RESEARCH ARTICLE

Editorial Process: Submission:12/23/2022 Acceptance:04/17/2023

Follow-Up Strategies and Detection of Recurrent Breast Cancer in the Modern Era

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Abstract

Background: Regular history assessments and physical examination with annual breast imaging have been recommended as the standard surveillance protocol for breast cancer patients who underwent curative-intent therapy. Based on randomized studies conducted in the 2000s, surveillance with regular chest or abdominal imaging, chemistry panels, or tumor marker measurements does not improve survival in such patients. Given the remarkable recent improvements of systemic therapy, we hypothesized that more intensive surveillance may lead to early detection and improve treatment outcomes in the modern era. **Methods:** We retrospectively evaluated the follow-up strategies and benefits of investigations used in usual practice. Breast cancer patients who had initial adjuvant therapy were recruited and classified according to the receipt of standard follow-up (history, physical examination, and annual breast imaging) or alternative follow-up (surveillance with at least annual chest or abdominal imaging or biannual liver function testing). The primary outcome was overall survival. Secondary outcomes included disease-free survival and the indicator of recurrence detection. **Results:** Of 412 recruited patients, 213 (51.7%) and 199 patients (49.3%) were included in the standard follow-up group and alternative follow-up group, respectively. Among 90 patients (21%) with disease recurrence, the most frequent indicators of recurrence were newly reported symptoms or physical examination abnormalities (64%), followed by abnormal breast imaging (23%) and abnormal chest X-ray (10%). After a median follow-up of 85 months, approximately 90% of patients remained alive after 5 years in both groups. The mean overall survival was similar between the standard and alternative follow-up groups (154.5 months vs. 151.9 months, p = 0.54). There was no difference in terms of the proportion of interval visits, specific cancer treatment received, and disease-free survival. **Conclusion:** Standard follow-up with history assessments, physical examination, and annual breast imaging remains the recommended surveillance strategy in the modern era. Alternative follow-up strategy did not improve oncologic outcomes.

Keywords: Breast cancer- follow-up- surveillance- recurrence detection

Asian Pac J Cancer Prev, **24 (4)**, 1359-1366

Introduction

Breast cancer is the most common cancer in Thai woman. Approximately 80 percent of Thai patients with breast cancer were diagnosed with non-metastatic disease amenable to curative treatment (Sangkittipaiboon et al., 2015). After surgery and adjuvant therapy, surveillance is critical for detecting disease recurrence and long-term treatment complications in breast cancer survivors to optimize outcomes.

Breast cancer is a heterogeneous disease with a varied clinical course. Breast cancer is classified into three main molecular subtypes, namely luminal tumors (estrogen receptor-positive [ER+] or progesterone receptor-positive), triple-negative, and human epidermal growth factor receptor 2-positive (HER2+). Luminal tumors are typified by slow progression, but late recurrence occasionally occurs. Meanwhile, patients with HER2+ and triple-negative tumors more frequently experience rapid progression. The optimal follow-up measures for detecting disease recurrence might differ among the breast cancer subtypes.

The American Society of Clinical Oncology (ASCO) recommends clinical surveillance including regular history assessments, physical examination, and annual breast imaging as a proper surveillance protocol among patients with breast cancer who completed primary therapy with curative intent (Khatcheressian et al., 2013). Scheduled visits consisting of symptom assessment and physical examination should be performed every 3-6 months in the first 3 years after treatment, every 6-12 months up to 5 years, and annually thereafter, together with annual breast imaging. Complete blood counts, chemistry panels, bone scan, chest or abdominal imaging, and/or tumor marker

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measurements are not recommended for routine follow-up in asymptomatic patients without specific findings on clinical examination (Cardoso et al., 2019). Consistent with previous studies from Western countries published in the past decade, the aforementioned investigations do not improve survival in patients with early breast cancer (Investigators, 1994; Rosselli Del Turco et al., 1994; Palli et al., 1999; Kokko et al., 2005).

Although clinical studies and recommendations from Western organizations support the use of only clinical examination with annually breast imaging as a proper surveillance breast cancer schedule, the application of this policy in Thai patients remains controversial. Because of a lack of awareness or limited opportunity to urgently reach cancer experts in Thailand, some patients developed rapid and extensive symptomatic metastasis requiring unscheduled emergency visits. Some of these patients cannot undergo chemotherapy because of organ dysfunction or poor performance status due to the widespread disease. Consequently, in Thai clinical practice, some experts prefer chest or abdominal imaging as well as blood chemistry panels as surveillance tools to better detect recurrence and increase the chance for patients to receive specific breast cancer treatment. Contrarily, intensive monitoring may lead to unnecessary investigations, causing anxiety, higher patient costs, and a greater burden on medical personnel.

However, with recent remarkable improvements in systemic therapy for advanced breast cancer, the earlier detection of asymptomatic breast cancer recurrence and earlier treatment may lead to better outcomes in the modern era. The recent recommendations for breast cancer surveillance are mainly based on the results of clinical studies performed in the 1990s and 2000s. Therefore, this retrospective study compared outcomes among patients with breast cancer between standard clinical surveillance and more intensive surveillance measures.

Materials and Methods

Patients

The data of patients with stage 1–3 breast cancer who completed surgical treatment and received adjuvant systemic treatment between 2010 and 2013 and who underwent follow-up at Siriraj Hospital, Bangkok, Thailand were retrospectively reviewed. Patients with questionable metastasis at diagnosis, other primary cancer, or incomplete data were excluded from the study.

Baseline characteristics, breast cancer subtypes, stage, treatment, surveillance schedules, site of recurrence, date of recurrence or death, and follow-up data were obtained from electronic medical records. Surveillance measures of interest included breast imaging, chemistry panels, chest or abdominal imaging, and serum tumor markers. The patients were categorized into the standard or alternative follow-up group. Standard follow-up measures included history assessments and physical examination by a physician every 3–4 months in the first 2 years, every 6 months in the following 3 years, and annually thereafter, as well as annual breast imaging. Patients who underwent other investigations because of suspicion of recurrence based on standard surveillance were categorized into standard follow-up group. Patients with alternative follow-up were defined as asymptomatic patients who completed the same scheduled visits as those in the standard follow-up group in addition to annual chest or abdominal imaging or biannual liver function testing. The two follow-up and surveillance patterns were performed according to physician's preference. The study was approved by the Siriraj Institutional Review Board (Protocol number 083/2561(EC4)). The patients were not required to obtain consent form due to its retrospective method.

Statistical analysis

Comparisons of clinico-pathological parameters, breast cancer subtypes, and surveillance patterns between the groups were performed using the chi-squared test, Mann-Whitney U test and Fisher's exact test. Categorical data were reported as percentages, whereas continuous variables were reported as the median and range. Overall survival (OS) was defined as time from diagnosis to death from any cause. Death date was retrieved from hospital database and civil registration. Disease-free survival (DFS) was defined as time from diagnosis to disease progression or death. Overall survival and DFS were analyzed using the Kaplan-Meier survival method. Comparisons of overall survival, disease-free survival, and time to events between the groups were performed using the log-rank test. p values were two-sided, and 95% confidence intervals were presented. Multivariate analysis was assessed included only those variables that were positive in univariate analysis and were assessed using multiple binary logistic regression analysis. Statistical analysis was performed using SPSS version 20 (licensed by Mahidol University, Bangkok, Thailand).

From the literature review, the 5-year mortality rate of early-stage breast cancer is 13.2% (Chairat et al., 2014). We hypothesized that alternative or more intensive follow-up would improve the survival rate by approximately 10%. At least 197 patients in each follow-up pattern were required to achieve statistical power of 80% and a two-sided alpha error of 0.05. The primary endpoint was overall survival, defined as the time from diagnosis to death. Secondary outcomes included disease-free survival and patterns of recurrence detection.

Results

In total, 412 patients with non-metastatic breast cancer were included in the study. The cohort included 269 (65%), 37 (9%), 33 (8%) and 42 patients (10.2%) with ER+/HER2−, ER+/HER2+, triple-negative, and ER−/HER2+ breast cancer, respectively (Table 1). Meanwhile, 213 (51.7%) and 199 patients (49.3%) were included in the standard and alternative follow-up groups, respectively. Most patients had stage 2–3 breast cancer. There was no significant difference in breast cancer treatment modalities between the two groups. There was no difference in terms of chemotherapy used among patients in standard and alternative follow-up group. Of 96 patients with HER2+ breast cancer, 23 patients (46%) in alternative follow-up group and 12 patients (26%) in standard follow-up group

received adjuvant trastuzumab (p=0.04). All patients with luminal breast cancer received hormonal therapy with mainly aromatase inhibitor in both follow-up groups (74% in standard follow-up group vs 87% in alternative follow-up group, p=0.4). All patients were reviewed for new or abnormal symptoms or submitted to physical examination during each scheduled visit. All patients received appropriate annual breast imaging, i.e., breast ultrasound, mammography, or MRI. Approximately 40% of patients underwent surveillance chest X-ray annually, whereas 30% of patients underwent semiannual liver function testing. Among the patients in the alternative follow-up group, some underwent both chest imaging and blood chemistry analysis per their oncologists' discretion. Fifty-three patients (24.9%) with standard follow-up experienced disease recurrence, compared to 37 patients (18.6%) who received alternative follow-up (p = 0.12).

Among the 90 patients (21.8%) with disease recurrence, the most common site of recurrence was the ipsilateral breast or chest wall (40%), followed by the lungs or pleura (33.3%) and bone (26.7%), Table 2. Considering the site of first relapse according to the mode of surveillance, no association was detected. The lungs were comparably identified as the first site of recurrence despite annual chest X-ray in most patients in the alternative follow-up group. The most frequent sign of recurrence was new symptoms detected via history assessment and physical examination (64%), followed by breast imaging (23.3%) and abnormal surveillance chest X-ray results (10%, Table 2). Meanwhile, 39 of 90 patients with disease recurrence (39%) experienced with symptomatic recurrence requiring an urgent visit. There was no significant difference in the rate symptomatic or urgent visits between the standard and alternative follow-up groups (35.8% and 42.1%, respectively, Table 2).

After a median follow-up of 85 months, the median overall survival was not reached. Approximately 90% of patients in both groups survived for 5 years. The mean overall survival was similar between the standard and alternative follow-up groups (154.5 and 151.9 months, respectively, p = 0.54, Tables 3–4). However, disease-free survival tended to be shorter in the standard follow-up group (111.4 months vs. 139.3 months, p = 0.07). Multivariate analysis adjusted for known prognostic factors revealed that disease-free survival was significantly longer among patients who underwent liver function testing (Table 5). Considering follow-up patterns in breast cancer subtypes, multivariate analysis adjusted for known prognostic factors and treatment received showed that alternative follow-up did not associate with longer

Table 1. Baseline Characteristics

Baseline characteristics		Standard follow-up Total = 213 n (%)	Alternative follow-up Total = 199 n (%)	p
Menstrual status	Pre-/perimenopausal	98 (46)	88 (44.2)	0.73
	Postmenopausal	111 (52.1)	105 (52.8)	
	Undetermined	4 (1.9)	6 (3)	
Stage	1	23 (10.8)	16 (8)	0.37
	2	130 (61)	116 (58.3)	
	3	60 (28.2)	67 (33.7)	
Pathology type	Invasive ductal carcinoma	198 (93)	186 (93.4)	0.57
	Invasive lobular carcinoma	10 (4.7)	10 (5.1)	
	Others	5(2.3)	2 (1)	
Breast cancer subset	Luminal	138 (64.8)	131 (65.8)	0.52
	Luminal HER-2	29 (13.6)	8 (11.6)	
	Triple-negative	11 (16.4)	22 (11.1)	
	ER−, HER2+	18 (8.5)	24 (12.1)	
Grade	1	21 (9.9)	17 (8.5)	0.93
	2	118 (55.4)	112 (56.3)	
	3	59 (27.7)	58 (29.1)	
	Missing	15 (7)	12 (6)	
Resection	Mastectomy	154 (72.3)	148 (74.4)	0.64
	Breast conservative surgery	59 (27.7)	51 (25.6)	
Axillary node surgery	Sentinel node biopsy	87 (40.8)	66 (33.2)	0.11
	Axillary node dissection	126 (59.2)	133 (66.8)	
Neoadjuvant chemotherapy	No	187 (87.8)	170 (85.4)	0.48
	Yes	26 (12.2)	29 (14.6)	
Radiotherapy	No	84 (39.4)	67 (33.3)	0.23
	Yes	129 (49.4)	132 (50.6)	

n, number of patients; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

Table 2. Breast Cancer Recurrence and Patterns of Recurrence Detection

Breast cancer recurrence	Standard follow-up Total = 53 n (%)	Alternative follow-up Total = 37 n (%)	p
Breast cancer recurrence			
Yes	53 (24.9)	37 (18.6)	0.12
No	160 (75.1)	162 (81.4)	
First site (s) of recurrence			
Ipsilateral breast or chest wall	14 (26.4)	9 (24.3)	0.82
Contralateral breast	5 (9.4)	4 (10.8)	0.83
Ipsilateral axillary node	13 (24.5)	4 (10.8)	0.1
Non-regional nodes	3 (5.7)	1 (2.7)	0.5
Bone	12 (22.6)	12 (32.4)	0.3
Liver	6 (11.3)	6 (16.2)	0.5
CNS	3 (5.7)	5 (13.5)	0.2
Lung or pleura	15 (28.3)	15 (40.5)	0.23
Period of recurrence detection			0.45
Follow-up visit	34 (64.2)	21 (57.9)	
Emergency room/ interval visit	19 (35.8)	16 (42.1)	
Indicator of recurrence			
History assessment or abnormal physical examination	38 (71.7)	20 (54.1)	0.029
Surveillance breast imaging	13 (24.5)	8 (21.6)	
Surveillance chest X-ray	2 (3.8)	7 (18.9)	
Others	0	2 (5.4)	

n, number of patients; CNS, central nervous system

overall survival and disease-free survival in subgroup of ER-positive. Interestingly, alternative follow-up pattern especially annual chest-x-ray associated with longer disease-free survival in patients with HER2-positive breast cancer (Table 6).

Patients with recurrent breast cancer received specific cancer treatment, excluding three patients who did not receive treatment because of their poor performance status. Of these three patients, two patients who underwent standard surveillance required additional visits because of the appearance of new symptoms. The median time from the suspicion of recurrence to the start of treatment tended to be longer in the standard follow-up group (50 days vs. 42 days, p = 0.81, Table 7). In addition, there was no meaningful difference in the time from suspicion of recurrence to disease progression and the time from definite recurrence to disease progression between the groups.

Table 3. Overall Survival Depends on the Follow-up Strategy

Follow-up strategy	Five-year OS (%)	OS (months) Mean (95% CI)	p
Follow-up type			
Standard (n = 219)	90.9	154.5 (146.8, 162)	0.538
Alternative (n = 199)	90.8	151.9 (146.4, 157.4)	
Surveillance chest X-ray			
Yes (n = 167)	90.9	151.86 (145.9, 157.8)	0.569
No (n = 245)	90.8	154.8 (147.6, 162)	
Surveillance LFT			
Yes (n = 125)	92.6	155.97 (150.25,161.68)	0.116
No (n = 287)	90.4	153.96 (147.7, 160.2)	

OS, overall survival; CI, confidence interval; LFT, liver function test

Discussion

Although convincing scientific evidence is lacking to date, most physicians assume that the early detection of recurrent breast cancer will have a favorable impact on survival. Most available data regarding surveillance recommendations were generated in an era with less advanced radiographic or tools for breast cancer recurrence as well as less efficacious therapy. However, the hypothesis regarding possibility of cure with aggressive multimodality therapy has arisen for patients with oligo-metastases (Hortobagyi, 2002). To support this approach, effective surveillance protocol for early detection of limited metastasis is crucial. According to our study, chest X-ray is the most common additional diagnostic test, followed by liver function testing. However, indicators of breast cancer recurrence primarily included symptoms recorded during clinical examinations and breast imaging, in line with previous reports from Western countries (Loomer et al., 1991). In our study,

Table 4. Univariate and Multivariate Factors Associated with Overall Survival

Factors	Event/total	Univariate		Multivariate	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Stage					
1	2/39	1		1	
2	20/246	1.30 (0.30–5.59)	0.722	1.24 (0.28–5.42)	0.776
3	22/127	3.18 (0.75–13.55)	0.117	2.51 (0.57–11.04)	0.222
Breast cancer subset					
Luminal	28/269	1		1	
Luminal HER2	5/51	0.96 (0.37–2.48)	0.929	0.82 (0.31–2.16)	0.689
Triple-negative	6/50	1.22 (0.51–2.95)	0.656	0.95 (0.36–2.36)	0.855
ER−/HER2+	5/42	1.19 (0.46–3.07)	0.727	0.95 (0.36–2.51)	0.91
Grade					
1	1/38	1		1	
2	21/230	3.65 (0.49–27.15)	0.206	3.19 (0.42–24.27)	0.262
3	19/117	6.89 (0.92–51.45)	0.06	5.81 (0.74–45.38)	0.093
Unavailable	3/27	4.12 (0.43–39.67)	0.22	3.46 (0.34–34.74)	0.292
LVI					
Negative	13/182	1		1	
Positive	13/95	1.86 (0.86–4.02)	0.113	1.32 (0.58–2.96)	0.503
NA	18/135	1.84 (0.90–3.76)	0.094	1.62 (0.78–3.36)	0.198
Follow-up type					
Standard	24/213	1.21 (0.67–2.18)	0.539	0.67 (0.18–2.45)	0.541
Alternative	20/199	1		1	
Surveillance CXR					
Yes	17/167	0.84 (0.47–1.54)	0.569	0.68 (0.21–2.22)	0.525
No	27/245	1		1	
Surveillance LFT					
Yes	9/125	0.56 (0.27–1.17)	0.122	0.49 (0.20–1.21)	0.122
No	35/287	1		1	

CI, confidence interval; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; NA, not available; LVI, lympho-vascular invasion; CXR, Chest X-ray: LFT, Liver function test

the standard follow-up group underwent follow-up as recommended by ASCO in 2013, which recommended only clinical examination and annual breast imaging. Both overall survival and disease-free survival were similar between the groups. Our standard surveillance approache corresponds with a guideline developed from European Society Medical Oncology (ESMO) which also supported clinical evaluation and annual breast imaging only (Cardoso et al., 2019). The recurrence rate in our study was similar that in a previous study conducted in Thailand (Chairat et al., 2014). Therefore, our study indicated that patients with breast cancer in Thailand do not benefit from alternative diagnostic tests performed in addition to routine medical surveillance.

Our study is the first to demonstrate the follow-up patterns of patients with breast cancer in Thailand in the modern era with markedly advanced and effective systemic therapy. Although limited patients with recurrent breast cancer were included in our study, we described a retrospective cohort with an adequate follow-up duration. Additional diagnostic tests such as chest X-ray or blood chemistry might increase the workload of radiologists and laboratory technicians. The routine use of more intensive follow-up both results in the consumption of additional resources and leads to additional tests because of equivocal results or insignificant lesions. Moreover, intensive follow-up possibly causes unnecessary anxiety in patients with false-positive results. According to a study in France, the cost of intensive follow-up was 2.2–3.6-fold higher than that of standard follow-up (Mille et al., 2000). Further analysis of the financial impact of the follow-up strategy in Thailand might result in cost savings.

Conversely, intensive follow-up might enhance early disease detection rates, thereby permitting proper and timely management. In our retrospective study, three patients with disease recurrence could not undergo systemic treatment because of their poor performance status. However, this phenomenon was not significantly different between the two groups. Based on previous randomized trials together with our retrospective cohort reflecting the modern era, the earlier detection of metastatic disease using any investigation modality has not improved oncologic outcomes. Larger populations and randomized controlled studies are needed to reassess

Table 5. Univariate and Multivariate Factors Associated with Disease-Free Survival

Factors	Event/total	Univariate		Multivariate	
		Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Stage					
1	6/38	1		1	
2	44/246	0.95 (0.40–2.23)	0.901	0.88 (0.37–2.10)	0.773
3	40/127	1.93 (0.82–4.57)	0.133	1.69 (0.69–4.13)	0.248
Breast cancer subset					
Luminal	57/269	1		1	
Luminal HER2	13/51	1.26 (0.69–2.30)	0.453	1.02 (0.55–1.90)	0.948
Triple-negative	10/50	0.99 (0.50–1.93)	0.966	0.95 (0.46–1.94)	0.881
ER−/HER2+	10/41	1.26 (0.65–2.48)	0.494	1.14 (0.57–2.27)	0.715
Grade					
1	4/38	1		1	
2	51/229	2.78 (0.82–6.30)	0.113	2.01 (0.71–5.70)	0.191
3	25/117	2.28 (0.79–6.60)	0.125	1.97 (0.65–5.95)	0.228
Unavailable	10/27	4.34 (1.36–13.84)	0.013	3.75 (1.13–12.45)	0.031
LVI					
Negative	33/181	1		1	
Positive	27/95	1.58 (0.95–2.63)	0.078	1.19 (0.69–2.05)	0.525
NA	30/135	1.21 (0.74–1.99)	0.448	1.13 (0.68–1.86)	0.647
Follow-up type					
Standard	53/213	1.47 (0.97–2.24)	0.072	0.80 (0.30–2.13)	0.655
Alternative	37/198	1		1	
Surveillance CXR					
Yes	31/166	0.69 (0.45–1.07)	0.099	0.66 (0.28–1.59)	0.357
No	59/245	1		1	
Surveillance LFT					
Yes	17/124	0.50 (0.29–0.84)	0.01	0.48 (0.24–0.96)	0.037
No	73/287	1		1	

CI, confidence interval; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; NA, not available; LVI, lympho-vascular invasion; CXR, chest X-ray; LFT, liver function test

whether proper intensive follow-up strategy increases the likelihood of breast cancer-specific treatment or leads to improved survival among patients with breast cancer in the modern era.

Since biology of breast cancer impacts patterns of recurrence including sites of metastasis and timing of recurrence (Kennecke et al., 2010; Jatoi et al., 2011; Metzger-Filho et al., 2013), it is interesting to determine optimal follow up or surveillance schedule designed more specifically for individual breast cancer subtypes. Subset analysis looking at ER+ breast cancer patients showed no additional benefit of alternative surveillance measure compared to standard surveillance protocol. Patients with HER2+ breast cancer in our cohort recruited in standard follow-up group experienced higher recurrence compared to alternative follow-up group. This phenomenon could be a result of higher proportion of patients in alternative follow up group received adjuvant trastuzumab (46% vs 26%, p = 0.04). Multivariate analysis demonstrated association of alternative follow-up protocol and better disease-free survival among patients with HER2+ breast cancer. However, the advantage of alternative follow-up protocol in HER2+ subgroup did not translate to overall survival benefit. Based on our report, alternative follow-up surveillance protocol might provide meaningful benefit to early disease recurrence detection for patients with HER2-positive breast cancer.

The limitations of this study included its retrospective design, which resulted in variation of the follow-up strategies and limited the sample size. Patients categorized into the alternative follow-up group were heterogeneous. Moreover, the result from our study reflected oncologic practice during the past decade when the targeted therapy was widely available, but it may not totally reflect the current practice when numerous newly approved targeted drugs have emerged. Another unknown issue is the intensity of surveillance needed to detect disease recurrence. The alternative surveillance measures used in our hospital may not be sufficient to detect early disease recurrence. Although PET/CT scan is more sensitive to detect metastatic disease (Vogsen et al., 2021), the value of PET/CT evaluation to detect recurrence in asymptomatic patients is still low (Taghipour et al., 2016). In the future, sensitive imaging or emerging molecular diagnostics, such

Table 6. Univariate and Multivariate Factors Associated with Disease-Free Survival in HER2-Positive Breast Cancer Patients

Factors	Event/total	Univariate		Multivariate	
		Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Follow up patterns					
Standard	17/47	3.28 (1.29-8.32)	0.013	4.24 (1.54-11.68)	0.005
Alternative	6/45	1		1	
Surveillance chest X-ray					
Yes	5/38	0.34 (0.12-0.90)	0.031	0.31 (0.11-0.88)	0.027
No	18/54	1		1	
Surveillance liver function test					
Yes	3/26	0.33 (0.10-1.12)	0.076	0.30 (0.09-1.03)	0.055
No	20/66	1		1	
Neo-Adjuvant regimen					
Yes	5/15	1.56 (0.58-4.20)	0.38	2.20 (0.66-7.33)	0.2
No	18/77	1		1	
Anti HER2					
Yes	9/35	1.01 (0.44-2.33)	0.986	0.67 (0.26-1.73)	0.407
No	14/57	1		1	

CI, confidence interval; HER2, human epidermal growth factor receptor 2; Multivariate adjusted hazard ratio for stage, breast cancer subsets, grade, and lympho-vascular invasion.

Table 7. Time to Recurrence and Disease Outcomes in Patients with Recurrence

	Standard follow-up Total = 53	Alternative follow-up Total = 37	p
Median time to recurrence	39.4 months	45.16 months	0.236
median (IQR)	(19.13–62.30)	(29.17–65.60)	
Time from suspicion of recurrence to treatment	50 days	42 days	0.525
Median (IQR)	(25.00–91.00)	(16.00–77.00)	
Time from suspicion of recurrence to progressive disease	13.07 months	10.97 months	0.715
Median (IQR)	(4.23–29.90)	(5.77–23.43)	
Time from definite recurrence to progressive disease	12.33 months	7.87 months	0.709
Median (IQR)	(3.00–27.70)	(4.40–23.10)	

Comparisons of medians between the two groups were performed using the Mann–Whitney U test. IQR, interquartile range

as circulating tumor cells or circulating DNA detection, might play role to the early detection of relapse. Another limitation of this study was its single-institutional nature, which could limit the applicability to patients in other institutions.

In conclusion, standard follow-up schedules with history assessments, physical examination, and annual breast imaging should remain the standard follow-up strategy in this era. Additional follow-up with chest X-ray, chemistry panels, or liver ultrasound did not improve overall survival and disease-free survival among patients with breast cancer who had completed curative-intent therapy. However, there is a trend of benefit of using alternative follow-up protocol for patients with HER2-positive breast cancer. Further research is needed to identify potential efficacious tools and determine specific subgroup that will benefit the most from more aggressive follow-up protocol in order to better detect disease recurrence or facilitate early treatment, which may improve breast cancer treatment outcomes.

Author Contribution Statement

Study concepts: SI. Study design: SI, NL. Data acquisition: SI, NL, CW. Quality control of data and algorithms: SI, CW. Data analysis and interpretation: All authors. Statistical analysis: SI, CW, Manuscript preparation: SI. Manuscript editing: All authors. Manuscript review: All authors. All authors have read and approved the manuscript.

Acknowledgements

We thank Miss Khemjira Karnkejklang, Department of Medicine, Faculty of Medicine Siriraj Hospital, for her statistical review.

Study approval and funding sources

The study was approved by Siriraj Institutional Review Board. It is not the part of an approved student thesis. There was no funding for the study.

Data availability

The data analyzed in this study are available from the corresponding author, (Suthinee Ithimakin, E-mail: aesi105@yahoo.co.th) on reasonable requests.

Conflict of interest

The authors have no conflict of interest to declare.

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