

Effectiveness and safety of hypofractionated radiation therapy in postmastectomy breast cancer

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Objectives Hypofractionated radiotherapy (HFRT) is an alternative treatment in postmastectomy breast cancer women. This study was conducted to assess the effectiveness and safety of HFRT at the Chonburi Cancer Hospital by evaluating the outcomes of treatment.

Methods Clinical and demographic characteristics of 486 breast cancer patients with mastectomy who had received complete adjuvant radiotherapy treatment between January 2012 and December 2015 were retrospectively analyzed. All patients had received HFRT 2.65-2.67 Gy daily for 15-18 fractions for a total dose of 39.75-47.86 Gy. The study outcomes included 5-year local recurrence free survival (LRFS), disease free survival (DFS), and overall survival (OS) including grade 2 or more acute and late toxicities in different age groups.

Results The median follow-up was 66.1 months (range 2.1-100.4 months). Five-year LRFS was 93.7%, five-year DFS was 61.5% and 5-year OS was 66.4%. There was slightly higher grade 3 arm edema and cardiovascular toxicity in the > 60 age group. There were no differences in the incidence rates of other toxicities including skin atrophy, subcutaneous tissue fibrosis, brachial plexopathy and pulmonary fibrosis among the different age groups.

Conclusions The implementation of HFRT in postmastectomy breast cancer patients is both effective and safe. HFRT is particularly beneficial during the COVID-19 pandemic as it consumes fewer hospital resources. **Chiang Mai Medical Journal 2021;60(4):415-26. doi: 10.12982/CMUMEDJ.2021.37**

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Introduction

The most commonly diagnosed cancer among Thai women is breast cancer. Unlike most other malignancies, the prognosis for patients with a locally advanced disease is favorable. Multidisciplinary treatment of breast cancer includes surgery, chemotherapy and/or targeted therapy, hormonal therapy and radiotherapy. Locoregional control and increased overall survival in locally advanced post mastectomy breast cancers have been shown to improve with the use of radiotherapy (1-4).

Conventional radiotherapy fractionation (CFRT) traditionally involves giving a dose of 2-Gy daily over 5-6 weeks at the postmastectomy chest wall and/or supraclavicular area. In addition, the radiobiological model of breast cancer tissue treatment using hypofractionated radiotherapy (HFRT) has been reported to be as effective as the conventional schedule (5). HFRT has been used as an adjuvant to breast conserving surgery and has become a standard fractionation in radiation treatment with results documented by large randomized

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trials (6-8). However, in spite of many reports showing similar efficacy and toxicity of HFRT and CFRT (9-11) in postmastectomy radiation therapy (PMRT), HFRT is still not a standard part of postmastectomy radiation (PMRT) care in most countries.

Since 2012, radiotherapy resources have been occasionally limited in the eastern part of Thailand. In 2012, we introduced HFRT for the treatment of postmastectomy breast cancers at the Chonburi Cancer Hospital. Prior to that, the authors had already demonstrated that treatment outcomes of HFRT and CFRT are comparable (12). The authors also conducted a follow-up study to monitor long term toxicities of HFRT with a larger number of patients and longer follow-up. This report is an update of our 2019 evaluation of hypofractionated radiotherapy.

Methods

Patients

The clinical and demographic data of female postmastectomy breast cancer patients who received complete adjuvant radiotherapy with HFRT schedules at the Chonburi Cancer Hospital during January 2012 to December 2015 were retrospectively reviewed. Patients with breast cancer categorized as stage II or III using the American Joint Committee on Cancer staging version 7 and who had histologically proven invasive epithelial breast cancer were enrolled in the study (13). Patients were excluded if there was evidence of a surgical margin of mastectomy specimen of less than 1 mm, immediate postmastectomy reconstruction, bilateral breast cancer, inadequate medical records, a history of systemic lupus erythematosus, scleroderma or previous breast/chest irradiation.

The demographic and clinicopathological data included age, cancer staging, histopathology, hormonal status, chemotherapy, targeted therapy, hormonal treatment, radiotherapy field and total doses. Chemotherapy regimens included anthracycline, taxanes and cyclophosphamide, methotrexate, 5-fluorouracil (CMF). Adjuvant targeted therapy included trastuzumab while hormonal treatment involved tamoxifen and aromatase inhibitors.

Radiotherapy

All patients were placed in a supine position on a breast board with ipsilateral arm support using a 2D conventional simulator. They received treatment with a SIEMENS MEVATRON MX2 or VARIAN CLINAC CX 2300C linear accelerator 6MV machine. The target volume included the chest wall either with or without axillary, and the supraclavicular lymph nodes. Radiotherapy was given as tangential and anteroposterior supraclavicular fields. A bolus over the chest wall field was used daily for the first half of the radiotherapy course. Patients with positive dissected axillary lymph nodes were given an anterior supraclavicular field. Some patients diagnosed to be in stage T2N0 with the presence of lymphovascular invasion (LVI), tumor grade 3, inadequate node dissection (less than 10 nodes) and/or negative hormone receptor and HER2 receptor (triple negative) also received anterior supraclavicular field. Axillary boost was given if there was clinical N2 disease and inadequate node excision or extracapsular nodal extension (ENE). The internal mammary nodes (IMN) were irradiated in a separate single field in some patients. The patients were irradiated with a hypofractionated schedule of 39.75-47.86 Gy (2.65-2.67 Gy in 15-18 fractions). Some patients received an additional chest wall boost with conventional fractionation (10 Gy in 5 fractions) when ordered by a radiation oncologist for the benefit of the patient.

The average total dose of HFRT per patient in the study is equivalent to a dose of 2 Gy per fraction as 44.52-54.2 Gy according to the α/β ratio of 3.0 Gy for breast cancer. Patients who had a chest wall boost received a total dose of 58.18 Gy.

Endpoints

The primary endpoints included loco-regional recurrence free survival (LRFS), disease-free survival (DFS), and overall survival (OS). LRFS is defined as the time from the date of surgical treatment to in-field radiotherapy recurrence. DFS is defined as the time from the date of surgical treatment to any breast cancer related events (loco-regional recurrence and distant metastasis) or

death. OS defined as the time from the date of surgical treatment to death.

The secondary endpoints of this study were grade 2 or higher acute and late toxicities in HFRT as assessed using RTOG/EORTC radiation morbidity scoring criteria (14). The brachial plexopathy was evaluated using a modified LENT/SOMA scale (15). The Chonburi Cancer Hospital's Lymphedema score developed by the department of surgery was adapted from Canadian clinical practice guidelines for the care and treatment of breast cancer, was used for evaluating lymphedema (16). Arm circumference was measured at the middle of the dorsum of the hand at the wrist level and 10 cm above and below the lateral epicondyles, and was compared with the opposite arm. The greatest difference during follow-up was taken as the final measurement. The scale used for scoring lymphedema is shown in Table 1. All patients were assessed for acute/late toxicities weekly during radiotherapy, at 6 weeks after the end of radiotherapy, and then every 3-6 months. A follow-up phone interview was conducted with some patients who could not return to the hospital in person. The Ethics Committee of the authors' hospital approved the study. Informed consent to participate in the study was obtained by mailing an informed consent document to the potential patient for her agreement to use her collected data. The signed document was returned by mail.

Statistical analysis

SPSS statistical software version 22 (SPSS Inc., Chicago, IL, USA) was used to perform data analysis. Descriptive statistics were used to analyze clinicopathological and treatment data, reported as number and percentage. The Kaplan-Meier method was used to determine five-year and seven-year loco-regional recurrence free survival, disease-free survival and overall survival rates. Univariate and multivariate analysis with backward elimination (p -to-remove > 0.10) were performed to identify the prognostic factors associated with locoregional recurrence and overall survival using the Cox proportional hazards model to calculate the hazard ratio with 95% CI.

Table 1. Chonburi Cancer Hospital's Lymphedema score by arm circumference

Score	Difference in arm circumference
Grade 0	No difference
Grade 1	< 2 cm
Grade 2	2-5 cm
Grade 3	> 5 cm

The results were considered statistically significant if the $p < 0.05$.

Results

Patient characteristics

A total of 486 patients were eligible and were enrolled in this study. The median age was 50 years (range 26 to 81 years). The median follow-up time was 66.1 months (range 2.1 to 100.4 months). Patient characteristics are shown in Table 2. The maximum lung distance included in the radiation field was 3.5 cm with a mean of 1.7 cm (range 0-3.5 cm). The physical dose range was 39.75-47.86 Gy.

Disease control

At the median follow up time of 66.1 months, 271 (55.8%) of the patients had no evidence of recurrence or metastasis while 22 (4.5%) were alive but had progression of disease. A total of 193 patients had died at the time of the analysis of whom 163 (33.5%) died from cancer, 18 (3.7%) died from other causes and 12 (2.5%) died from unknown causes. Of the 486 patients, 6.1% had locoregional recurrences (LRR) with the most common sites being the chest wall, the supraclavicular and the axillary lymph nodes in that order. Distant relapse was found in 36.8% of patients, with lungs being the most frequent site followed by bone, liver and brain. Overall, the 5-yr LRFS was 93.7% (95% CI: 91.3-96.1, Figure 1A), DFS was 61.5% (95% CI: 57.2-65.8, Figure 1B) and OS was 66.4% (95% CI: 62.2-70.6, Figure 1C). The 7-year LRFS was 92.8% (95% CI: 90.0-95.5, Figure 1A), DFS was 55.6% (95% CI: 50.9-60.2, Figure 1B) and OS was 59.6% (95% CI: 55.1-64.2, Figure 1C). Univariate analysis (shown in Table 3) revealed that cancer stage III, LVI and ENE were

Table 2. Patient characteristics (N = 486)

Characteristics	N (%)
Age	
< 40	70 (14.4)
40-60	340 (70.0)
> 60	76 (15.6)
Cancer staging	
II*	168 (34.6)
III*	318 (65.4)
Histopathology	
Invasive ductal	463 (95.3)
Invasive lobular	9 (1.8)
Other	14 (2.9)
Grade	
1	22 (4.5)
2	238 (49.0)
3	197 (40.5)
Unknown	29 (6.0)
Side	
Right	250 (51.4)
Left	236 (48.6)
Tumor stage	
T1	37 (7.6)
T2	276 (56.8)
T3	108 (22.2)
T4	65 (13.4)
Nodal stage	
N0	74 (15.2)
N1	154 (31.7)
N2	159 (32.7)
N3	99 (20.4)
Number of node dissections	
0-9	109 (22.4)
10 or more	377 (77.6)
Lymphovascular invasion	
Negative	287 (59.0)
Positive	199 (41.0)
Extracapsular nodal extension	
Negative	412 (84.8)
Positive	74 (15.2)
ER	
Negative	182 (37.4)
Positive	289 (59.5)
Unknown	15 (3.1)
PR	
Negative	262 (53.9)
Positive	208 (42.8)
Unknown	16 (3.3)

Table 2. Patient characteristics (N=486)

Characteristics	N (%)
HER2	
Negative (0/+1/+2)	339 (69.8)
Positive (+3) or ISH +	124 (25.5)
Unknown	23 (4.7)
Type of chemotherapy	
None	1 (0.2)
Neoadjuvant	43 (88.5)
Adjuvant	380 (78.2)
Neoadjuvant + adjuvant	62 (12.8)
Chemotherapy regimen	
None	1 (0.2)
Antracyclin-based	134 (27.6)
Taxane-based	339 (69.8)
CMF	6 (1.2)
Unknown	6 (1.2)
Trastuzumab	
No	463 (95.3)
Yes	23 (4.7)
Hormonal treatment	
None	208 (42.8)
Tamoxifen	204 (42.0)
Aromatase inhibitors	41 (8.4)
Tamoxifen + aromatase inhibitors	33 (6.8)
Radiotherapy field	
Chest wall	21 (4.3)
Chest wall + IMN	3 (0.6)
Chest wall + SPC	366 (75.3)
Chest wall + SPC + axilla boost	82 (16.9)
Chest wall + SPC + IMN	9 (1.9)
Chest wall + SPC +	5 (1.0)
IMN + axillary boost	
Dose per fraction (Gy)	
2.65	49 (10.1)
2.66	413 (85.0)
2.67	24 (4.9)
Axilla irradiation	87 (17.9)

*For patients who did not receive neoadjuvant chemotherapy, we used pathological stage as it is more accurate than clinical stage. For patients who received neoadjuvant chemotherapy, we used whichever stage was higher (clinical or pathological) to reflect the actual tumor burden.

ER, estrogen receptor; HER 2, human epidermal growth factor receptor 2; N, regional lymph nodes; PR, progesterone receptor; T, primary tumor

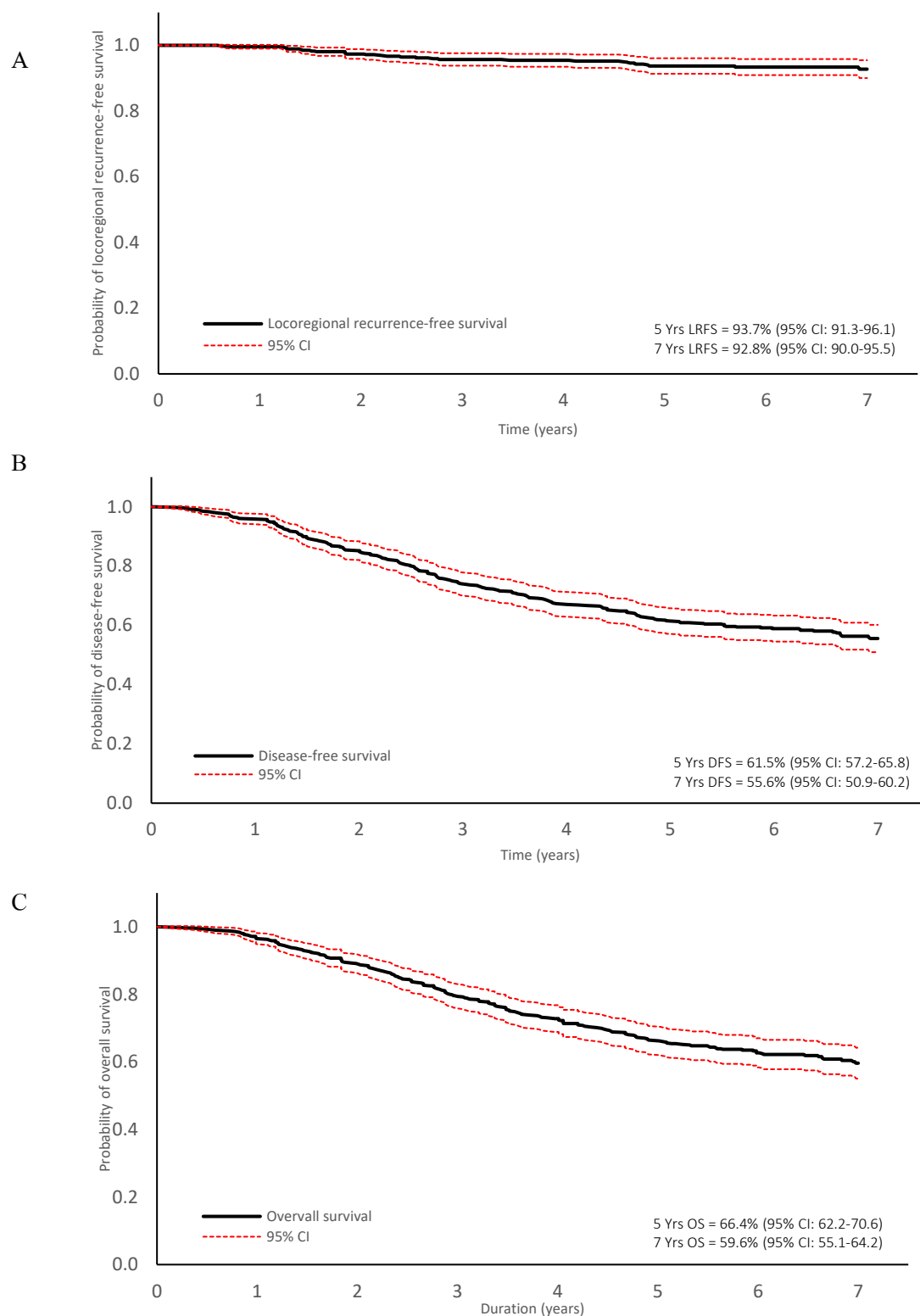


Figure 1. Kaplan-Meier curves of Loco-Regional Recurrence Free Survival Rate (A); disease-free survival rate (B); overall survival rate (C)

Table 3. Univariate and multivariate analysis of correlation with locoregional recurrence

Variables	Event/n	Univariate		Multivariate	
		HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age (years)			0.35		
< 40	3/70	1		1	
40-60	25/340	1.61 (0.49-5.33)		-	
60 or more	2/7	0.64 (0.11-3.83)		-	
Cancer staging			0.04		0.06
II	6/168	1		1	
III	24/318	2.535 (1.035-6.21)		2.60 (0.97-6.95)	
Tumor stage			0.32		
T1 & T2	18/313	1		1	
T3 & T4	12/173	1.45 (0.70-3.02)		-	
Nodal stage			0.08		
N0 & N1	10/228	1		1	
N2 & N3	20/258	1.95 (0.91-4.16)		-	
Lymphovascular invasion (LVI)			0.04		
Negative	13/287	1		1	
Positive	17/199	2.09 (1.01-4.31)		-	
Extracapsular nodal extension (ENE)			0.02		0.05
Negative	21/412	1		1	
Positive	9/74	2.48 (1.135-5.42)		2.24 (1 -5.03)	
ER			0.81		
Negative	10/182	1		1	
Positive	20/304	1.10 (0.51-2.34)		-	
PR			0.34		
Negative	13/262	1		1	
Positive	17/224	1.42 (0.69-2.92)		-	
Histology			0.90		
IDC	29/463	1		1	
ILC	1/9	1.60 (0.22-11.75)		-	
Other	0/14	0		-	
Grade			0.72		
1	1/22	1		1	
2	17/238	1.82 (0.24-13.72)		-	
3	10/197	1.41 (0.18-11.04)		-	

Variables were excluded from the equation when *p*-to-remove was greater than 0.10; age, 40-60 years (*p* = 0.22); > = 60 years (*p* = 0.25); tumor stage, T3&T4 (*p* = 0.54); nodal stage, N2&N3 (*p* = 0.82); lymphovascular invasion, positive (*p* = 0.16); ER status, positive (0.97); PR, positive (*p* = 0.46); histology, ILC (*p* = 0.76), other (*p* = 0.51); grade, 1 (*p* = 0.37), 2 (*p* = 0.53)

IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma

significantly unfavorable prognostic factors for LRR. Age group was not an unfavorable prognostic factor. Nevertheless, multivariate analysis identified no significant prognostic factors related to LRR. The univariate analysis of correlation of parameters with overall survival (Table 4) revealed

that cancer stage III, tumor stage 3-4, nodal stage 2-3, LVI and tumor grade 2-3 were significantly correlated with OS, but were not correlated with age group. Multivariate analysis also indicated that age group was not associated with OS.

Table 4. Univariate and multivariate analysis of factors correlated with overall survival

Variables	Event/n	Univariate		Multivariate	
		HR (95% CI)	p-value	HR (95% CI)	p-value
Age (years)			0.11		
< 40	30/70	1		1	
40-60	126/340	0.81 (0.55-1.21)		-	
60 or more	37/76	1.18 (0.73-1.91)		-	
Cancer staging			< 0.001		< 0.001
II	44/168	1		1	
III	149/318	2.20 (1.57-3.08)		1.92 (1.34-2.75)	
Tumor stage			< 0.001		< 0.001
T1 & T2	102/313	1		1	
T3 & T4	91/173	1.97 (1.48-2.61)		1.93 (1.43-2.61)	
Nodal stage			0.01		
N0 & N1	79/228	1		1	
N2 & N3	114/258	1.43 (1.07-1.91)		-	
Lymphovascular invasion (LVI)			0.01		0.004
Negative	99/287	1		1	
Positive	94/199	1.50 (1.13-1.99)		1.56 (1.15-2.12)	
Extracapsular nodal extension (ENE)			0.42		0.03
Negative	168/412	1		1	
Positive	25/74	0.84 (0.55-1.28)		0.61 (0.39-0.95)	
ER			0.11		
Negative	78/182	1		1	
Positive	115/304	0.79 (0.59-1.05)		-	
PR			0.10		
Negative	111/262	1		1	
Positive	82/224	0.79 (0.59-1.05)		-	
Histology			0.17		
IDC	189/463	1		1	
ILC	1/9	0.23 (0.03-1.67)		-	
Other	3/14	0.49 (0.16-1.53)		-	
Grade			0.01		0.01
1	2/22	1		1	
2	93/238	5.02 (1.24-20.37)		5.43 (1.34-22.05)	
3	89/197	6.61 (1.63-26.84)		7.085 (1.74-28.79)	

Variables were excluded from the equation when p-to-remove was greater than 0.10; age, 40-60 years ($p = 0.11$), ≥ 60 years ($p = 0.40$); Nodal stage, N2&N3 ($p = 0.69$); ER status, positive ($p = 0.20$); PR, positive ($p = 0.11$); histology, ILC ($p = 0.34$), other ($p = 0.18$)

IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma

Treatment toxicities

Both acute and late toxicities classified by age group are shown in Table 5. The most common acute toxicity was radiation dermatitis. Overall grade 2 skin toxicity was reported in 42 patients (8.6%). There were no significant differences of grade 2 skin toxicities in the age groups 40-60 or

> 60 (8.5% vs. 7.9%), although skin toxicity was slightly higher in the age group < 40 (10%). No grade 2 pneumonitis or esophagitis was found in any of the patients.

Thirty-one patients died before being evaluated for late toxicity, so only 455 patients were evaluated. Skin atrophy grade 2 occurred in 12 patients

Table 5. Treatment-related toxicities classified by age group (N=486)

Treatment toxicities	Prevalence								
	Age < 40 (N=70) (%)			Age 40-60 (N=340) (%)			Age > 60 (N=76) (%)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Acute	N=70			N=340			N = 76		
Dermatitis	31 (44.3)	7 (10)	0	136 (40)	29 (8.5)	0	29 (38.2)	6 (7.9)	0
Pneumonitis	0	0	0	3 (0.9)	0	0	0	0	0
Esophagitis	0	0	0	1 (0.3)	0	0	0	0	0
Late	N=65 (NA 5)			N=321 (NA 19)			N=70 (NA 6)		
Skin atrophy	48 (73.8)	2 (3.1)	0	227 (70.7)	7 (2.2)	0	45 (64.3)	3 (4.3)	0
Subcutaneous tissue fibrosis	44 (67.7)	2 (3.1)	0	214 (66.7)	8 (2.5)	0	47 (67.1)	2 (2.9)	1 (1.4)
Cardiovascular events	3 (4.6)	0	0	2 (0.6)	0	1 (0.3)	1 (1.4)	0	4 (5.7)
Esophageal stricture	0	0	0	1 (0.3)	0	0	1 (1.4)	0	0
Shoulder stiffness	2 (3.1)	0	0	14 (4.4)	2 (0.6)	1 (0.3)	5 (7.2)	1 (1.4)	0
Arm edema	3 (4.6)	0	1 (0.6)	13 (4.0)	13 (4.0)	3 (1.0)	2 (2.8)	3 (4.3)	3 (4.3)
Brachial plexopathy	4 (6.2)	0	0	24 (7.5)	2 (0.6)	0	7 (10.0)	0	0
Lung fibrosis (clinical)	0	0	0	7 (2.9)	0	0	1 (2.0)	0	0
Lung fibrosis (chest film)	7 (41.2)	0	0	32 (42.1)	0	0	7 (36.8)	1 (5.3)	0

All other data are presented as the number (%) of patients.

*31 patients died before late toxicity assessment, therefore late toxicity could be evaluate in only 455 patients.

**Chest film was evaluated for late toxicity in 112 patients, 17 patients (26.1%) in age group < 40, 76 patients (23.7%) in age group 40-60, and 19 patients (27.1%) in age group > 60 respectively.

***No grade 4 toxicities were found in this study.

(2.6%) and was identified in all three age groups (3.1%, 2.2% and 4.3%). Subcutaneous fibrosis grade 2 toxicity was not significantly different among the age groups (3.1%, 2.5% and 2.9%). Only 1.4% of patients from the age group > 60 had grade 3 fibrosis. Grade 2-3 arm edema occurred in 5% of patients. No grade 2 arm edema was found in age group < 40 and there were no differences in grade 2 between the age groups 40-60 and > 60 (4.0% vs. 4.3%). Nevertheless, grade 3 arm edema in 4.3% of the age group > 60 was slightly higher than the 1.6% in the age group < 40 and 1% in the age group 40-60. Grade 2 brachial plexopathy was merely 0.4% overall whereas no grade 3 was found.

Development of grade 2-3 shoulder stiffness was insignificant at 0.9% and 1% in age groups 40-60 and > 60. In the lungs and heart, important organs in the radiation field, grade 3 cardiovascular toxicities were identified in 1.1% of patients.

However, there were 0.3% in the age group 40-60 and 5.7% in the age group > 60. The maximum grade of lung fibrosis was grade 2; 5.3% of patients in the age group > 60 had grade 2 lung fibrosis as identified by chest x-ray, but none showed symptoms. No grade 2-3 esophageal stricture was identified in any of the patients.

Discussion

HFRT is an alternative treatment in postmastectomy breast cancer women, but it requires further evaluation regarding the benefit to patients. The authors' previous study found that the 5-yr LRFS, DFS and OS of patients who had received HFRT were not significantly different from the CFRT group. In this study, a larger number of patients were added to increase the statistical power. The results of HFRT in 5-yr LRFS, DFS and OS were 93.7%, 61.5% and 66.4%, respectively. Seven-year LRFS, DFS and OS were 92.8%, 55.6%, and

59.6%, respectively. The 5-yr DFS and OS were lower than the 5-yr DFS and OS of 72% and 74% reported in a Chiangmai University study (11). When the authors performed subgroup analysis of 5-yr LRFS, DFS and OS stratified by cancer stages, they found 5-yr DFS and OS in stage III were significantly lower at 53.4% and 59.1% compared to stage II 5-yr DFS and OS of 76.8% and 80.4%. However, 65.4% of patients in this study were in stage III, so this might have led to lower percentages of 5-yr DFS and OS. This study found that overall 6.2% of patients had LRR, and that 0.6% were in the age group < 40, 5.1% in the age group 40-60 and 0.6% in the age group > 60. Factors potentially affecting locoregional control were explored further. The results of univariate analysis showed that LVI and ENE were significantly associated with LRR, whereas age group was not. These findings are similar to the results from a study in Poland (17). In addition, univariate and multivariate analysis of factors potentially correlated with OS revealed that age group was not associated with OS, whereas cancer stage III, tumor stage 3-4, LVI, ENE and tumor grade 2-3 were associated with OS.

Minimizing toxicity is an important objective in radiotherapy. In this study neither acute toxicity of HFRT nor grade 2 radiation dermatitis differed by age group. No cases of grade 2 esophagitis or pneumonitis were found. As to late skin toxicity, no significant differences of grade 2 skin atrophy were found among the different age groups, and no grade 3 skin atrophy was observed. Only one patient (0.2%) in the age group > 60 developed grade 3 subcutaneous tissue fibrosis, while grade 2 subcutaneous tissue did not differ by age group.

Lymphedema emerges in up to 42% of patients following breast cancer treatment. Severity is associated with the number of axillary lymph node dissections, and is higher when the number of lymph nodes dissections ≥ 10 and is worse when combined with axillary radiation (18). Grade 2 arm edema in this study was reported at 4% in the age group 40-60 and 4.3% for the age group > 60, while grade 3 arm edema was highest in the age group > 60. When the authors reviewed the

records 16 patients with grade 2 arm edema, they found 13 had axillary lymph node dissection of from 10-37 nodes and 3 out of the thirteen patients had also received axillary boost. The other three patients were found to have had less than 10 axillary lymph node dissections, but they had received axillary boost. The three patients who had grade 3 arm edema in the age group > 60 we found to have greater than 15 axillary lymph node dissections. In the other age groups, grade 3 was found in patients with more than 10 axillary lymph node dissections and/or patients who had received axillary boost. Thus, axillary lymph node dissection of ≥ 10 nodes and axillary boost were associated with lymphedema in PMRT and might be the cause of the grade 2-3 arm edema found in this study.

In the authors' previous report, late cardiotoxicity in the HFRT group was not seen; however, in the present study, late grade 3 cardiotoxicity was found in 4 patients (5.7%) in the age group > 60 compared to one patient (0.3%) in the age group 40-60. Many studies have reported on factors that influence late cardiac adverse effects in PMRT, e.g., left side chest wall RT, and comorbidities (diabetes, hypertension, dyslipidemia) and BMI ≥ 25 (18-20). Out of five patients in our study who received RT, three received the RT at the left chest wall. Those three patients also had comorbidities (DM, hypertension and dyslipidemia) and two of them had a BMI greater than 25, while the other two patients had no comorbidities at first diagnosis but had received IMN RT. Another study reported that anthracycline-based chemotherapy and IMN irradiation (2D technique) substantially increases the incidence of several cardiovascular diseases (21), suggesting that under those circumstances, late grade 3 cardiotoxicity could occur. However, the overall incidence of late grade 3 cardiotoxicity (1.1%) in this study was minimal and comparable to the results of other HFRT studies (0.6-1.6%) and to conventional fractionation (0.6-1%) (9,10, 22). Pulmonary fibrosis grade 2 (evaluated by chest x-ray) was found in only one patient (0.9%) who was in the age group > 60. However, that patient was asymptomatic.

Brachial plexopathy can develop following radiation. This form of late toxicity is associated with surgical procedures involving axilla, chemotherapy and supraclavicular radiation (18,23). A review of the literature from Poland revealed the risk of radiation-induced brachial plexopathy in HFRT to be smaller than 1% using schedules with doses per fraction between 2.2 and 2.5 Gy and a total dose of between 34 and 40 Gy (23). Grade 2 brachial plexopathy in this study was only 0.6%, indicating the HFRT schedule did not increase the risk of brachial plexopathy. In addition, only a low percentage of grade 2 (0.6%) and 3 (0.3%) of shoulder stiffness were seen and no grade 2-3 esophageal stricture was found.

Currently the Chonburi Cancer Hospital has converted from using 2D to 3D radiotherapy planning for postmastectomy breast cancer which is more advantageous in dose homogeneity, and minimizes toxicity to normal tissue, making HFRT safer for postmastectomy breast cancer patients.

The main limitation of this study was that the study was retrospective. Additionally, some patients had follow-up visits at other hospitals leading to incomplete medical records. Therefore, outcomes, especially those related to toxicity, could have been under reported.

Conclusions

HFRT is effective and safe for postmastectomy breast cancer patients of all ages. Even with the longer follow-up time and larger number of patients recruited into this study, the authors did not see any of the significant differences in grade 2 or higher toxicities reported in other studies. HFRT and CFRT have similar effectiveness, but HFRT requires a shorter period of treatment which is an additional benefit during the COVID-19 pandemic as it reduces hospital visits for radiation treatment and thus decreases the risk of COVID-19 exposure.

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Conflict of interests

The authors declared no conflicts of interests.

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ประสิทธิผลและความปลอดภัยของการฉายรังสีแบบสัดส่วนน้อยกว่ามาตรฐานในผู้ป่วยมะเร็งเต้านมหลังการผ่าตัดเต้านมทั้งเต้า

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มหาวิทยาลัยนวมินทราชินา, ³กลุ่มงานเคมีบำบัด โรงพยาบาลมะเร็งชลบุรี จังหวัดชลบุรี

วัตถุประสงค์ การฉายรังสีแบบสัดส่วนน้อยกว่ามาตรฐานเป็นวิธีการฉายรังสีอีกรูปแบบหนึ่งนอกเหนือจากการฉายรังสีแบบมาตรฐานในผู้ป่วยมะเร็งเต้านมหลังการผ่าตัดเต้านมทั้งเต้า ซึ่งการศึกษานี้จัดทำขึ้นที่โรงพยาบาลมะเร็งชลบุรีเพื่อประเมินประสิทธิผลและความปลอดภัยของการฉายรังสีวิธีดังกล่าว

วิธีการ การศึกษานี้เป็นการศึกษาย้อนหลังในผู้ป่วยมะเร็งเต้านมที่ได้รับการฉายรังสีเสริมหลังการผ่าตัดเต้านมทั้งเต้า ในช่วงระหว่างเดือนมกราคม พ.ศ. 2555 ถึงเดือนธันวาคม พ.ศ. 2558 โดยมีผู้ป่วยเข้าเกณฑ์ที่กำหนด 486 ราย และได้รับการฉายรังสีแบบสัดส่วนน้อยกว่ามาตรฐาน โดยขนาดรังสีที่ได้รับ 2.65-2.67 เกรย์ต่อวัน จำนวน 15-18 ครั้ง ปริมาณรังสีรวมตั้งแต่ 39.75-47.86 เกรย์ ผลการศึกษาประเมินจากอัตราการรอดชีวิตโดยปราศจากการกลับเป็นซ้ำเฉพาะที่ของโรคที่ 5 ปี, อัตราการรอดชีวิตโดยปราศจากโรคที่ 5 ปี, อัตราการรอดชีวิตที่ 5 ปี และภาวะแทรกซ้อนจากการฉายรังสีระยะเฉียบพลันและระยะยาวที่มีความรุนแรงตั้งแต่ระดับ 2 ขึ้นไป

ผลการศึกษา จากผู้ป่วยจำนวน 486 ราย ค่ามัธยฐานระยะเวลาติดตามผลเท่ากับ 66.1 เดือน (ช่วงระหว่าง 2.1-100.4 เดือน) อัตราการรอดชีวิตโดยปราศจากการกลับเป็นซ้ำเฉพาะที่ของโรคที่ 5 ปีเท่ากับร้อยละ 93.7 อัตราการรอดชีวิตโดยปราศจากโรคที่ 5 ปีเท่ากับร้อยละ 61.5 และอัตราการรอดชีวิตที่ 5 ปีเท่ากับร้อยละ 66.4 จากการศึกษาพบว่าผู้ป่วยมีภาวะแทรกซ้อนระยะยาวแขนบวมและหัวใจและหลอดเลือดที่มีความรุนแรงระดับ 3 ในกลุ่มผู้ป่วยอายุมากกว่า 60 ปีซึ่งสูงกว่าผู้ป่วยกลุ่มอายุน้อยเล็กน้อย อย่างไรก็ตามภาวะแทรกซ้อนอื่น ๆ ได้แก่ ผิวหนังผื่น พังผืดชั้นใต้ผิวหนัง ภาวะการทำงานของต่อมไทรอยด์ผิดปกติ (brachial plexopathy) และการเกิดพังผืดในปอดไม่ต่างกันในแต่ละกลุ่มอายุ

สรุป ผลการศึกษาพบว่าการฉายรังสีแบบสัดส่วนน้อยกว่ามาตรฐานในผู้ป่วยมะเร็งเต้านมที่ผ่าตัดเต้านมทั้งเต้ามีประสิทธิผลและมีความปลอดภัยและการฉายรังสีแบบสัดส่วนน้อยกว่ามาตรฐานยังเหมาะสมที่จะนำมาใช้รักษาผู้ป่วยมะเร็งเต้านมที่ผ่าตัดทั้งเต้าในช่วงการระบาดของโรคติดเชื้อไวรัสโคโรนา 2019 ด้วย เนื่องจากใช้ระยะเวลาในการรักษาโดยรวมสั้นกว่าการฉายรังสีแบบมาตรฐาน **เชียงใหม่เวชสาร 2564;60(4):415-26. doi: 10.12982/CMUMEDJ.2021.37**

คำสำคัญ: การฉายรังสีแบบสัดส่วนน้อยกว่ามาตรฐาน ผู้ป่วยมะเร็งเต้านมหลังการผ่าตัดเต้านมทั้งเต้า