



Radioterapi & Onkologi Indonesia

Journal of Indonesian Radiation Oncology Society



Utilization of hypofractionated radiotherapy for breast cancer among Indonesian Radiation Oncologists during and after pandemic COVID-19

Rafiq Sulistyono Nugroho¹, Elia Aditya Bani Kuncoro², Aida Lufti Huswatun³

¹Radiation Oncologist, Radiotherapy Department, Dr. Saiful Anwar General Hospital, Malang, Indonesia

²Radiation Oncologist, Radiotherapy Department, Ken Saras Hospital, Semarang, Indonesia

³Radiation Oncologist, Radiotherapy Department, Persahabatan Central General Hospital, Jakarta, Indonesia

Article information:

Received: December 2023

Accepted: January 2024

Correspondence:

Rafiq Sulistyono Nugroho

Saiful Anwar General Hospital
Jl. Jaksu Agung Suprpto No.2,
Klojen, Kec. Klojen, Kota
Malang, Jawa Timur 65112

Email:

nugroho83dr@gmail.com

Abstract

Background: The incidence of breast cancer (BC) increases over time. However, the availability of radiotherapy machines is minimal, especially after the COVID-19 pandemic. Hypofractionated radiotherapy (HFRT) may provide a solution for this situation. We intended to evaluate the practice of HFRT for BC patients amongst the Indonesian Radiation Oncologist Society members.

Material and methods: This study uses a Google Form questionnaire distributed personally in early October 2021. Statistical analysis uses descriptive and Chi-square/Fisher tests.

Results: Twenty-nine participants filled out the questionnaire. One-third of participants worked at Academic Hospital and were aged 35 - 45 years old. Most of the participants had working experience of fewer than ten years. 4 (13.8%) and 3 (10.3%) participants preferred HFRT for Whole Breast Irradiation (WBI) with or without regional node irradiation. Only one participant selected HFRT for Post-Mastectomy Radiation Therapy (PMRT). 9 (31%) and 8 (27.5%) participants chose both HFRT and CFRT for postmastectomy with or without reconstruction.

Conclusion: The use of HFRT in routine practice amongst Indonesian RO is still low despite proven clinical benefits. Continuing medical education about evidence-based may increase the translation of clinical trials into daily practice.

Keywords: Hypofractionated, Radiotherapy, Breast Cancer

Copyright ©2024 Indonesian Radiation Oncology Society

Introduction

Breast cancer (BC) is the highest prevalence cancer worldwide, with an estimated increase in new cases reaching more than 40% by 2040. Almost 17% of cancer cases in Indonesia are breast cancer. The estimated incidence is 65,858, with 22,430 deaths in 2020. The number of new possibilities and death rates will increase by 45% and 60% in the next twenty years.¹

As an adjuvant treatment, radiotherapy reduces recurrence and mortality rates after surgery. The Early Breast Cancer Trialist Collaborative Group's meta-analysis in 2011 reported that radiotherapy reduced any recurrences from 35 to 19.3 % and the breast cancer death rate from 25.2 to 21.4 % in early-stage disease after breast-conserving surgery.² After mastectomy and axillary dissection, radiotherapy also reduces recurrence and mortality in locally advanced breast cancer.³

According to national guidelines, the total dose used in radiotherapy to the breast is 50 Gy in 25 fractions for five weeks as conventional fractionation (CFRT). In addition, the guidelines also recommend utilizing hypofractionation radiotherapy (HFRT), which

has an equivalent outcome. The HFRT dose fractionation is 40 - 42.5 Gy in 15-16 fractions over 3-4 weeks.⁴

Indonesian radiation oncology society (IROS) recommends hypofractionated utilization to minimize hospital visits during the Covid-19 pandemic. This policy is under international guidelines published in the clinical oncology journal.⁵ This recent study aims to evaluate the preference of radiotherapy fractionation for BC amongst Indonesian radiation oncology members during the Covid-19 pandemic.

Methods

This study is a cross-sectional study evaluating the practice of HFRT for BC using a questionnaire developed from Ratosa's study. The question was multiple choice distributed to radiation oncologist (RO) IROS members through private message or email during October 2021. The question consists of participants' information (such as hospital type, province, age, working experience, workload, the number of RO) and the decision to treat breast cancer

Table 1. Characteristics of respondents (N = 29)

Characteristic	n	(%)	
Province	North Sumatera	2	6.9
	West Sumatera	1	3.4
	South Sumatera	1	3.4
	Lampung	1	3.4
	Jakarta	8	27.6
	West Java	2	6.9
	Central Java	8	27.6
	Jogjakarta Special Region	2	6.9
	East Java	3	10.3
	South Sulawesi	1	3.4
Hospital Type	Academic General Hospital	19	65.5
	Non-academic General Hospital	4	13.8
	Private Cancer Hospital	5	17.2
	Other	1	3.4
Age	< 35 years	3	10.3
	35 – 45 years	19	65.5
	45 - 60 years	4	13.8
	61 – 70 years	1	3.4
	> 70 years	2	6.9
Working experience	< 5 years	12	41.4
	5 – 10 years	14	48.3
	11 – 20 years	1	3.4
	> 20 years	2	6.9
Number of RO	1	2	6.9
	2	12	41.4
	3	2	6.9
	4	1	3.4
	> 5	12	41.4
Average breast cancer patients / month	< 5	2	6.9
	5 – 10	10	34.5
	11 – 20	12	41.4
Decision making	> 20	5	17.2
	Tumor board for selected case	9	31
	Internal discussion RO	2	6.9
	Internal discussion only for difficult case	9	31
Treatment management by RO incharge	9	31	

(such as fractionation in breast cancer after BCS and mastectomy, delineation, the organ at risk and the dose constraints). We use descriptive statistics to analyze the data.

Results

Twenty-nine RO filled and returned the questionnaire. The majority of participants were from Java and Academic General Hospitals. Two-thirds were

35 to 45 years old. Only three participants had working experience of more than ten years. Most of the participants have a minimum of one radiation oncologist colleague in their center. Five participants treated more than 20 breast cancer patients in a month. Only two participants treated less than five breast cancer patients in a month. Twenty-five participants preferred to use ESTRO and RTOG contouring guidelines.

Table 2. Respondent's contouring guidelines

Contouring Protocol	n	%
ESTRO 2015 (doi: 10.1016/j.radonc.2014.11.030.)	14	48.3
ESTRO ACROP 2019 (doi: 10.1016/j.radionc.2019.04.010.)	4	13.8
RTOG (https://www.rtog.org/CoreLab/ContouringAtlas/s/BreastCancerAtlas.aspx)	11	37.9
Hospital guidelines	-	-

This study is divided into categories according to radiotherapy procedure (whole breast irradiation and post-mastectomy), regional nodes irradiation, and reconstruction.

The participants preferred conventional fractionation for patients who received whole breast irradiation with or without regional (80 and 70%, respectively). Most of the participants also selected conventional fractionation than hypofractionated for post-mastectomy radiotherapy. In the analysis of factors that influenced the utilization of HFRT, four ROs did not select any factor, and two ROs selected one factor only. Almost 80% of them selected more than two factors. Average RO chooses more than four factors. The most common factors were age, stage, dose to the organ at risk, regional node irradiation, and surgical margin.

Discussions

Covid-19 is a disease caused by a novel coronavirus (SARS CoV2) from Wuhan, spreading worldwide and becoming pandemic.⁶ Cancer patients were more susceptible to infected covid-19 during their treatments, such as radiotherapy. Because of limited radiotherapy facilities and increased patient load in Indonesia, radiotherapy centers are always full of patients. So the risk of covid-19 infection among patients who underwent radiotherapy was high. A survey among radiotherapy centers in Indonesia showed that most centers decreased their services to reduce the risk of covid-19 disease.⁷ In the UK, the covid-19 pandemic has changed the breast radiotherapy practice. They preferred to change the dose fractionation from moderate (40 Gy in 15 fractions) to ultra (26 Gy in 5 fractions) hypofractionation. This approach may decrease the risk of infection by minimizing hospital visits.⁸

Table 3. Radiation oncologist's preferences fractionation for breast radiotherapy

Breast Irradiation	Conventional	Hypofractionated	Both	Other
Whole breast irradiation without RNI	13	4	12	
Whole breast irradiation with regional node irradiation	18	3	8	
Post-mastectomy without reconstruction	20	1	8	
Post-mastectomy with reconstruction	21	1	7	
Boost	24	2	1	1

HFRT may improve radiotherapy capacity, especially in hospitals with limited resources. The decline in economic growth in Indonesia during the pandemic could reduce investment in radiotherapy equipment. Meanwhile, new breast cancer cases will increase rapidly from 65.9 thousand to 96.8 thousand instances. Deaths from breast cancer may increase beyond estimates if the ratio between treatment facilities and patients is not balanced.

The rationale for HFRT is the low alpha/beta ratio data for breast cancer. An article published in a green journal stated that breast cancer's alpha/beta ratio was 3.89 +/- 6.25 based on the post-breast-conserving surgery. This data support implementation of HFRT for breast cancer.⁹ The UK Standardization of Breast Radiotherapy (START) trials demonstrated the equivalent of HFRT compared to CFRT for BC. The START trials use 39 or 41.6 Gy in 13 fractions (START A) and 40 Gy in 15 fractions (START B).^{10,11} Moreover, The FAST-forward research showed that the ultra-fractionated regimen is as comparable outcome and safety as moderate hypofractionated.¹²

A meta-analysis study in 14 RCTs in the last two decades succeeded in proving the efficacy of HFRT for early-stage breast cancer patients. The CFRT and HFRT were 4,869 and 6,027 patients, respectively. The outcomes were not significantly different in local

relapse (HR = 0.99, 95%CI = 0.97–1.02, p = 0.476), recurrence-free survival (HR = 0.99, 95%CI = 0.97–1.02, p = 0.485), overall survival (HR = 1.00, 95%CI = 0.97–1.03, p = 0.879), and cosmetic outcomes (RR = 1.03, 95%CI = 0.95–1.12, p = 0.53). HFRT had less toxicity such as acute skin, induration, breast atrophy, and the pain.¹³

Liu et al. conducted a meta-analysis to compare hypofractionated and conventional fractions in post-mastectomy radiotherapy. The meta-analysis showed the equivalent outcome (OS, DFS, LRR, DM) and acute and late skin toxicity, lymphedema, shoulder restriction, and late cardiac toxicity between the two groups.¹⁴

The majority of participants consider age as factor that influence HFRT utilization. The financial factor in Indonesian practice is the BPJS reimbursement system, which is paid per fraction, not per course. So, the fewer fractions per course, the more the hospital will lose income opportunities. In this study, we found five of participants consider financial as factor influence HFRT utilization. However, hypofractionated radiotherapy has less total cost than conventional regimens in terms of the direct and additional expenses. It reduces direct cost by decreasing fractionation from 25 to 16 fractions. The extra cost means expenses incurred by patients for transportation, lodging, and food during treatment, especially if patients live far

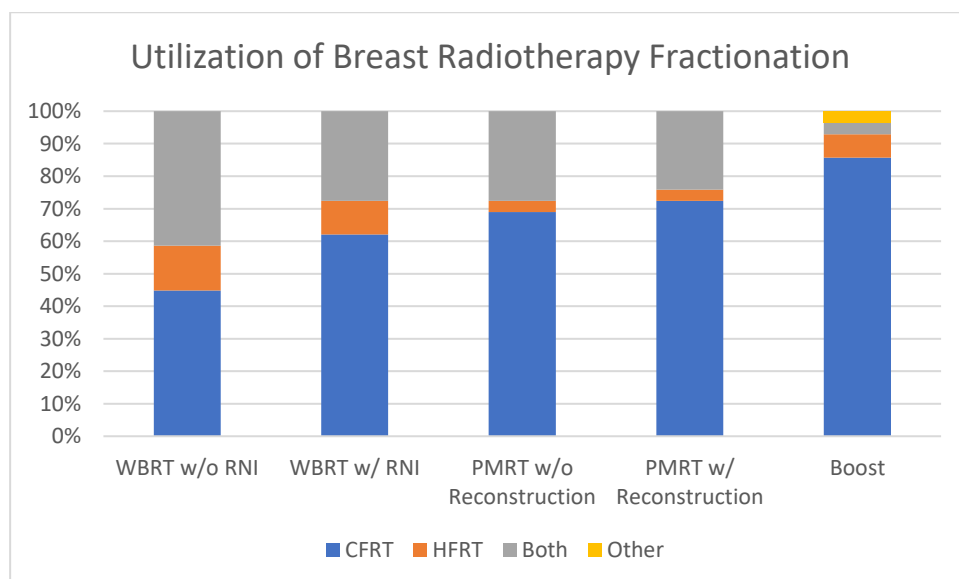


Figure 1. Radiation oncologists' preference fractionation for breast radiotherapy.

Table 4. Factors that influence HFRT utilization.

Factor	n	%
Age	20	15.4
Stage	17	13.1
Dose to organ at risk	17	13.1
Regional node irradiation	11	8.5
Surgical margin	10	7.7
BC grade	9	6.9
Laterality (left vs right)	7	5.4
BC molekular subtype	7	5.4
Implant base reconstruction	3	2.3
Flap-based breast reconstruction	6	4.6
Dose inhomogeneity	6	4.6
Financial issues/Reimbursement	5	3.8
Breast size	4	3.1
None of factors	4	3.1
Use of high tangents	4	3.1

from the facility. In low-middle income countries, the mega-voltage radiotherapy facility is usually limited in big cities. So, the patients from outer must come near to the hospital that has these facilities. Patients also have to stay in their residences far from the hospital. This situation will inevitably increase the overall cost and the cost of treatment for the patient. The total will undoubtedly burden the patient and family or insurance, especially if the patient does not work during the treatment period. An article published in *The Breast Journal* supports that HFRT could replace CFRT because it lowers costs with the same effectiveness.¹⁵ We believe that HFRT can also reduce radiotherapy waiting times.

Ivica Ratoso et al. study showed that the overall choice for hypofractionated radiotherapy was more than 50 % in the European country. All RO practicing in the Netherlands, Israel, Belgium, Ireland, UK, and Denmark choose HFRT than CFRT. More than one-half of RO practicing in Turkey and Romania still prefer CFRT.¹⁶

The weakness of this study is the limited number of participants. Only about one-fourth of IROS members took part. It could lead to a publication bias. The strength of this study is that the participants were almost all from large radiotherapy centers in Indonesia and aged around 35 years old. This study also evaluates the respondents' contouring guidelines for breast cancer. Only a few respondents use the latest RADCAMP guidelines.

Further study with broad involvement of all IROS members and another Southeast RO may give a global description of breast radiotherapy practice. Using more simple questionnaires with technical aspects of

breast radiotherapy could access the knowledge of RO. Thus, we can empower the professional through education or training.

Conclusions

The utilization of HFRT in routine practice among Indonesian RO is still low despite the proven clinical benefit. Continuing medical education may speed up the adoption of the latest guidelines.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer* [Internet]. 2019;144:1941–53. Available from: <https://pubmed.ncbi.nlm.nih.gov/30350310/>
2. Darby S, McGale P, Correa C, Taylor C, Arriagada R, Clarke M, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* [Internet]. 2011;378:1707–16. Available from: <https://pubmed.ncbi.nlm.nih.gov/22019144/>
3. McGale P, Taylor C, Correa C, Cutter D, Duane F, Ewertz M, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* [Internet]. 2014;383:2127–35. Available from: <https://pubmed.ncbi.nlm.nih.gov/24656685/>
4. Komite Penanggulangan Kanker Nasional. Pedoman Nasional Pelayanan Kedokteran Kanker Payudara. Panigoro S, Purwanto H, Gondhowiardjo S, Giselvania A,

- Widodo NH, editors. Jakarta, Indonesia: Kementerian Kesehatan Republik Indonesia;
5. Coles CE, Aristei C, Bliss J, Boersma L, Brunt AM, Chatterjee S, et al. International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic. *Clin Oncol (R Coll Radiol)* [Internet]. 2020;32:279–81. Available from: <https://pubmed.ncbi.nlm.nih.gov/32241520/>
 6. Li J, Huang DQ, Zou B, Yang H, Hui WZ, Rui F, et al. Epidemiology of COVID-19: A systematic review and meta-analysis of clinical characteristics, risk factors, and outcomes. *J Med Virol* [Internet]. 2021;93:1449–58. Available from: <https://pubmed.ncbi.nlm.nih.gov/32790106/>
 7. Handoko, Permata TBM, Giselvania A, Nuryadi E, Octavianus S, Jayalie VF, et al. Ensuring safety and sustainability of radiotherapy services during the COVID-19 pandemic in resources constrain country: An Indonesian experience. *Radiotherapy and Oncology* [Internet]. 2020;150:57. Available from: [/pmc/articles/PMC7275138/](https://pubmed.ncbi.nlm.nih.gov/33493433/)
 8. Spencer K, Jones CM, Girdler R, Roe C, Sharpe M, Lawton S, et al. The impact of the COVID-19 pandemic on radiotherapy services in England, UK: a population-based study. *Lancet Oncol* [Internet]. 2021;22:309–20. Available from: <https://pubmed.ncbi.nlm.nih.gov/33493433/>
 9. Qi XS, White J, Li XA. Is α/β for breast cancer really low? *Radiother Oncol* [Internet]. 2011;100:282–8. Available from: <https://pubmed.ncbi.nlm.nih.gov/21367477/>
 10. Agrawal RK, Aird EGA, Barrett JM, Barrett-Lee PJ, Bentzen SM, Bliss JM, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* [Internet]. 2008;371:1098–107. Available from: <https://pubmed.ncbi.nlm.nih.gov/18355913/>
 11. Bentzen S, Agrawal R, Aird E, Barrett J, Barrett-Lee P, Bliss J, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* [Internet]. 2008;9:331–41. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1470204508700779>
 12. Brunt AM, Haviland J, Sydenham M, Algurafi H, Alhasso A, Bliss P, et al. FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results (CRUKE/04/015). *International Journal of Radiation Oncology*Biophysics* [Internet]. 2018;102:1603–4. Available from: <http://www.redjournal.org/article/S0360301618336915/fulltext>
 13. Gu L, Dai W, Fu R, Lu H, Shen J, Shi Y, et al. Comparing Hypofractionated With Conventional Fractionated Radiotherapy After Breast-Conserving Surgery for Early Breast Cancer: A Meta-Analysis of Randomized Controlled Trials. *Front Oncol* [Internet]. 2021;11. Available from: <https://pubmed.ncbi.nlm.nih.gov/34660318/>
 14. Liu L, Yang Y, Guo Q, Ren B, Peng Q, Zou L, et al. Comparing hypofractionated to conventional fractionated radiotherapy in postmastectomy breast cancer: a meta-analysis and systematic review. *Radiat Oncol* [Internet]. 2020;15. Available from: <https://pubmed.ncbi.nlm.nih.gov/31952507/>
 15. Yang J, Qi SN, Fang H, Song YW, Jin J, Liu YP, et al. Cost-effectiveness of postmastectomy hypofractionated radiation therapy vs conventional fractionated radiation therapy for high-risk breast cancer. *Breast* [Internet]. 2021;58:72–9. Available from: <https://pubmed.ncbi.nlm.nih.gov/33933925/>
 16. Ratosa I, Chirilă ME, Steinacher M, Kozma E, Vojtíšek R, Franco P, et al. Hypofractionated radiation therapy for breast cancer: Preferences amongst radiation oncologists in Europe - Results from an international survey. *Radiother Oncol* [Internet]. 2021;155:17–26. Available from: <https://pubmed.ncbi.nlm.nih.gov/33065187/>