Original Article

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Survival Outcomes in Breast Cancer Patients and Associated Factors in a Border Province of Thailand: A Hospital-based Review

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Abstract:

Objective: To evaluate the outcomes of breast cancer (BC) patients in Naradhiwas Rajanagarindra Hospital and factors associated with the outcomes.

Material and Methods: A hospital-based retrospective review of patients who were diagnosed with BC in a tertiary-level hospital in a Thailand border province was performed. Familial histories were obtained by telephone interviews.

Results: There were 234 female patients diagnosed with BC during the 6-year study period. The mean age at diagnosis was 52.6 years. At presentation, 46.2% of the patients had locally advanced disease and 26.5% already had distant metastasis. Invasive ductal carcinoma (IDC) was the most common pathological subtype (84.6%) and 4.3% were ductal carcinoma in-situ. The five-year overall survival (OS) was 54% (95% confidence interval (CI) 40.25%-58.15%). On univariate analysis, factors associated with poorer survival were age >50 years, IDC pathology, T stage 3-4, N stage 2-3, distant metastasis, negative estrogen receptors, negative progesterone receptors, or both, positive human epidermal growth factor receptors 2, and Ki67 immunoreactivity >20%. Multivariate analysis showed that advanced T stage (adjusted HR1.97 95% CI 1.15-3.38), N stage (adjusted HR1.95 95% CI 1.05-3.64) and distant metastasis (HR1.86 95% CI 1.27-2.71). Forty-nine percent of the BC women met the hereditary cancer criteria.

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Conclusion: The survival outcome of BC in Narathiwat province was poorer than that reported in other parts of the country. Delayed presentation might be an explanation for this disparity and a BC screening program is recommended to improve early detection.

Keywords: breast cancer, prognosis, rural area, survival outcome

Introduction

Breast cancer (BC) is the most common site-specific cancer in women and the leading cause of cancer-related deaths worldwide.[1] While the incidence of BC is declining in high-income countries, it is increasing in low/middle-income countries.[2] In Thailand, BC ranks the first among cancers in women and the incidence is rapidly increasing, with over 19,400 new cases expected in 2025.[3] Although the southern part of the country had the lowest incidence of BC in the past, the figure is predicted to increase continuously.[4]

The southernmost part of Thailand is located in the middle of the Malay peninsula, consisting of 3 provinces, Yala, Narathiwat, and Pattani, situated close to the northern border of Malaysia. Political unrest has been ongoing for the last 3 decades in this area. The population of this area is approximately 2 million, of whom 83% are Muslim, sharing ethnicity, culture, language and religion with the Malays[5] while the remainders are mostly Chinese-Thai who are closer in ethnicity to Thais in other areas of the country[6] who are Asian immigrants, known as Buddhist-Thai. A previous study found that cancer incidences were different between the Muslim-Thai and Buddhist-Thai subpopulations.[7] Another previous study in Songkhla province, just north of Pattani, found that BC in Muslim-Thais was more common in younger age women, who were more likely to have a higher stage at diagnosis, higher rates of triple-negative BC, and significantly poorer survival. These data lead to speculation that BC in the Muslim-Thai majority provinces might have distinct clinical outcomes, which might be explained by either cultural or biological differences, or both. In high-income societies, current presentation of BC is mostly abnormal mammogram. However, without the availability of mammograms or other effective screening programs, patients with BC often only seek medical attention when there is a palpable lump in their breast. Although BC screening is included in the Thailand universal health coverage program, the availability of mammogram machines is still limited in many rural areas of Thailand, including the 3 southernmost provinces. In addition, the compliance with standard management recommendations in Muslims, especially surgery, could be an issue precluding effective management of BC in the southern region. The same problems of late presentation and relatively poor adherence to modern management have also been reported in case series from other countries in the same region.[8,9]

This study aimed to address the clinical outcomes and factors associated with the outcomes of BC in Narathiwat province. The study was also interested in exploring the incidence of BC patients in the region who may be indicated for genetic testing and counselling. These data could be useful in planning appropriate strategies for disease screening and therapy in these provinces.

Material and Methods

The study retrospectively reviewed the medical records of female patients diagnosed with epithelial BC from Naradhiwas Rajanagarindra Hospital, the main tertiary care hospital in the area, during the period from June 2016 to May 2021. Qualifying patients were identified using the hospital database through the ICD10 code C50.0-C50.9 (malignant neoplasm of breast). Extracted data included demographic data such as age at diagnosis, BC-specific

data including stage at diagnosis and histopathology and family history of cancer. BC staging was based on the American Joint Committee on Cancer classification (7th edition). The TNM system was based on tumor size and extension (T), regional lymph node metastasis (N), and evidence of distant metastasis (M). The group of TNM staging data summarized the pathologic stage group.[10] In cases of BC-related death, mortality date was taken from the death register of the local government office. In cases with no clear familial history information, the data was obtained by telephone interview.

Treatment of BC in Naradhiwas Rajanagarindra Hospital followed the Clinical Practice Guideline of the National Institute of Cancer (NCI) of Thailand. The hospital provides primary surgical treatment or surgical treatment after neoadjuvant chemotherapy. BC patients who need postoperative adjuvant treatment are referred to a regional center or the large university hospital in Southern Thailand. Surgical treatment was the first step for almost all patients diagnosed with breast cancer in this series.

Data on BC biomarkers in this study used the immunohistochemical subtypes estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptors 2 (HER2).[11] Hormonal receptors (HR) positive were defined as ER+ and/or PR+. Ki67 is a biomarker that evaluates the proliferative index in breast cancer, grouped to more than 20% and less than 20%.[12] BC patients were defined as having a genetic risk when they met the criteria of the National Comprehensive Cancer Network (NCCN) guidelines 2022, which included I. diagnosis of BC at age less than 46 years, II. diagnosis of BC at age 46-50 years with an unknown family history or with multiple primary breast cancers. III. diagnosis of BC at any age with at least one close family member with breast, ovarian, pancreatic, or prostate cancer. IV. diagnosis at any age with triple-negative breast cancer (TNBC).

Before analysis, the data were re-checked and cleaned in Microsoft-Excel. Mean with standard deviation (S.D.) or median with interquartile range were used as representative values for parametric data. Survival outcomes were presented as overall survival using death as a failure criterion and presented as survival probability with a 95% confidence interval (95% CI) Comparisons used t-test, Mann-Whitney U test or chi-square test as appropriate. Univariate survival analysis used log-rank test and Kaplan-Meier survival plots with cancer-related death as a censor in overall survival (OS) analysis. The beginning date was defined as the diagnosis date and survival status was as of December 2021. Multivariate analysis used Cox's proportional hazard analysis. All data were analyzed with Statistical Package Stata 14.0 (Stata Corporation, TX). A p-value of less than 0.05 was considered statistically significant.

Results

A total of 234 female patients were diagnosed with BC in Naradhiwas Rajanagarindra Hospital during the 6-year study period. Age at diagnosis ranged from 23-84 years, with an average age of 52.6 years (S.D. 12.0 years). Regarding the primary tumor, 103/234 cases (46.2%) had locally advanced disease at the diagnosis and 62/234 cases (26.5%) had metastasis. 123/234 cases (53.0%) received primary surgical treatment while 178/234 cases (76.1%) received chemotherapy.

The largest BC histopathology finding in our cases was invasive ductal carcinoma which was diagnosed in 84.6% of the patients, followed by ductal carcinoma in-situ in 4.3% and 11.1% with other pathologies (Table 1). Regarding breast cancer subtypes, hormonal receptors (ER and/or PR) were positive in 61.2%, HER2 was positive in 36.1% and 18.7% of patients were TNBC. Considering the Ki67 proliferative index, 162 (75.6%) of the cases were

reported as more than 20% positive. When considering family history related to genetic risk, 114/233 patients met at least one criterion according to the NCCN guideline, with age being the most common item recommending BC patients for genetic testing.

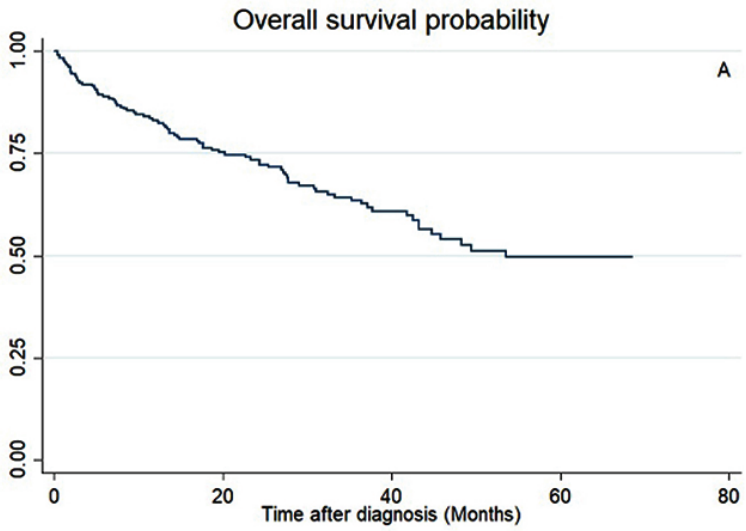
Table 1 Distribution of clinical parameters in breast cancer patients in this study and univariate survival analysis with Log-rank test

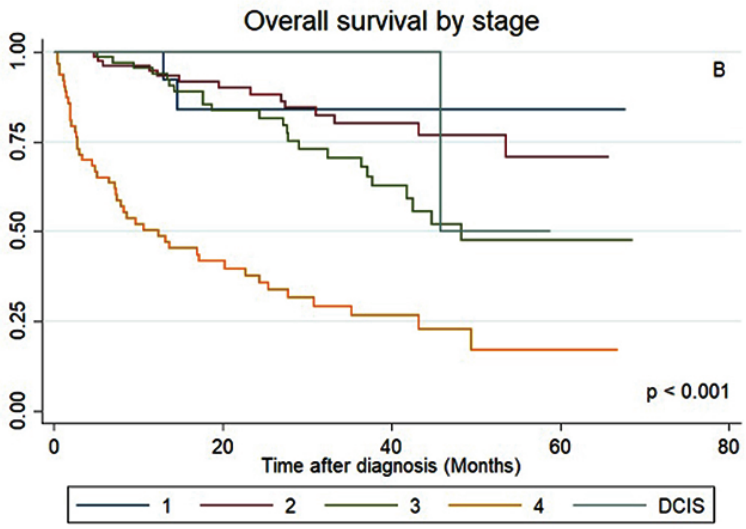
Parameter	N (%)	5-year OS (%)	Log-rank p-value
All	234 (100)	49.54	-
Age group			
<50 years	109 (46.58)	59.61	0.029
>50 years	125 (53.42)	40.18	
Pathological group			
IDC	198 (84.62)	47.44	0.0215
Others	36 (15.38)	59.37	
T stage			
Tis-2	126 (58.85)	67.36	<0.001
T3-4	108 (46.15)	29.28	
N stage			
N 0-1	119 (51.07)	71.69	<0.001
N 2-3	114 (48.93)	28.09	
M stage			
M0	170 (73.28)	61.20	<0.001
M1	63 (27.04)	16.89	
Stage group			
Stage 0-1	25 (10.73)	77.73	<0.001
Stage 2	78 (33.48)	71.14	
Stage 3	67 (28.76)	47.10	
Stage 4	63 (27.04)	16.89	
Estrogen receptors*			
Negative	94 (40.52)	43.77	0.012
Positive	138 (59.48)	54.42	
Progesterone receptors*			
Negative	119 (51.29)	38.88	0.001
Positive	113 (48.71)	61.41	
Hormone receptors (any)*			
Negative	99 (38.79)	40.85	0.002
Positive	142 (61.21)	56.08	
HER2 expression*			
Negative	147 (63.91)	55.62	0.008
Positive	83 (36.09)	40.79	
TNBC*			
Non-TNBC	187 (81.30)	51.40	0.249
TNBC	43 (18.70)	44.69	
KI67 index*			
<20%	54 (24.43)	60.79	0.024
>20%	167 (75.57)	47.56	
Hereditary risk			
No	120 (51.28)	44.05	0.454
Yes	114 (48.72)	56.10	

*with missing data

IDC=invasive ductal carcinoma, HER2=human epidermal growth factor receptors 2, TNBC=triple-negative breast cancer

Two-year and five-year overall survival (OS) were 73.45% (95% CI 77.7%-87.49%) and 54% (95% CI 40.25%-58.15%), respectively (Figure 1). On univariate analysis of factors associated with survival after diagnosis (Table 1), older age (>50 years), IDC pathology, higher stage, expression of hormone receptors, expression of HER2 and high Ki67 proliferative index (>20%) were found to have significant associations with poorer OS (Table 1). On univariate logistic regression, N stage had the highest hazard ratio (HR 3.93, 95% CI 2.41-6.39), followed by T stage (HR 3.52, 95% CI 2.22-5.61) and IDC pathology (HR 2.77, 95% CI 1.12-6.84). However, when stepwise regression was conducted, 3 factors were retained in the final model, T stage, the N stage and metastatic status, with T stage having the highest adjusted HR at 1.97 (95% CI 1.15-3.38) (Table 2).





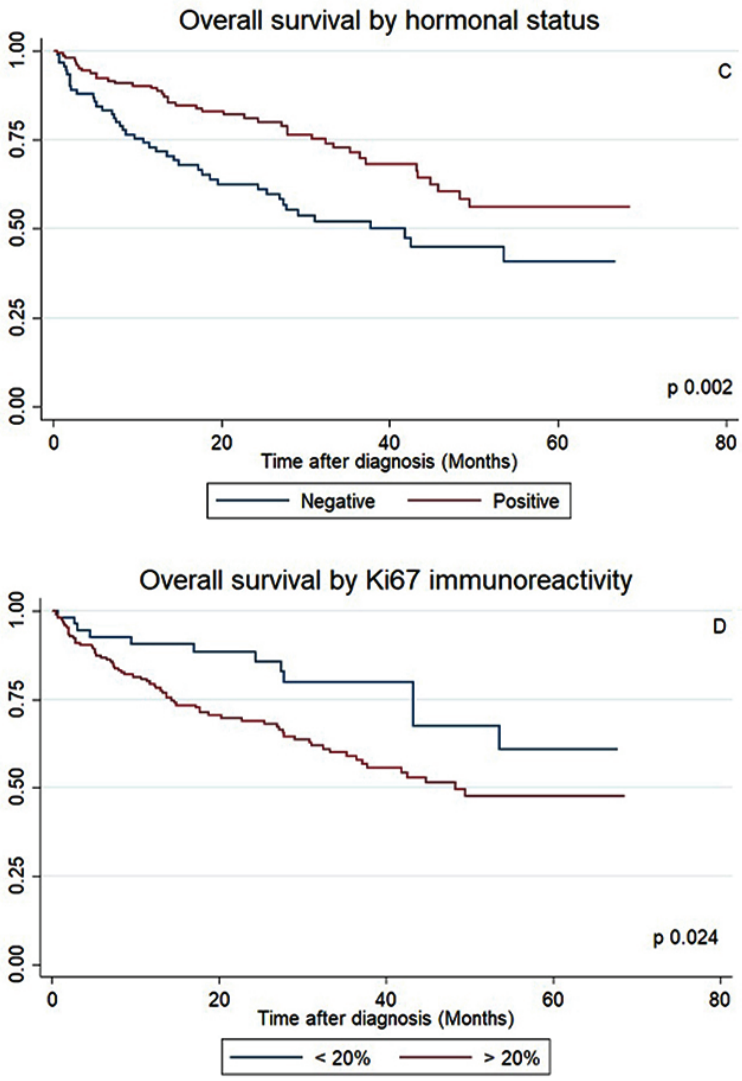


Figure 1 Survival probability of breast cancer patients in this study.

A: Overall survival

B: Overall survival by stage

C: Overall survival by hormonal status

D: Overall survival by Ki67 status

Table 2 Univariate Cox proportional hazard analysis of factors associated with survival in breast cancer patients in Narathiwat and multivariate analysis by stepwise regression

Parameters	Hazard ratio	95% confidence interval	Adjusted Hazard ratio	95% confidence interval
Age >50 years	1.63	1.05–2.54		
Invasive ductal carcinoma	2.77	1.12–6.84		
T stage (T3–4)	3.52	2.22–5.61	1.97	(1.15–3.38)
N stage (N2–3)	3.93	2.41–6.39	1.95	(1.05–3.64)
M stage	2.51	1.92–3.29	1.86	(1.27–2.71)
Estrogen receptors	1.72	1.12–2.63		
Progesterone receptors	2.05	1.31–3.22		
HER2 expression	1.77	1.52–2.73		
KI67 >20%	2.00	1.08–3.69		

HER2=human epidermal growth factor receptors 2

Discussion

With standard screening and therapeutic programs, 5–year survival of BC in high–income countries has been reported at more than 90%.[13–15] In Thailand, Chitapanarux I and colleagues reported a study of BC outcomes in the Northern part of the country during 2006–2015, in which OS was at 75% and survival in localized disease (stages I and II) was 85–94%.[16] In our 234 BC patients, the average age of diagnosis at 53 years was comparable to other reports from Asian countries including Thailand. The 5–year OS in our patients at 54% was obviously lower than in other reports from countries with comparable economic levels[17,18] which might partly be explained by the fact that nearly half (46%) of our group had locally advanced disease at presentation, 62% of them had lymph node metastasis and 27% had evidence of distant metastasis. Our patients had significantly poorer survival outcomes because of advanced–stage disease. In addition, when compared stage–by–stage, overall mortality was similar between our and other Asian studies.[17,19] In a cooperative hospital–based study from Singapore and Malaysia reported in 2011, the size of the primary tumor significantly decrease after the implementation of mammographic screening and the same study showed that only 10% of the patients had distant metastasis at presentation and the figure decreased with time.[20] A nation–wide survey in China in 2011, which had begun a screening program, reported that 18.7% of their BC patients were in stage III, and only 2.4% were in stage IV.[21] A study in the Northeastern provinces of Thailand found that factors associated with delayed treatment in BC included poor socioeconomic status and prolonged referral duration.[22] The evidence from our study suggests that early screening might be a key strategy to reduce BC–related deaths in our population. When the other part of the country has embraced modern screening methods such as radiologic and genetic screening, implementation of these technologies in rural areas like the 3 border provinces of Thailand still has a long journey to go.

Currently, there are 2 effective strategies for detecting patients at risk of developing BC, mammograms and genetic screening. Mammograms have been reported to change the stage at diagnosis to earlier stages and reduce cancer–specific mortality in population–based studies in Europe and America.[23–25] In our community, the availability of this technology is still limited to private hospitals and breast centers situated hours away from the province. A

mammogram is thus not a generally accessible technology at this time but should be a developmental goal. According to the NCCN guideline, 48.7% of our patients should be screened for risk of vertical transmission. Genetic testing for BRCA gene mutation has been included in the Thailand Universal Coverage (UC) scheme since 2021, which may have some impact on the primary prophylaxis of BC through the identification of more hereditary cases. Germline genetic tests not only provide benefits for cancer surveillance and prophylaxis but may also help in precision cancer therapies.[26] Recently, the American Society of Breast Surgeons recommended germline genetic testing for all breast cancer patient.[27]

Our study found similar frequencies of hormone receptor positivity in our BC patients when compared to the Western series.[28,29] Hormonal profiles, including ER and PR, are predictive and prognostic markers for hormonal therapy. As in other studies, our patients who had positive ER or PR or both markers had significantly better survival, while patients with positive HER2 had poorer outcomes, possibly because of limitations in access to trastuzumab in most of our cases. However, the levels of hormonal receptors and HER2 positivity reflect an acceptable standard of pathological studies in our BC patients.

The main limitation of this study was in the nature of retrospective and hospital-based studies as there were missing data, especially in the details of the management of each patient. However, we were certain of the demographic, pathological and survival data retrieved from the well-established registry.

Conclusion

The study reviewed BC in a tertiary care level hospital in Narathiwat province in Thailand and found that delayed presentation is associated with poor survival outcomes. Early detection of the disease by an effective screening program including mammography and genetic studies should be included in the government healthcare policy for this patient group.

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Conflict of interest

We declare no conflicts of interest.

References

1. Ghoncheh M, Pournamdar Z, Salehiniya H. Incidence and mortality and epidemiology of breast cancer in the world. Asian Pac J Cancer Prev 2016;17:43-6.
2. El Saghir NS, Adebamowo CA, Anderson BO, Carlson RW, Bird PA, Corbex M, et al. Breast cancer management in low resource countries (LRCs): consensus statement from the Breast Health Global Initiative. Breast 2011;20(Suppl 2):S3-11.
3. Insamran W, Sangrajrang S. National cancer control program of thailand. Asian Pac J Cancer Prev 2020;21:577-82.
4. Virani S, Bilheem S, Chansaard W, Chitapanarux I, Daoprasert K, Khuanchana S, et al. National and subnational population-based incidence of cancer in Thailand: assessing cancers with the highest burdens. Cancers 2017;9.
5. Albritton RB. Political diversity among Muslims in Thailand. Asian Studies Review 1999;23:233-46.
6. Thompson EC. Anthropology in Southeast Asia: national traditions and transnational practices. Asian J Soc Sci 2012; 40:664-89.
7. Sriplung H, Bilheem S, Kuntipundee T, Geater SL. Differences in cancer incidence among predominantly Muslim and Buddhist subpopulations in Songkhla. Asian Pac J Cancer Prev 2014; 15:9979-83.
8. Giri M, Giri M, Thapa RJ, Upreti B, Pariyar B. Breast Cancer in Nepal: current status and future directions. Biomed Rep 2018;8:325-9.

9. Fan L, Goss PE, Strasser-Weippl K. Current status and future projections of breast cancer in Asia. Breast Care (Basel) 2015; 10:372-8.
10. Cancer Ajco. AJCC cancer staging manual. 7th ed. New York: Springer; 2015.
11. Iwamoto T, Kajiwara Y, Zhu Y, Iha S. Biomarkers of neoadjuvant/adjuvant chemotherapy for breast cancer. Chin Clin Oncol 2020;9:27.
12. Hashmi AA, Hashmi KA, Irfan M, Khan SM, Edhi MM, Ali JP, et al. Ki67 index in intrinsic breast cancer subtypes and its association with prognostic parameters. BMC Res Notes 2019;12:605.
13. Holleczek B, Jansen L, Brenner H. Breast cancer survival in Germany: a population-based high resolution study from Saarland. PLoS One 2013;8:e70680.
14. Davidson A, Chia S, Olson R, Nichol A, Speers C, Coldman AJ, et al. Stage, treatment and outcomes for patients with breast cancer in British Columbia in 2002: a population-based cohort study. CMAJ Open 2013;1:E134-41.
15. Tan BK LG, Czene K, Hall P, Chia KS. Do Asian breast cancer patients have poorer survival than their western counterparts? A comparison between Singapore and Stockholm. Breast Cancer Res 2009;11(R4).
16. Chitapanarux I, Sripan P, Somwangprasert A, Charoentum C, Onchan W, Watcharachan K, et al. Stage-specific survival rate of breast cancer patients in Northern Thailand in accordance with two different staging systems. Asian Pac J Cancer Prev 2019;20:2699-706.
17. Tan KF, Adam F, Hussin H, Mohd Mujar NM. A comparison of breast cancer survival across different age groups: a multicentric database study in Penang, Malaysia. Epidemiol Health 2021;43:e2021038.
18. Rahimzadeh M, Pourhoseingholi MA, Kavehie B. Survival Rates for Breast Cancer in Iranian Patients: a Meta- Analysis. Asian Pac J Cancer Prev 2016;17:2223-7.
19. Kwong A, Mang OW, Wong CH, Chau WW, Law SC, Hong Kong Breast Cancer Research G. Breast cancer in Hong Kong, Southern China: the first population-based analysis of epidemiological characteristics, stage-specific, cancer-specific, and disease-free survival in breast cancer patients: 1997-2001. Ann Surg Oncol 2011;18:3072-8.
20. Pathy NB, Yip CH, Taib NA, Hartman M, Saxena N, Iau P, et al. Breast cancer in a multi-ethnic Asian setting: results from the Singapore-Malaysia hospital-based breast cancer registry. Breast 2011;20(Suppl 2):S75-80.
21. Li J, Zhang BN, Fan JH, Pang Y, Zhang P, Wang SL, et al. A nation-wide multicenter 10-year (1999-2008) retrospective clinical epidemiological study of female breast cancer in China. BMC Cancer 2011;11:364.
22. Poum A, Promthet S, Duffy SW, Parkin DM. Factors associated with delayed diagnosis of breast cancer in northeast Thailand. J Epidemiol 2014;24:102-8.
23. Bleyer A, Baines C, Miller AB. Impact of screening mammography on breast cancer mortality. Int J Cancer 2016;138:2003-12.
24. Schopper D, de Wolf C. How effective are breast cancer screening programmes by mammography? Review of the current evidence. Eur J Cancer 2009;45:1916-23.
25. Duffy SW, Tabar L, Yen AM, Dean PB, Smith RA, Jonsson H, et al. Mammography screening reduces rates of advanced and fatal breast cancers: Results in 549,091 women. Cancer 2020;126:2971-9.
26. Piccinin C, Panchal S, Watkins N, Kim RH. An update on genetic risk assessment and prevention: the role of genetic testing panels in breast cancer. Expert Rev Anticancer Ther 2019;19:787-801.
27. Manahan ER, Kuerer HM, Sebastian M, Hughes KS, Boughey JC, Euhus DM, et al. Consensus Guidelines On Genetic` Testing For Hereditary Breast Cancer from the American Society of Breast Surgeons. Ann Surg Oncol 2019;26:3025-31.
28. Julia YS, Tsang GMT. Molecular classification of breast cancer. Adv Anat Pathol 2020;27:27-35.
29. Bonacho T, Rodrigues F, Liberal J. Immunohistochemistry for diagnosis and prognosis of breast cancer: a review. Biotech Histochem 2020;95:71-91.