RESEARCH ARTICLE

Survival Time and Molecular Subtypes of Breast Cancer after Radiotherapy in Thailand

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Abstract

Background: Breast cancer is an important cause of death among women. One way of classifying different forms of breast cancer is by molecular features, usually in terms of the four subtypes: luminal A, luminal B, HER2-enriched, and triple negative. Objectives: This study aimed to investigate the association between molecular subtypes and survival among breast cancer patients treated with radiotherapy. Materials and Methods: A retrospective cohort study was conducted. The subjects were 272 breast cancer patients who had received treatment in the radiotherapy unit at Srinagarind Hospital, Thailand, between 1 January, 1999, and 31 May, 2009. The end of the study was 1 June, 2014. Overall survival was defined as the time elapsing between initial registration at the radiotherapy unit and death or the end of the study. Survival curves were estimated by the Kaplan-Meier method, and a multivariate analysis was performed using Cox's proportional hazard regression model. Results: The patient mean age was 47.5±10.4 at the time of diagnosis. Of the 272 patients, 146 (53.7%) were classified as luminal A, 12 (4.4%) as luminal B, 30 (11.0%) as HER2-enriched, and 84 (30.9%) as triple negative. The overall survival rates at 1, 3 and 5 years were 87.1%, 68.4% and 59.2%, respectively. According to molecular subtypes, HER2-enriched patients had the lowest 5-year survival rate (30.0 %, 95%CI: 15.02-46.55). The median follow-up time was 8.37 years. In the Cox model analysis a higher risk of death was found for patients with HER2-enriched (HR_{adj}=3.34, 95%CI:1.96-5.67), triple negative (HR_{adj}=2.17, 95%CI: 1.44-3.27), and stage IIIB (HR_{adj}=2.20, 95%CI: 1.16-4.17) cancers. Conclusions: The worst survival rates were among patients classified as HER2-enriched, triple negative and at stage IIIB. Early detection and an advanced treatment modality are needed to help these patients.

Keywords: Breast cancer - survival - molecular subtypes - radiotherapy

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Introduction

Breast cancer is an important health problem worldwide. It is the most common cancer in women and still increasing. It is one of the five most common causes of death from cancer in women (Khuhaprema et al., 2012; Ferlay et al., 2013). For the female population worldwide, the incidence rate is 38.9 per 100,000, and the mortality rate is 13.0 per 100,000 (Ferlay et al., 2013). Breast cancer incidence among Thai women is 30.7 per 100,000 and the mortality rate is 10.8 per 100,000 (Vatanasapt et al., 1995; Khuhaprema et al., 2012; Wirasorn et al., 2014).

Recently, it has been suggested that there are various biomarkers such as an estrogen receptor (ER), a progesterone receptor (PR) and HER2/neu (HER2) which can be detected by immunohistochemistry (Dedes et al., 2011). These biomarkers are prognostic indicators of the survival in breast cancer patients (Cheang et al., 2009; Phipps et al., 2010). Breast cancers can be classified into four groups in terms of the phenotype of the biomarkers: luminal A, luminal B, HER2-enriched and triple negative (Phipps et al., 2010; Park et al., 2012). For each subtype there are differences reported in response to treatment, risk factors, clinical presentation and histology, all of which contribute to differences in the overall prognosis of the disease (Dedes et al., 2011; Wong et al., 2011; Park et al., 2012).

In Thailand, there have been few studies about breast cancer survival and no study about survival after radiotherapy or in terms of biomarkers and molecular subtypes (Sriamporn et al., 1995; Suwanrungruang et al., 2011; Chuthapisithet al., 2012; Poum et al., 2012; Chuangsuwanichet al., 2014). This study aimed to investigate the association between molecular subtypes and survival among breast cancer patients treated with radiotherapy. It is hoped that the findings will help in making recommendations for future improvements in the early diagnosis and treatment of invasive breast cancer.

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Materials and Methods

A retrospective cohort study of 272 breast cancer patients was conducted. All the patients had received radiotherapy treatment in the radiotherapy unit at Srinagarind Hospital, Khon Kaen University, Thailand, between 1 January, 1999, and 31 May, 2009. The data were extracted from medical records and pathology reports, and the inclusion criteria were: 1) a histologically proven diagnosis of female primary invasive breast cancer based on the International Classification of Diseases for Oncology 3rd edition (sites C50.0-C50.9) (Fritz et al., 2000); 2) age between 18 and 80 years; 3) had received surgery, and 4) a complete set of data required for the study was available. The patients were followed up until death or the end of the study (1 June, 2014).

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The independent variables were age at diagnosis, parity, presence/absence of HER2/neu, ER, PR, Ki-67, molecular subtypes, resection margin (negative or positive), size/extent of primary tumor, degree of involvement of regional lymph nodes, stage of disease, and histological type. The dependent variable was the survival time of patients with breast cancer. In order to calculate the survival time, the starting point was defined as the date of registration at the radiotherapy unit, and the follow-up period ended when a patient died or on completion of the study. Censored data were used for those still alive at the end of the study or lost to follow-up. The follow-up status of each patient was determined from the medical record and by linkage with the death registry of the national statistics database.

Immunohistochemistry was used to detect the biomarker phenotypes of ER, PR and HER2, and hierarchical clustering analysis was employed to classify the patients onto one of the four molecular subtypes: 1) luminal A (ER+/PR+/HER2-, ER+/PR-/HER2-, ER-/PR+/HER2-); 2) luminal B (ER+/PR+/HER2+, ER+/PR-/HER2+, ER-/PR+/HER2+); 3) HER2-enriched (ER-/PR-/HER2+) and 4) triple negative (ER-/PR+/HER2-) (Parise et al., 2009).

Descriptive statistics were used for an exploratory data analysis. Percentages were used to summarise categorical data, and means with standard deviations or medians with ranges were used for continuous data. The observed survival rates were calculated by the Kaplan-Meier method. Median survival times with 95% confidence intervals (CIs) and the log-rank test were used for comparisons between groups. The Cox proportional hazard regression model with backward elimination was used to assess associations between the various independent variables (covariates) and survival, and the adjusted hazard ratios were tested for significance using the partial likelihood test. The level of significance was set as $p<0.05$. All analyses were performed using STATA version 10.0 (StataCorp LP, 2007).

The research was approved by the Khon Kaen University Ethics Committee for Human Research (Reference no. HE571081).

Results

The analyses were based on all the 272 patients selected for inclusion in this study. Their mean age was 47.5±10.39 at the time of diagnosis, and 146 (53.7%) were classified as luminal A, 12 (4.4%) as luminal B, 30 (11.0%) as HER2-enriched and 84 (30.9%) as triple negative. Regarding cancer staging, stages lllA and lllB were the most common, and almost all (99.3%) were found to have the ductal carcinoma type of the disease (Table1).

Table 1. Demographic and Clinical Characteristics of Breast Cancer Patients after Radiotherapy (N=272)

Variables		No.	%
Age (years)	≤ 45	122	44.9
	> 45	150	55.1
	Mean (SD)	47.5 (10.4)	
Parity	0	63	23.2
	1	27	9.9
	2	85	31.3
	≥ 3	97	35.7
	Median (min,max)	2 (0, 9)	
Estrogen Receptor	Negative	129	47.4
	Positive	143	52.6
Progesterone Receptor	Negative	190	69.9
	Positive	82	30.1
HER-2/neu	Negative	230	84.6
	Positive	42	15.4
Ki-67	Negative	89	32.7
	Positive	183	67.3
Molecular subtypes	Luminal A	146	53.7
	Luminal B	12	4.4
	HER2-enriched	30	11.0
	Triple negative	84	30.9
Resection margin	Yes	189	69.5
	No	83	30.9
Primary tumor	T1	58	21.3
	T2	103	37.9
	T3	46	16.9
	T4	65	23.9
Regional lymph nodes	N0	115	42.3
	N1	107	39.3
	N2	46	16.9
	N3	4	1.5
Stage of disease	Stage I	32	11.8
	Stage IIA	58	21.3
	Stage IIB	49	18.0
	Stage IIIA	64	23.5
	Stage IIIB	63	23.2
	Stage IIIC	6	2.2
Histological type	Ductal carcinoma	270	99.3
	Lobular carcinoma	2	0.7

*SD= Standard deviation

At the end of the study, there had been 123 deaths which represents a mortality rate of 9.13 per 100 person-years (95% CI: 7.65 -10.89), and the median survival time after radiotherapy was 8.37 years (95%CI: 6.96-9.78). The overall survival rates for 1, 3 and 5 years were 87.1% (95%CI: 82.54 -90.59), 68.4% (95%CI: 62.49-73.55) and 59.2% (95%CI: 53.09 -64.76), respectively (Figure 1). Regarding molecular subtypes, the 5-year survival rates were: luminal B =75.0% (95%CI: 40.84-91.17), luminal A=70.5 (95%CI: 62.40-77.22), triple negative=47.6% (95%CI: 36.65-57.79), and HER2-enriched=30.0% (95%CI: 15.02-46.55) (Figure 2).

In the Cox final model, statistically significant risks of death were found to be associated with HER2-enriched (HRadj=3.34, 95%CI: 1.96-5.67), triple negative (HRadj=2.17, 95%CI: 1.44-3.27), and stage IIIB (HRadj=2.20, 95%CI: 1.16-4.17) (Table 2).

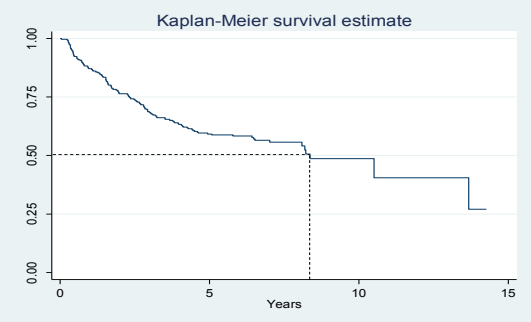

Figure 1. Kaplan–Meier Curve of Overall Survival of Breast Cancer Patients after Radiotherapy

Table 2. Multivariate Analyses of the Factors Associated with Overall Survival by Cox Proportional Hazard Model

Factors	Crude HR (95% CI)	Adjust HR * p-value (95% CI)	
Molecular subtypes			<0.001
Luminal A	1	1	
Luminal B	1.02 (0.40-2.59)	0.95 (0.37-2.45)	
Triple negative	2.14 (1.43-3.19)	2.17 (1.44-3.27)	
HER2-enriched	3.77 (2.27-6.26)	3.34 (1.96-5.67)	
Stage of disease			<0.001
Stage I	1	1	
Stage IIA	0.62 (0.301.29)	0.74 (0.35-1.56)	
Stage IIB	0.80 (0.39-1.66)	1.04 (0.50-2.16)	
Stage IIIA	1.35 (0.71- 2.57)	1.33 (0.68-2.60)	
Stage IIIB	1.98 (1.06-3.70)	2.20 (1.16-4.17)	
Stage IIIC	2.07 (0.67-6.36)	2.61 (0.84-8.09)	

*Adjusted for Ki-67, regional lymph nodes, primary tumor and resection margin; HR= Hazard ratio, CI= Confidence interval; p-value from partial likelihood ratio test

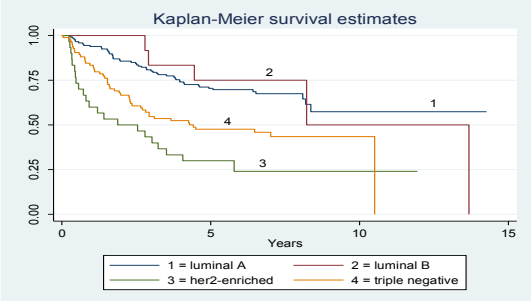

Figure 2. Kaplan Meier Curves of Survival for the Molecular Subtypes

Discussion

In this present study, we employed a retrospective cohort design, using data on breast cancer patients who had received radiotherapy at our local University Hospital over a 10 year period. The results showed that the median survival time was 8.37 years, and survival rates after receiving the radiotherapy at 1, 3 and 5 years were 87.1%, 68.4% and 59.2%, respectively. These rates are consistent with those of another study in Northeastern Thailand, which found that the survival rates at 1, 3 and 5 years were 83.3%, 59.9% and 42.9%, respectively (Poum etal., 2012). Outside Thailand, while our median survival rate is higher than the 5.7 years found by a study of breast cancer patients in Malaysia (Abdullah et al., 2013), our findings are lower than those reported in Iran. A study of breast cancer patients after receiving radiotherapy in Iran found that the survival rates at 1, 3 and 5 years were 96.0% , 86% and 81.0%, respectively (Ziaei et al., 2013).

Our finding that breast cancer patients with triple negative and HER2-enriched had lower survival rates than patients with luminal A and B is in line with outcomes of study done in Italy. The Italian study reported that the survival of breast cancer patients with triple negative and HER2-enriched had lower survival rates than patients with other molecular subtypes (Minicozzi et al., 2013). Our findings are also supported by a study of breast cancer in black women, which found that triple negative and HER2-enriched patients had the lowest survival 5-year survival rates (Ihemelandu et al., 2008). Our findings and those of others indicate that different molecular subtypes are associated with different survival rates and that the rates are likely to be lowest in breast cancer patients with triple negative and HER2-enriched molecular subtypes. However, a study of breast cancer patients in California, USA, found that the 5-year survival of triple negative and HER2-enriched patients were 69.2% and 76.2% which are higher than our findings (Parise et al., 2009). This may due to differences in racial characteristics, treatment modality, and stage. In addition to providing information about prognosis molecular subtypes may also have implications for the choice of optimum treatment modality (Chae & Gonzalez-Angulo, 2014).

The present study found that breast cancer patients with stage IIIB had a significantly higher risk of death. This is consistent with the findings of a study of African-American women with breast cancer (Ihemelandu et al., 2008), which reported that patients with stage III and IV cancers had a higher risk of death than patients with stage I and II malignancies (HR=2.33, 95%CI: 1.11-44.89).

Limitation of the study

The 272 patients included in this study were those for whom a complete set of data was available. The exclusion of those with incomplete data is potential source of bias. However, the characteristics of those excluded due to incomplete data were similar to and not statistically different from those with complete data.

In conclusion, the overall survival at 1, 3, 5 years were 87.1%, 68.4% and 59.2%. The worst survival rates were among the HER2-enriched and triple negative subtypes and those at stage IIIB. Early detection and an advanced treatment modality are needed to help these patients. .

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