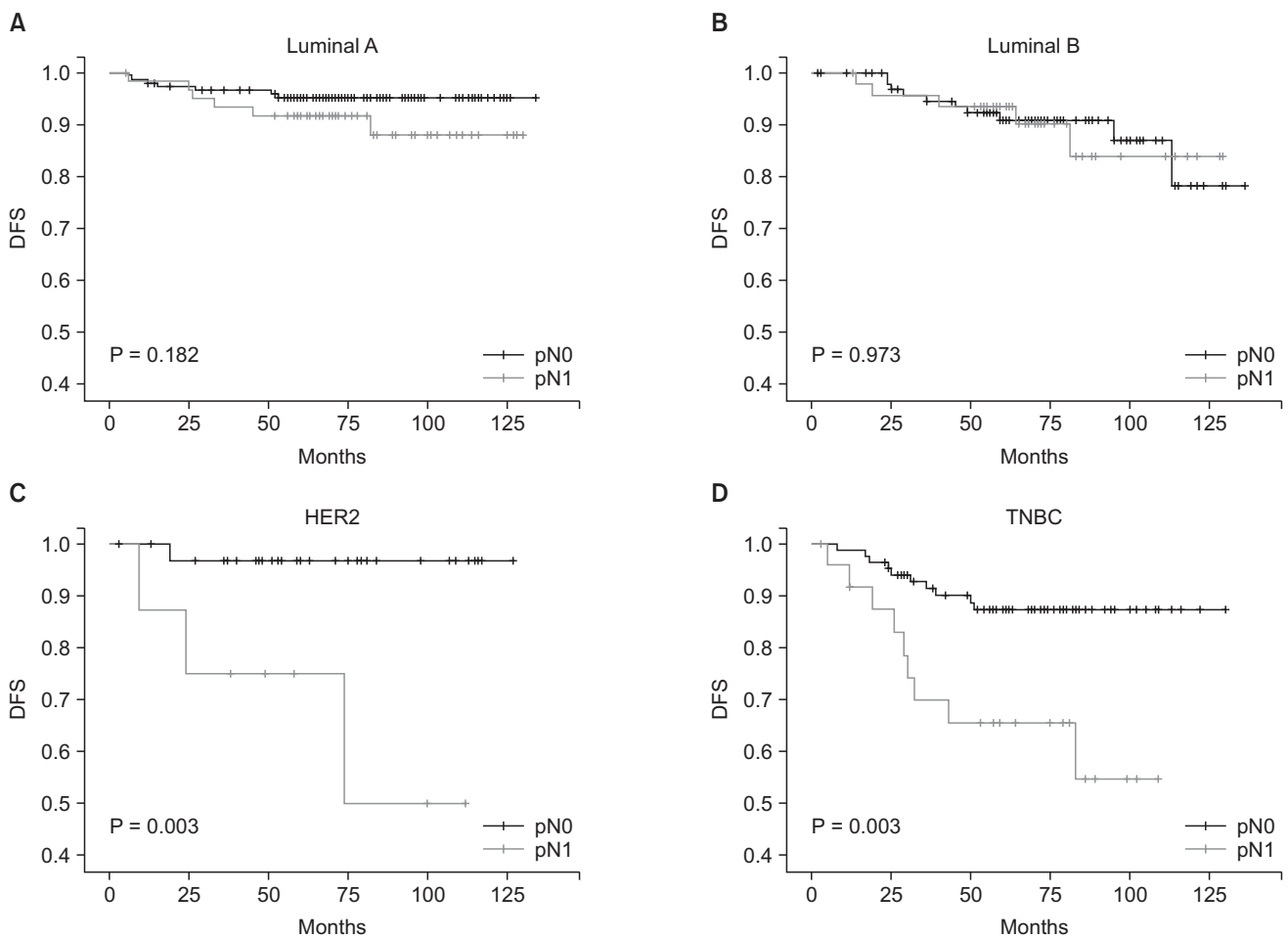
Fig. 3. (A–D) Subgroup analysis of disease-free survival (DFS) according to intrinsic subtype and nodal status. HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.

luminal A subtype (Table 3). In order to analyze the effect of lymph-node involvement and intrinsic subtypes on DFS in breast cancer patients, we performed subgroup analysis according to the following combination groups: luminal A with pN0, luminal A with pN1, TNBC with pN0, and TNBC with pN1.

As expected, the longest 5-year DFS was seen in the luminal

Table 3. Hazard ratio for disease-free survival of total patients using Cox proportional regression model

Variable	HR[a)]	95% CI	P-value
pN1 disease	2.813	1.512–5.231	0.001
Subtype			
Luminal B type	1.870	0.851–4.111	0.119
HER2 type	1.432	0.377–5.445	0.598
TNBC type	2.580	1.103–6.032	0.029
Age less than 40 yr	3.307	1.793–6.098	<0.001
Histologic grade 3	1.313	0.638–2.701	0.459
Tumor size ≥ 2 cm	1.796	0.985–3.276	0.056

HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2; TNBC, triple negative breast cancer.
[a)]Hazard ratio of 5 variables was estimated with Cox proportional hazard regression model with adjustment to negative node status, luminal A subtype, age over 35 years, histolotic grade 1 or 2 and tumor size less than 2 cm.
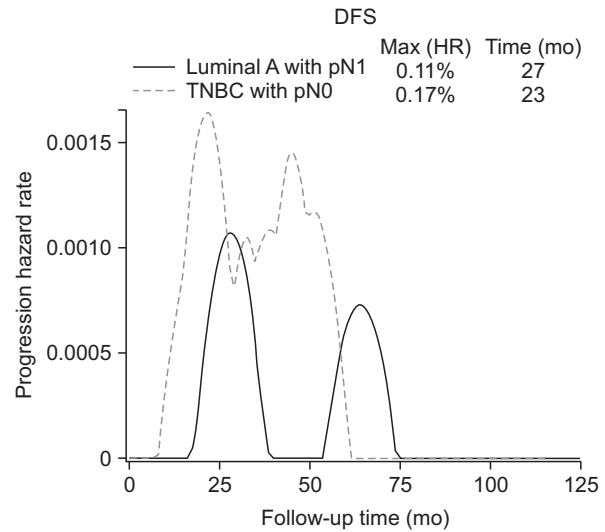
Table 4. Hazard ratio for disease-free survival in luminal A type and triple negative type combined with nodal status

Type	Disease-free survival (%)		HR (95% CI)	P-value
	5 Year	10 Year		
Luminal A with pN0	95.1	95.1	1 (reference)	
Luminal A with pN1	91.7	87.8	2.061 (0.693–6.132)	0.194
TNBC with pN0	87.3	87.3	2.647 (1.007–6.956)	0.048
TNBC with pN1	65.5	54.6	9.554 (3.554–25.683)	<0.001

HR, hazard ratio; CI, confidence interval; TNBC, triple negative breast cancer.

Fig. 4. Progression hazard rate for recurrence between luminal A type with pN1 and triple negative type with pN0. DFS, disease-free survival; TNBC, triple negative breast cancer.

regimen 40.5%, adriamycin plus taxane regimen 2.4%) and endocrine treatment, due to the lack of lymph node involvement and hormone-receptor negativity in this group. The luminal A-pN1 group had more stage II patients and more frequent use of chemotherapy (93.4%; CMF 4.9%, adriamycin based regimen 14.8%, adriamycin plus taxane 73.8%) and endocrine treatment (Table 5).

DISCUSSION

Involvement of axillary nodes has been the most important prognostic factor for breast cancer. Decisions regarding the use of adjuvant treatment in breast cancer have also largely been based on axillary node involvement. However, since the subtyping of breast cancer using gene expression profiling by Perou et al. [1], heterogeneity in breast cancer has been widely studied. This led to recommendations for adjuvant treatment of early breast cancer according to ER and HER2 status since the 9th St Gallen International Breast Cancer Conference in 2005; the National Comprehensive Cancer Network guidelines also recommend similar subtype-based adjuvant treatment.

Many recent studies have shown prognostic differences between different intrinsic subtypes, but most of these studies have included only node-negative breast cancer or both early and advanced breast cancer. In several studies of axillary node-negative breast cancer, poor prognosis was associated with hormone receptor-negative, HER2, and TNBC subtypes. A large-scale study that included axillary node-negative patients showed that overexpression of HER2 was poor prognostic factor for recurrence [8]. In studies of patients with node-negative small tumors, <1 cm in size, the HER2 and TNBC subtypes

A-pN0 group (95.1%, P < 0.001). TNBC-pN0 were associated with shorter 5-year DFS (87.3% *vs.* 91.7%) and higher hazard ratio (2.64 *vs.* 2.06) when compared to the luminal A-pN1 group. There were not statistically significant differences between the 10-year DFS of the luminal A-pN1 and TNBC-pN0 groups (P = 0.618). The hazard ratio for recurrence of the TNBC-pN1 group was 9.55 (Table 4). While the hazard function for recurrence in the luminal A-pN1 group showed a bimodal peak, the TNBC-pN0 group was associated with a higher hazard, but most recurrences occurred within 60 months (Fig. 4).

We compared the clinicopathologic factors in following groups: TNBC-pN0 group and luminal A-pN1 group. Histologic grade 3 was more frequent in the TNBC-pN0 group than in the luminal A-pN1 group. No differences in age, surgical procedure, or tumor size were seen between two groups. The TNBC-pN0 group included more stage I patients and was associated with less chemotherapy (77.4%; CMF 34.5%, adriamycin-based

Table 5. Comparison of clinicopathologic factors between node positive luminal A type and node negative triple negative type

Characteristic	Luminal A with pN1 (n = 61)	TNBC with pN0 (n = 84)	P-value
Age (yr)			0.498
≤40	13 (21.3)	22 (26.2)	
>40	48 (78.7)	62 (73.8)	
Operation method			0.689
Breast conserving surgery	27 (44.3)	40 (47.6)	
Mastectomy	34 (55.7)	44 (52.4)	
Tumor size (cm)			0.212
≤2	34 (55.7)	38 (45.2)	
>2	27 (44.3)	46 (54.8)	
Histologic type			0.050
Ductal	59 (96.7)	76 (90.5)	
Lobular	2 (3.3)	1 (1.2)	
Others	0 (0)	7 (8.3)	
Histologic grade			<0.001
1 and 2	36 (62.1)	8 (9.9)	
3	22 (37.9)	73 (90.1)	
Stage			<0.001
I	0 (0)	37 (44)	
IIA	34 (55.7)	45 (53.6)	
IIB	27 (44.3)	2 (2.4)	
Adjuvant chemotherapy			<0.001
Yes	57 (93.4)	65 (77.4)	
No	4 (6.6)	19 (22.6)	
Adjuvant endocrine therapy			<0.001
Yes	58 (95.1)	10 (11.9)	
No	3 (4.9)	74 (88.1)	
Adjuvant radiotherapy			0.196
Yes	19 (31.1)	35 (41.7)	
No	42 (68.9)	49 (58.3)	
Recurrence			0.695
Yes	6 (9.8)	10 (11.9)	
Locoregional only	0 (0)	2 (2.4)	
Distant metastasis only	4 (6.6)	3 (3.6)	
Locoregional and distant	2 (3.3)	5 (6.0)	
No	55 (90.2)	74 (88.1)	
Survival			0.965
Yes	58 (95.1)	80 (95.2)	
No	3 (4.9)	4 (4.8)	

Values are presented as number (%).

were associated with shorter distant relapse-free survival compared to the luminal A subtype, which warrants the consideration of systemic chemotherapy in spite of small tumor size [9,10].

However, the pattern of recurrence differs between different subtypes, irrespective of nodal status. Hormone receptor-negative breast cancer shows of the highest rate of recurrence within 5 years, while hormone receptor-positive luminal type breast cancer shows lower hazards for recurrence within 5 years than hormone receptor-negative breast cancer, and much lower but persistent risk for recurrence after 5 years [11-13]. These studies demonstrate that follow-up duration of longer than 5 years is mandatory, and cumulative hazards and hazard ratios must both be taken into account when comparing the recurrence pattern between different subtypes.

We analyzed the recurrence pattern of the luminal A-pN1 and TNBC-pN0 groups in early breast cancer to compare the prognostic power of nodal involvement and intrinsic subtypes. In the analysis of 5-year DFS, luminal A-pN1 was associate with longer DFS compared to the TNBC-pN0 group (91.7% vs. 87.3%, P = 0.618), in spite of its higher nodal stage. However, there were no statistical differences in 10-year DFS between the two groups, and this is due to the late recurrence after 5 years in luminal A with pN1 group than TNBC with pN0 group as shown in hazard rate function graph.

Cytotoxic systemic chemotherapy is the mainstay of adjuvant treatment in TNBC, but tumor size and node involvement are currently the deciding factor for chemotherapy. Chemosensitivity tests were examined in various ways *in vitro* tests, however any specific regimen was not found to have selective effect according to breast cancer subtypes [14]. In clinical setting, classical CMF, anthracycline-based regimens and taxane-containing regimens have all been used as adjuvant treatment for TNBC. However, the superiority of any one regimen is still a cause of debate. The classical CMF regimen has recently been suggested to be effective in TNBC. Moreover, it also has the advantage of a low toxicity profile and lower cost, compared to the other regimens [15-17]. Rocca et al. [18] have reported that an epirubicin-containing regimen was associated with longer DFS and OS in early TNBC. The benefits of taxane in the treatment of TNBC type have also been reported in several [19-21]. However, selective use of taxane is not routinely recommended in node-negative early TNBC. Many of the studies carried out to analyze the efficacy of chemotherapy regimens in TNBC are retrospective in nature. Recently reported, large multi-institutional studies have not recommended chemotherapy for all subtypes of T1a-bN0M0 breast cancer because they show excellent prognosis with or without chemotherapy [22]. Platinum compounds, poly ADP ribose polymerase (PARP) inhibitors, epidermal growth factor receptor (EGFR) antibodies, antiangiogenic drugs, and mammalian target of rapamycin (m-TOR) inhibitors have been studied in large randomized controlled trials of recurrent or metastatic TNBC patients [23-26]; several phase III trials, analyzing the efficacy of adjuvant treatment in TNBC, are ongoing using various chemotherapeutic agents [27].

In conclusion, intrinsic subtype is an independent prognostic factor for recurrence, and its prognostic power is similar to

nodal involvement in early breast cancer. Further evaluation to delineate the intrinsic subtypes through gene analysis is indeed. Luminal A subtype breast cancer patients appear to have a decreased need for chemotherapy, even if they are pathologically 1–3 node involved, and TNBC patients may need more intensive adjuvant treatment, even in node-negative early-stage cases.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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