Hong Kong J Radiol. 2022;25:103-12 | https://doi.org/10.12809/hkjr2217419

ORIGINAL ARTICLE **CME**

Clinicopathological Features, Prognostic Factors, and Treatment Outcomes in Non-metastatic Breast Cancer in Young Asian Women in Hong Kong

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ABSTRACT

Objectives: *Breast cancer is the leading cause of death in young women (<40 years) and is a distinct entity. We reviewed the clinicopathological features and survival outcomes of young females with breast cancer in Hong Kong.*

Methods: *We performed a retrospective study of 497 women <40 years with non-metastatic breast cancer from a single institution in Hong Kong from 2005 to 2013, analysing clinicopathological, prognostic, survival, and treatment data.*

Results: *Median age at diagnosis was 36 years. The majority of patients (87.7%) had invasive ductal carcinoma. Grade III tumours composed approximately 40%. Proportions of stage I, II and III diseases were 34.8%, 46.1%, and 18.1%, respectively. Hormone receptor status was positive in 80.7%; human epidermal growth factor receptor 2 status was positive in 27.2%. In all, 53.7% underwent mastectomy while 46.3% received breast-conserving surgery. In total, 85.1% had neoadjuvant and/or adjuvant chemotherapy. Adjuvant radiotherapy was delivered in 78.5% and hormonal therapy was given in 73.4%. Over a 9.1-year median follow-up, 26% developed recurrence and 16.1% died. The 5-year and 10-year disease-free survival were 82.1% and 74.3%, respectively. The 5-year and 10-year overall survival were 90.5% and 83.5%, respectively. Nodal stage was the only independent prognostic factor for disease-free survival and overall survival.*

Conclusion: *Breast cancer in young patients tended to have aggressive features and presented at an advanced stage. Breast cancer in young Asian women may have distinct phenotypes with more hormone-positive disease compared to Western patients and warrants further investigations. Improved survival may be achieved with multimodality treatments.*

Key Words: *Breast neoplasms; Female; Prognosis; Treatment outcome*

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Submitted: 15 Jun 2021; Accepted: 16 Nov 2021

Contributors: HSC, JCHC and MHCL designed the study. HSC acquired the data. All authors analysed the data. HSC drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

Conflicts of Interest: As an editor of the journal, RKC Ngan was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Data Availability: All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Ethics Approval: The study was approved by the Research Ethics Committee of the Hospital Authority (Ref KC/KE-20-0220/ER-1). The requirement for patient consent was waived.

中文摘要

香港年輕亞洲女性非轉移性乳腺癌的臨床病理學特徵、預後因素和治療結果

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目的：乳腺癌是40歲以下年輕女性死亡的主要原因，是一個獨特實體。本文回顧香港年輕女性乳腺癌的臨床病理學特徵和存活結局。

方法：我們對2005年至2013年香港一家機構的497名40歲以下非轉移性乳腺癌女性進行回顧性研究，分析他們的臨床病理學、預後、存活和治療數據。

結果：患者平均年齡為36歲。大多數病例（87.7%）為浸潤性導管癌。組織學III級佔約40%。I、II和III期數分別佔34.8%、46.1%和18.1%。患者屬荷爾蒙受體陽性為80.7%；HER2擴增率為27.2%。整體而言，53.7%患者進行全乳切除術，46.3%則接受保乳手術。85.1%患者接受術前或術後輔助化療。78.5%病例進行輔助電療以及73.4%接受荷爾蒙治療。跟進期中位數為9.1年，有26%病例復發及16.1%患者死亡。5年和10年無病存活率分別為82.1%和74.3%。5年和10年總存活率分別為90.5%和83.5%。淋巴結轉移是唯一的獨立預後因素。

結論：年輕乳腺癌患者傾向有較高的惡性度及腫瘤期數。亞洲乳腺癌患者有獨特的表型，比起西方患者具有更多荷爾蒙受體陽性的病例，需要進一步研究。綜合治療方案能改善存活率。

INTRODUCTION

Breast cancer diagnosed at a young age requires special attention due to its specific clinicopathological features and unique psychosocial sequelae. It is associated with more aggressive biology, advanced stage, and unfavourable prognosis with increased risk of recurrence and mortality, as compared with the disease in older patients.[1] In fact, the differences in risk factors, gene expression, tumour characteristics, and clinical outcomes suggest that breast cancer arising in young women represents a distinct entity, as reported in previous studies.[2,3] Because of the nature of the disease, these patients usually undergo more aggressive multimodality treatments that may have significant complications, including reduced fertility and genetic concerns, which can all pose serious impacts on patients' lives.

Currently, there is no widely agreed consensus on the definition of a cut-off for young age for breast cancer. The cut-off differs among studies, but most have used 40 years of age as a threshold.[4] Guidelines have been developed for management of this distinct disease entity.[5]

Due to its relative rarity, breast cancers in young patients are often underrepresented in clinical studies. Moreover, the majority of reports have been based on Western cohorts and data on Asians remain limited. Breast cancer tends to occur earlier in Chinese women than in Caucasian women,[6] and its incidence in the under-40 Asian population may be two to three-fold greater.[7] In Hong Kong, approximately 7.7% of all breast cancers are diagnosed before age 40 years according to the most recent statistics.[8] More evidence on biological characteristics and treatment strategies is needed to help clinicians better manage the disease in this age-group.

The aim of this study was to evaluate the clinicopathological features and survival outcomes of young female breast cancer in the Hong Kong Chinese population. In addition, we investigated the differences among various molecular subtypes and assessed the prognostic factors of survival.

METHODS

All consecutive, non-metastatic, invasive female breast cancer cases from January 2005 to December 2013 were retrospectively identified from a single institutional breast cancer database. Inclusion criterion was age <40 years at the time of diagnosis. Exclusion criteria were non-Chinese ethnicity and incomplete clinical data.

Medical records were reviewed and details of clinicopathological features, surgery, and adjuvant therapies were recorded. Surgery and adjuvant treatments were performed according to standard guidelines at the time of diagnosis (Table 1, online supplementary Appendix).

Cancer staging was carried out according to the AJCC (American Joint Committee on Cancer) system (7th ed). For tumour and nodal classifications, if patients underwent neoadjuvant therapy, clinical or pathological stage, whichever was higher, was used to reflect the tumour burden more accurately. Hormone receptor (HR) expression, including oestrogen receptor (ER) and progesterone receptor (PR), was evaluated based on the percentage of tumour cells with nuclear staining by immunohistochemistry. The threshold for ER and PR positivity was ≥1%. Human epidermal growth factor receptor 2 (HER2) positivity was defined as either 3+ staining by immunohistochemistry, or the presence of *HER2* amplification by in situ hybridisation. Breast cancer subtype projection was determined according to HR status, HER2 status and tumour grade (Ki-67 index was not universally available thus not included in the projection)[9,10]: luminal A (ER+/PR+, HER2-, grade 1-2), luminal B (ER+/PR+, HER2+, grade 1-2 or ER+/PR+, HER2+/-, grade 3), *HER2*-amplified (ER-, PR-, HER2+) and basal-like (ER-, PR-, HER2-).

Statistical Analysis

Duration of follow-up was measured from the date of histological diagnosis to the date of death or data cut-off, i.e., 1 September 2020. Disease-free survival (DFS) was defined as the duration from diagnosis to any recurrence (local, regional, or distant relapse), contralateral breast cancer, or death of any cause. Overall survival (OS) was defined as the duration from diagnosis to death of any cause.

Descriptive analyses were used to summarise patient demographics, tumour pathological characteristics, treatment details, and relapse pattern. The Kaplan–Meier method was used to estimate DFS and OS. Prognostic factors were evaluated using log-rank test and multivariable Cox regression. Significant variables identified from the univariate analysis were included in the Cox proportional hazard model. Statistical analyses were conducted using SPSS (Windows version 24.0; IBM Corp, Armonk [NY], United States). A p value <0.05 was considered statistically significant.

Table 1. Surgery and adjuvant treatments (n = 497).*

Types of breast surgical operations	
Mastectomy	267 (53.7%)
Wide local excision or partial mastectomy	230 (46.3%)
Axillary management	
Sentinel lymph node biopsy	159 (32.0%)
Sentinel lymph node biopsy followed by axillary dissection	55 (11.1%)
Upfront axillary dissection	279 (56.1%)
None	4 (0.8%)
Neoadjuvant chemotherapy ± targeted therapy	
Yes	44 (8.9%)
Anthracycline-based	6 (1.2%)
Taxane-based	10 (2.0%)
Combined taxane-anthracycline	28 (5.6%)
No	453 (91.1%)
Adjuvant chemotherapy ± targeted therapy	
Yes	389 (78.3%)
Anthracycline-based	146 (29.4%)
Taxane-based	112 (22.5%)
Combined taxane-anthracycline	125 (25.2%)
Others	6 (1.2%)
No	108 (21.7%)
Adjuvant radiotherapy	
Yes	390 (78.5%)
Breast/chest wall	260 (52.3%)
Breast chest wall and SCF/axilla	127 (25.6%)
Breast chest wall and SCF/axilla & IMC	3 (0.6%)
No	107 (21.5%)
Adjuvant hormonal therapy	
Yes	365 (73.4%)
TMX for 5 years	260 (52.3%)
TMX for 2-3 years, followed by AI switch to complete 5 years	4 (0.8%)
Extended TMX up to 10 years	91 (18.3%)
TMX for 5 years, then extended AI up to 10 years	2 (0.4%)
Others (e.g., LHRHa + TMX, other anti-oestrogens)	8 (1.6%)
No	132 (26.6%)

Abbreviations: AI = aromatase inhibitor; IMC = internal mammary chain; LHRHa = luteinising hormone-releasing hormone agonist; SCF = supraclavicular fossa; TMX = tamoxifen.
* Data are shown as No. (%).

RESULTS

Clinical and Pathological Features

All 6370 consecutive, non-metastatic, invasive breast cancer cases during the study period from January 2005 to December 2013 were identified. Of them, 538 (8.4%) were age <40 years at the time of diagnosis. A total of 41 cases were excluded: 31 had non-Chinese ethnicity and 10 had incomplete clinical data. Finally, 497 cases were eligible and included in the analysis (Table 2). The median age at diagnosis was 36 years (range, 20-39), 37.4% were aged ≤35 years. Nine (1.8%) patients had a history of breast cancer. Tumour laterality was even,

Table 2. Demographics and clinical and pathological characteristics (n = 497).*

Age	
Median (range)	36 (20-39)
36-39	311 (62.6%)
≤35	186 (37.4%)
History of breast cancer	
Yes	9 (1.8%)
No	488 (98.2%)
Laterality	
Right	252 (50.7%)
Left	234 (47.1%)
Bilateral	11 (2.2%)
Stage	
I	173 (34.8%)
II	229 (46.1%)
III	90 (18.1%)
Unknown	5 (1.0%)
T stage	
T1	248 (49.9%)
T2	195 (39.2%)
T3	36 (7.2%)
T4	17 (3.4%)
Unknown	1 (0.2%)
N stage	
N0	280 (56.3%)
N1	146 (29.4%)
N2	41 (8.2%)
N3	26 (5.2%)
Unknown	4 (0.8%)
Histology	
Ductal	436 (87.7%)
Lobular	2 (0.4%)
Others	59 (11.9%)
Grade	
I	53 (10.7%)
II	210 (42.3%)
III	193 (38.8%)
Unknown	41 (8.2%)
Lymphovascular invasion	
Yes	162 (32.6%)
No	280 (56.3%)
Unknown	55 (11.1%)
Ki-67	
≥20%	194 (39.0%)
<20%	96 (19.3%)
Unknown	207 (41.6%)
Multifocal	
Yes	35 (7.0%)
No	462 (93.0%)
Oestrogen receptor	
Positive	372 (74.8%)
Negative	121 (24.3%)
Unknown	4 (0.8%)
Progesterone receptor	
Positive	359 (72.2%)
Negative	134 (27%)
Unknown	4 (0.8%)
HER2 amplification	
Positive	135 (27.2%)
Negative	332 (66.8%)
Unknown	30 (6.0%)
Breast cancer subtype†	
Luminal A	176 (35.4%)
Luminal B	187 (37.6%)
HER2-amplified	34 (6.8%)
Basal-like	52 (10.5%)
Unknown	48 (9.7%)
Surgical margins	
Clear	472 (95.0%)
Involved	12 (2.4%)
Unknown	13 (2.6%)
Genetic test results	
BRCA1 mutation	2 (0.4%)
BRCA2 mutation	2 (0.4%)
BRCA variance of unknown significance	4 (0.8%)
Negative	5 (1.0%)
Unknown	484 (97.4%)

* Data are shown as No. (%) or median (range).

† Definition of breast cancer subtype in this study cohort: Luminal A: ER/PR+, HER2-, grade 1-2; Luminal B: ER/PR+, HER2+, grade 1-2 or ER+/PR+, HER2±, grade 3; *HER2*-amplified: ER-, PR-, HER2+; Basal-like: ER-, PR-, HER2-. Ki-67 index was not universally available and not included in the projection.

while 11 (2.2%) patients had synchronous bilateral breast cancer.

Group stage at presentation was I (34.8%), II (46.1%) and III (18.1%), respectively. The majority of the tumours were invasive ductal carcinoma subtype (87.7%), whereas invasive lobular histology constituted 0.4%. The most common histological grade was II (42.3%), followed by III (38.8%) and I (10.7%). In all, 39% of the tumours had high Ki-67 index (≥20%) and 7% had multifocal disease. Lymphovascular invasion and involved margins were present in 32.6% and 2.4% of tumours, respectively.

Overall, 401 (80.7%) cases were of hormone-positive disease (either ER or PR). In total, 135 (27.1%) of breast cancers were HER2+. Breast cancer subtypes were distributed as follows: 35.4% luminal A, 37.6% luminal B, 6.8% *HER2*-amplified, 10.5% basal-like, and 9.7% unclassified.

Genetic test results were available in 13 cases at the time of data analysis. Five cases had documented negative results, while two patients had the *BRCA1* mutation, two had the *BRCA2* mutation, and four had variances of unknown significance.

Surgery and Adjuvant Treatments

Information about surgical and adjuvant oncological treatment are detailed in Table 1. All 497 patients underwent surgery. A total of 267 (53.7%) patients

had mastectomy, while 230 (46.3%) received breast-conserving surgery. Axillary management included sentinel lymph node biopsy in 159 (32%), sentinel lymph node biopsy followed by axillary dissection in 55 (11.1%), and upfront axillary dissection in 279 (56.1%).

Among these patients, 390 (78.5%) patients underwent adjuvant radiotherapy. In all, 260 (52.3%) received local radiotherapy to either breast or the chest wall. A total of 127 (25.6%) patients underwent locoregional radiotherapy that included the supraclavicular fossa or axilla. Irradiation of the internal mammary chain was not a routine practice in our institution.

Overall, 423 (85.1%) cases received neoadjuvant and/or adjuvant chemotherapy, typically anthracycline or/and taxane-based. Anti-HER2 monoclonal antibody, trastuzumab, was administered to 54.8% HER2+ cases (74/135). We attempted to determine the rate of chemotherapy-related amenorrhoea (CRA), which was defined as amenorrhoea for ≥3 months during and within 12 months after the completion of adjuvant chemotherapy in this study. Of 423 cases undergoing chemotherapy, 150 (35.5%) developed CRA, and 200 (47.3%) did not experience CRA, while menstrual history was not available for 73 cases (17.3%). Of those who had CRA, 113 (75.3%) regained menstruation.

Among the 401 cases with hormone-positive disease (ER or PR+), 365 (91%) received hormonal therapy. Most cases received tamoxifen for at least 5 years, whereas some also received extended tamoxifen for up to 10 years, which is the current standard of care for selected high-risk cases. However, the discontinuation rate of adjuvant endocrine treatment (excluding disease progression) was approximately 10.4% (38/365). The most common reasons were adverse effects (including hot flashes, mood swings, and vaginal dryness) or plans for pregnancy (needed interruption of treatment due to teratogenicity of tamoxifen).

Survival Outcomes and Relapse Pattern

Over a median follow-up time of 9.1 years (range, 0.5-15.4), 129 (26%) cases had disease recurrences and 80 (16.1%) patients had died at the time of data collection.

The relapse patterns and sites are presented in Table 3. In total, 16 (3.2%) cases developed isolated locoregional recurrence and 96 (19.3%) had distant metastases. Seventeen (3.4%) patients developed contralateral breast cancer. The most common sites of distant metastases were bone (n = 63), followed by lung or pleura (n = 58), and liver (n = 43).

Table 3. Recurrence pattern and sites (n = 497).*

Site of recurrence	129 (26.0%)
Isolated locoregional	16 (3.2%)
Distant metastasis	96 (19.3%)
Contralateral breast cancer	17 (3.4%)
Site(s) of first distant metastasis (n = 96)	
Liver	43 (44.8%)
Lung/pleura	58 (60.4%)
Bone	63 (65.6%)
Brain	6 (6.3%)
Others	51 (53.1%)

* Data are shown as No. (%).

The survival curves of the overall population are shown in Figure 1. DFS at 5 years and 10 years was 82.1% and 74.3%, respectively. OS at 5 years and 10 years was 90.5% and 83.5%, respectively. Figure 2 depicts the stage-specific survivals. The survival outcomes for different breast cancer subtypes are illustrated in Figure 3; luminal A and B phenotypes had the best prognoses, followed by HER2+ disease, while basal-like tumours had the worst survival.

Prognostic Factors for Disease-free Survival and Overall Survival

The clinicopathological prognostic factors for DFS and OS are highlighted in Tables 4 and 5. Ki-67 index was not included in the model because of the high proportion (41.6%) of missing data. In univariate analyses, high T-stage, N-stage, and tumour grade were associated with a higher risk of disease recurrence. In multivariable analyses, advanced nodal status remained as the only independent negative prognostic factor for DFS ($p < 0.001$).

For OS, in univariate analyses, high T-stage, N-stage, and grade were significant negative prognostic factors, while positive hormonal status was associated with better OS. Multivariate analyses revealed only advanced nodal status to be an independent factor for OS ($p = 0.015$).

DISCUSSION

To our knowledge, the present study is the first in the literature to report the clinicopathological profile and treatment outcomes of young breast cancer cases in the Hong Kong Chinese population. Although this study was based on a single centre, our hospital had a large patient population and detailed records from an institutional breast cancer registry. With almost 500 patients and a

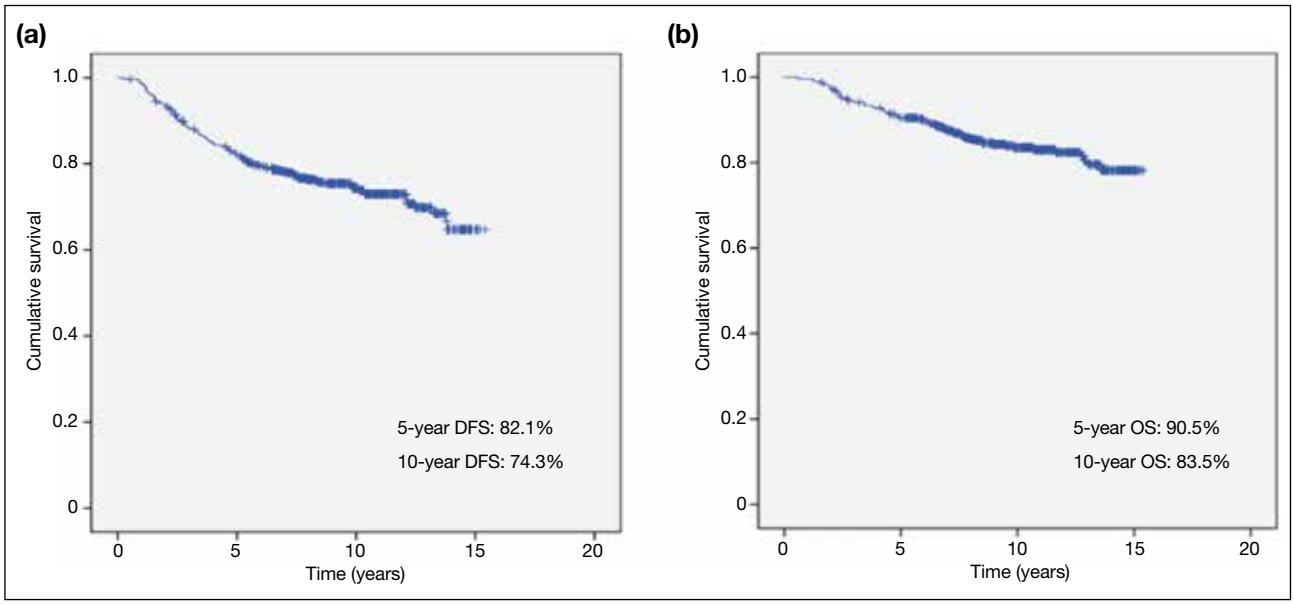

Figure 1. Survival of overall population: (a) disease-free survival (DFS), (b) overall survival (OS).

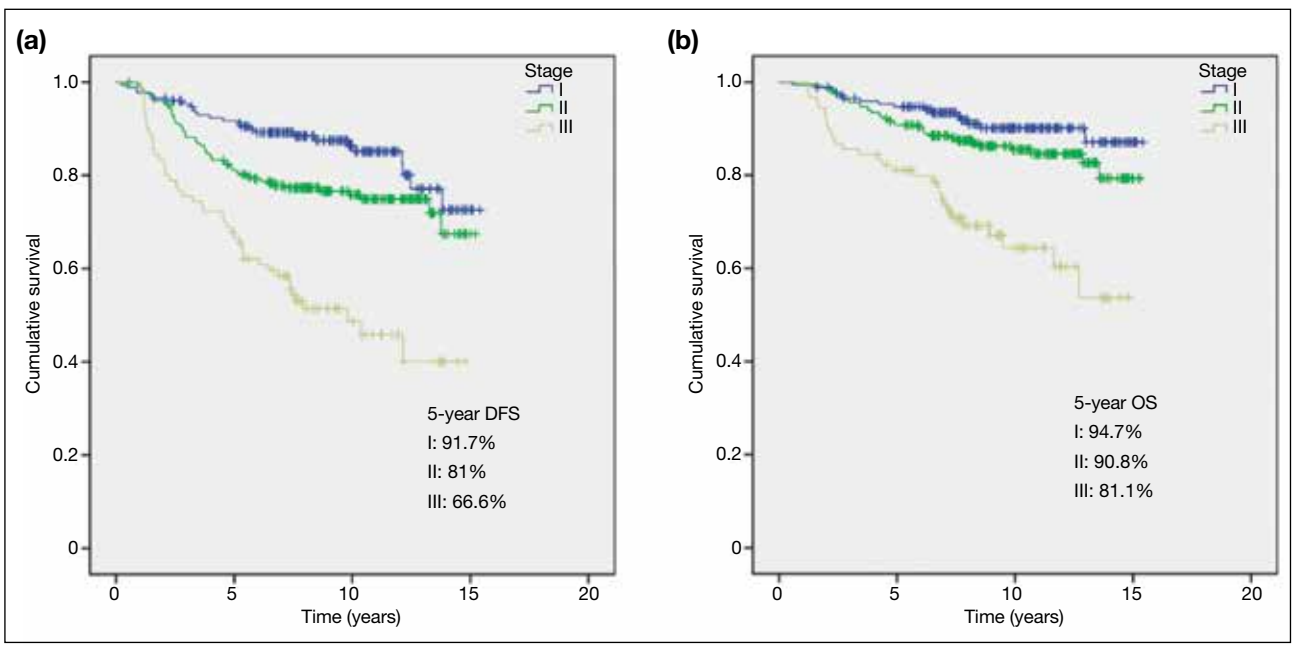

Figure 2. Survival stratified by stage: (a) disease-free survival (DFS); (b) overall survival (OS).

9-year follow-up period in this study, we were able to analyse and report the long-term clinical outcomes in an in-depth manner.

The biological features of breast cancer under age 40 were consistent with other published works in the West, with overrepresentation of aggressive characteristics, such as nodal positivity and high grade.[11,12] In our cohort, nearly half of the cases had node-positive disease, with 64.2% having stage II or III disease. Approximately 40% had grade III disease, in contrast to only around 10% with grade I. Additionally, *HER2* overexpression was detected in almost a third of cases (27.2%), similar to the high proportion reported in the literature.[13] It is well-known that HER2 positivity correlates with more aggressive disease behaviour and a poorer prognosis.[14]

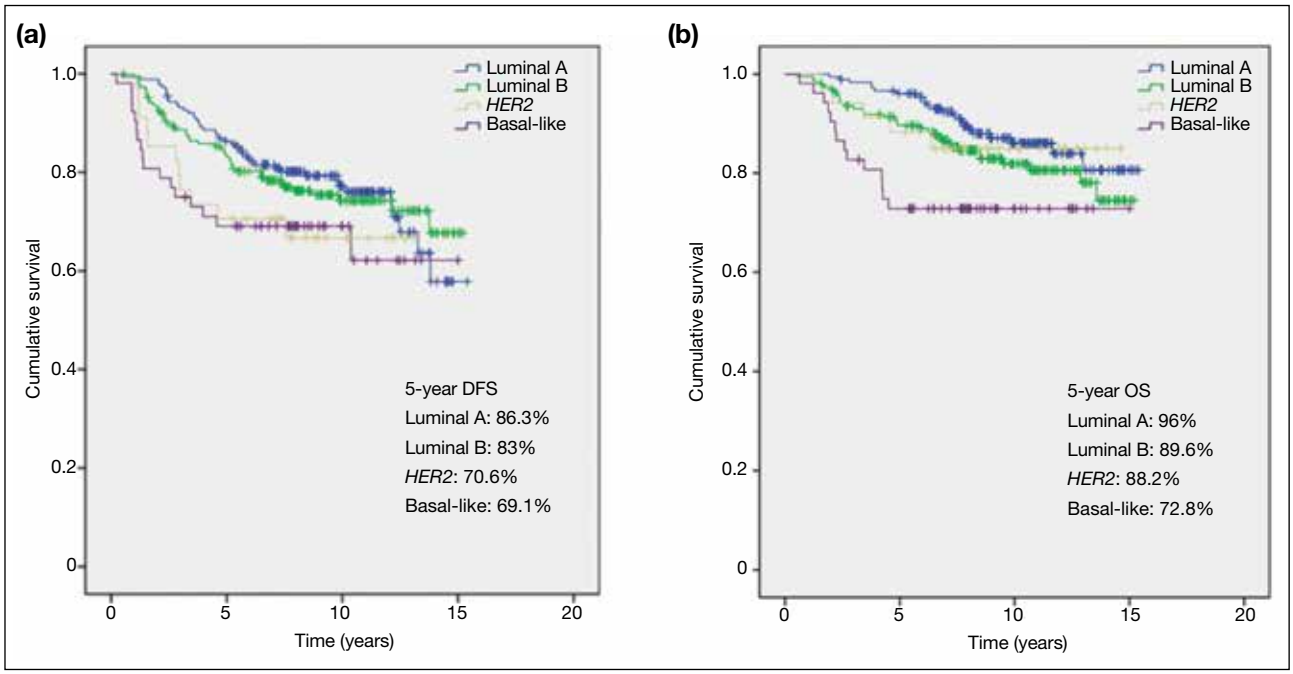

Figure 3. Survival of breast cancer subtypes: (a) disease-free survival (DFS); (b) overall survival (OS).

Table 4. Prognostic factors for disease-free survival (multivariable analyses).

	Hazard ratio	95% confidence interval	p Value
T stage			0.413
T1	1	-	-
T2	1.322	0.871-2.007	0.190
T3	1.406	0.692-2.857	0.346
T4	1.793	0.773-4.161	0.174
N stage			<0.001
N0	1	-	-
N1	1.804	1.167-2.788	0.008
N2	2.246	1.218-4.142	0.010
N3	4.223	2.142-8.327	<0.001
Grade			0.125
I	1	-	-
II	2.124	0.909-4.967	0.082
III	2.417	1.032-5.664	0.042

Table 5. Prognostic factors for overall survival (multivariable analyses).

	Hazard ratio	95% confidence interval	p Value
T stage			0.263
T1	1	-	-
T2	1.184	0.705-1.988	0.523
T3	1.775	0.782-4.028	0.170
T4	2.335	0.913-5.974	0.077
N stage			0.015
N0	1	-	-
N1	2.046	1.203-3.477	0.008
N2	2.464	1.177-5.157	0.017
N3	2.818	1.166-6.812	0.021
Grade			0.093
I	1	-	-
II	3.815	0.913-15.936	0.066
III	4.746	1.127-19.982	0.034
Positive hormone receptor (ER+ or PR+)	0.748	0.428-1.306	0.307

Abbreviations: ER = oestrogen receptor; PR = progesterone receptor.

Our cohort consisted of a larger percentage of hormone-positive tumours (80.7%), whereas the reported figure in the West was approximately 70%.[15] This supports the previous finding that a higher proportion of hormone-positive disease is found in young breast cancer patients in China and East Asia.[16,17] It adds to the evidence that the Asian pattern and pathology of premenopausal breast cancer may be different from that of the West, requiring more focused study.

In this cohort, the basal-like/triple-negative breast cancer rate was not particularly high. While the occurrence of many of the young breast cancer cases may be related to *BRCA* hereditary breast cancer, and the association of triple-negative breast cancer with the *BRCA1* mutation in particular, one may expect that the proportion of basal-like breast cancer would be much higher in young women

compared with older patients. However, the prevalence of *BRCA1/2* mutations might also play a role. In a local study, which recruited 2549 'high-risk' breast or ovarian cancer patients based on age, personal, and family history, *BRCA* mutations were found in 244 patients (9.6%), of which 110 (45.1%) had the *BRCA1* mutation and 134 (54.9%) had the *BRCA2* mutation.[18] Unlike Caucasian populations, there is a relative predominance of the *BRCA2* mutation over the *BRCA1* in the Chinese population.[19] In that case, since *BRCA2* disease tends to express ER/PR in contrast to *BRCA1*, it would seem to contribute to the HR-positive phenotypes. Nevertheless, data on *BRCA1/2* mutations specific to the young breast cancer population in our locality are lacking and further investigation is needed.

In this study, we performed univariate and multivariable analyses to gain further insights into the tumour characteristics of young breast cancer patients. Various clinicopathological factors, including large tumour size, positive nodal status, and high grade, have been found to be adverse prognostic factors of survival.[20-22] We demonstrated that nodal metastasis is a strong independent negative prognostic factor for both DFS and OS in this patient group. It highlighted the clinical significance of nodal staging on prognosis and might aid the prediction of relapse risk and guide treatment strategies.

Regarding treatment outcomes, previous studies of young breast cancer patients reported poor 5-year OS of 70% to 80% in older series.[23,24] However, the OS figure in our cohort was somewhat better, and comparable to the more recently published studies with 5-year OS up to 90%.[20,25] The possible reasons could include our universal access to tertiary healthcare, relatively high socio-economic status and recent advances in treatments for locoregional and recurrent or metastatic disease.

Looking into the disease course, 68.2% (88/129) of the relapses occurred within 5 years of surgery, including 61.6% of HR-positive (61/99) and 90% of HR-negative (27/30) diseases. This was compatible with the known observation that HR-positive disease can develop relapses in later years, in contrast to HR-negative disease, which mostly recurs within the first 5 years.[26] Five years also represents the time point when most of the HR-positive patients have discontinued their anti-oestrogen therapy. Studies have reported that recurrence rate of breast cancer continues to rise over 5 to 20 years following treatment,[27] and prolonged endocrine therapy has been proven beneficial for patients with a high recurrence risk.[28] Thus, there was increasing use of extended hormonal therapy observed in the latter part of the period in our cohort.

The observation that breast cancer subtypes carry different prognoses was obvious in this cohort of young women. Luminal disease had the best prognosis while triple negative disease had the worst DFS and overall OS. In this study, HER2 disease had equally poor DFS similar to that of triple negative disease, although its OS was superior. The high relapse rate of HER2 disease in our cohort, which began in the year 2005, could be due to the fact that only 54.8% of HER2+ cases (74/135) had received adjuvant trastuzumab, since it had just became the standard of care and was not universally reimbursed during that period. In fact, the importance of breast cancer subtypes is also reflected in the latest (eighth) edition of the AJCC Cancer Staging Manual.[29] With evolving knowledge of breast cancer biology, the incorporation of biomarkers, including hormonal receptor status, HER2 receptor status, and histological grade into anatomic staging indicates that biologic subtypes have become increasingly important in defining prognosis, estimating survival, and influencing the selection of therapies.

Treatment strategies for breast cancer have evolved rapidly over the past decade. In the adjuvant setting, for example, additional ovarian function suppression with luteinising hormone-releasing hormone agonists was not used outside of clinical trials. We started to discuss it with premenopausal patients with HR-positive breast cancer only in recent years, after the SOFT trial demonstrating its superior survival than that with tamoxifen alone.[30] In addition, the neoadjuvant approach has been more frequently used in recent years, especially for triple negative and HER2+ disease. Not only it can downstage the disease to improve resectability, but also it allows early assessment of response to systemic treatment and tailored adjuvant options based on pathological response as in the CREATE-X and KATHERINE trials.[31,32] With current effective treatments, we can expect survival for young women to continue to improve in the future.

Several points need to be emphasised during the care of patients in this age-group. Much of the treatment offered, both surgical and adjuvant, may have significant impacts on patients' lives. Organ preservation is important in young women. There is no evidence that mastectomy improves OS in this group of patients.[33] A secular trend was observed in our study with increasing

use of conservative breast treatment over mastectomy (49.4% patients [134/271] received breast-conserving surgery from 2009 to 2013, compared to 42.5% [96/226] from 2005 to 2008). The overall local recurrence rate remained low at 4% (20/497) in our study; 5.2% (12/230) after breast-conserving surgery and 3% (8/267) after mastectomy. A breast-conserving approach with oncoplastic surgical techniques should be discussed with patients in order to optimise cosmesis and body image. Looking at chemotherapy or endocrine therapy, fertility preservation options and family planning concerns need to be addressed before initiation of treatment. The vast majority of cases (85.1%) were administered chemotherapy in the study. With young age itself being a risk factor of relapse,[34] most of the patients would be recommended to receive chemotherapy. In our study, the rate of CRA (no menses ≥3 months within 12 months of chemotherapy) was found to be at least 35.5%. According to a local study which used the same definition of CRA, 91.1% young breast cancer patients (age ≤45) developed CRA.[35] The difference can be explained by the fact that our study recruited younger patients (age <40) who were less susceptible to CRA as suggested in the literature.[36] Other possible reasons include underreporting of CRA and missing data in our study, since menstrual history was not routinely recorded during follow-up. While some patients might regain menstruation later on (75.3% in our study vs. 66.7% in the local study), the potential consequences of chemotherapy-related infertility and premature menopause should not be overlooked and more data on these aspects are needed. Overall, personalised treatment plans are required for young women. Chemotherapy might be omitted in selected cases of low-risk HR+ early breast cancer after careful discussion of risks and benefits, and further studies on risk stratification by genomic signatures in young women might also help guide treatment decisions.[5] As for adjuvant endocrine therapy, one major issue is the high discontinuation rate observed in young patients, as up to 10.4% in our study, due to reasons including adverse effects and their effect on mood, work, and sexual function, and the desire to become pregnant.[37] Nonadherence to hormonal therapy has been found to be associated with increased mortality.[38] Education and interventions to improve compliance may be critical to improve breast cancer survival. Management of breast cancer in young patients is indeed challenging, and physicians should take into account these psychosocial aspects as well.

A few inherent limitations should be considered in our study. First, it was a retrospective hospital-based study. There was potential selection bias, and our study cohort might not fully represent the whole population. However, as one of the largest public oncology centres in Hong Kong, the data should reasonably reflect the real-world outcomes in our locality. Second, we did not have detailed records of family history or *BRCA* mutation status, which would be helpful in studying this young population. Breast cancer at an early age is more likely to be associated with underlying genetic abnormalities, especially germline *BRCA* mutations, which have potential impacts on prognosis and treatment options. Genetic screening is not widely carried out in Hong Kong, but it has been gaining more attention in recent years. Third, the Ki-67 index, a marker of cell proliferation, was missing in almost half of the cases in our cohort. According to the St. Gallen Consensus 2011, it is chiefly important for the distinction between 'luminal A' and 'luminal B (HER2-)' subtypes.[9] However, it was not routinely determined due to lack of standardisation of laboratory techniques and cut-off points. Therefore, histological grade was used as an alternative assessment of proliferation in this study. Routine analysis of Ki-67 index would be helpful to better classify and further understand the disease in the future.

CONCLUSION

This study described the clinicopathological features, prognostic factors, and treatment outcomes of breast cancer in young Chinese women (age <40 years) in Hong Kong. Young women tended to present with aggressive diseases with high grade and lymph node involvement. We found more hormone-positive disease seen in Asian than in Western populations. Breast cancer in young Asian women may represent a distinct subgroup that deserves more research. Addressing not only potential differences in host and tumour biology, but also psychosocial and behavioural issues will likely improve disease outcomes in this unique population.

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