

Adjuvant breast radiotherapy outcome in older women: A Malaysian experience

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SUMMARY

Adjuvant breast radiotherapy is offered to patients with localized breast cancer. We performed a retrospective review of older women receiving adjuvant breast radiotherapy in University Malaya Medical Centre, Malaysia (UMMC) in 2014. Out of 191 women, 23% (43) were 60 years old and above. At a median follow up of 6.6 years, 4.6% (2) had local recurrence and 19% (8) distant metastasis. In a subgroup of low risk older patients with hormone-sensitive, HER2 negative, T1N0 disease, all (3/43) are still alive with no local recurrence. We propose further research for treatment de-escalation in low risk elderly patients.

INTRODUCTION

World Health Organization (WHO) defines the older population as being 60 years old and above.¹ In Malaysia, older women (>60) represent almost 50% of breast cancer patients.² Our study investigates University Malaya Medical Centre, Malaysia (UMMC) practice of adjuvant radiotherapy in older women. The use of adjuvant radiotherapy has been shown to reduce locoregional recurrences, halving cancer relapse.^{3,4} However, the absolute benefit of radiotherapy in older low-risk women is low. UK PRIME's 5-year local relapse rate was 1.3% post radiotherapy compared with 4.1% without radiotherapy.⁴ This article dissects the impact of radiotherapy further on Malaysian population, comparing outcomes with pivotal studies.

MATERIALS AND METHODS

Retrospective review of Electronic Medical Records of patients receiving adjuvant breast radiotherapy in UMMC for the year 2014, aged 60 years old and above. Patients who received palliative radiotherapy for stage IV cancers, or patients with carcinoma in situ were excluded. Median overall survival and local recurrence free survival (LRFS) were calculated. LRFS is defined as the time interval between date of diagnosis and date of local relapse. Overall survival is defined as the time interval from date of diagnosis to date of death, or when censored. The analysis was carried out using SPSS, and Kaplan-Meier survival analysis was used to estimate survival. This study was approved by the Medical Ethics Committee of UMMC (MECID. NO.: 2021511-10131).

RESULTS

In 2014, 191 women underwent adjuvant breast radiotherapy and 23% (43) were over 60 years old; (86%) (37) aged 60-70, 14% (6) 70-80 years old. In this group, most (60%, 26) were Chinese, 23% (10) were Malay and 16% (7) were Indian. At a median follow-up of 6.6 years, 4.6% (2) had local recurrence; both had aggressive disease; stage 3, HER 2 positive, one with grade 3 and another with high Ki-67 index (Table 1). They both represent patients with higher risk locally advanced breast cancer at presentation. The median local recurrence-free survival was 79 months (95% CI 62-76 months) (Figure 1). Of note, all (3/43) low-risk T1N0, ER +, HER 2 - older patients are still alive, with no local recurrence. All patients completed their course of 40Gy in 15 fractions. 18% recorded radiation-induced dermatitis. 19% (8) developed distant metastasis, with aggressive subtypes (Triple Negative, Her2+, Luminal B) and advanced stage at presentation (Stage 3, Luminal A subtype) (Table I). 79% (34) patients are still alive and 21% (9) died at median follow-up of 6.6 years. The median overall survival for this cohort was 80 months (95% CI 65-78 months) (Figure 2). The log-rank test showed no significant difference in overall survival when comparing subtypes of breast cancer, but this is most likely due to small sample size ($p = 0.87$).

DISCUSSION

In 2014, a meta-analysis of 5 randomized trials, whereby 39% were elderly (>70 years old) with T1N0 hormone receptor-positive cancers.⁵ It showed the absolute benefit was modest (4.3%) with no overall survival benefit. Our study's results aligned with the meta-analysis. We showed regional recurrence of 4.6% (n=43) which is similar to the pivotal START-A trial (3.5% after 41.6Gy, n=2236).⁶

The limitation of our study is the retrospective study design. Our study defined older women using the age cut off of 60 years old. However, international studies use 65 and 70 years old. According to Department of Statistics Malaysia, average life expectancy for Malaysian women in 2020 is 77.6 years old.⁷ In the United Kingdom, average life expectancy for women in 2020 is 82.7 years old.⁸ Therefore, higher life expectancy in the UK compared to Malaysia justifies our choice of a slightly lower age cut-off.

Table I: The patient’s age, stage at diagnosis and tumor biology.

	Number of patients	Age at diagnosis	Staging (AJCC 7th edition)	Subtype
Local recurrence	1	71	Stage 3	HER 2+
	1	62	Stage 3	HER 2+
Distant metastasis	1	61	Stage 1	Triple-negative
	1	67	Stage 2	Luminal B
	1	61	Stage 2	Luminal B
	1	65	Stage 3	Luminal A
	1	62	Stage 3	HER 2+
	1	61	Stage 3	Luminal B
	1	67	Stage 2	Triple negative
	1	71	Stage 3	Luminal A

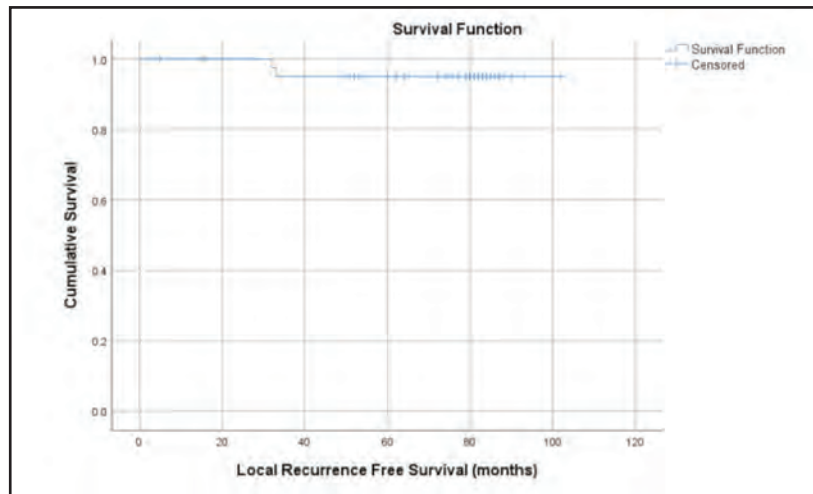


Fig. 1: Local recurrence-free survival in elderly breast cancer patients.

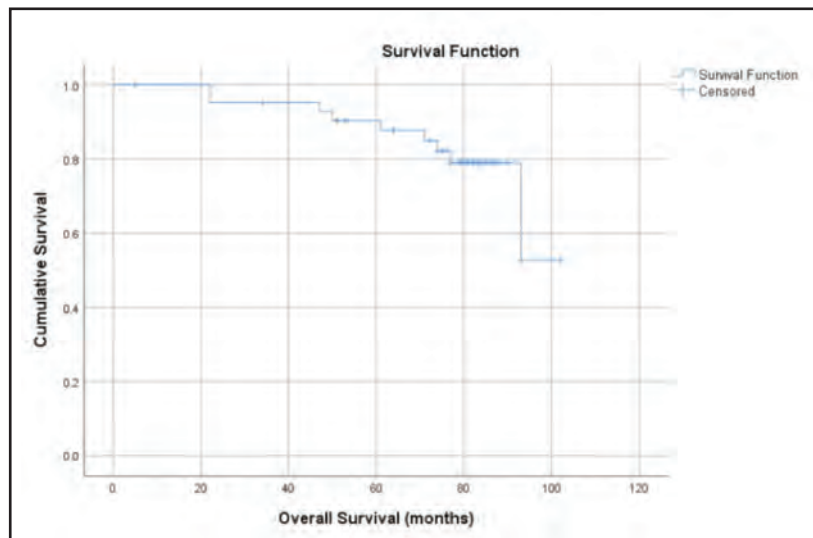


Fig. 2: The overall survival in elderly breast cancer patients.

The PRIME trial looked at the impact of radiotherapy in low-risk elderly patients, their quality of life and health economics.⁴ Over 15 months’ median follow up, they have concluded that radiotherapy for this population is not a cost-effective treatment, associated with increased breast symptoms and fatigue. Our rates of dermatitis (18%) were lower than the rates in START-B trial (23% in arm 40Gy in 15 fractions).⁶ This is most likely due to under-reporting in the medical record system.

Subsequent PRIME II trial studied the survival outcome and LRFs in this low-risk population.⁹ In this trial, 1326 women aged 65 years or older with early low-risk breast cancer were assigned to either whole-breast radiotherapy or no radiotherapy. A 5-year follow-up analysis showed no differences in regional recurrence or distant metastases. Furthermore, hormone-positive patients only had a 2.4% absolute gain in local relapse.

The PRIMETIME trial investigates the safe omission of radiotherapy following breast-conserving surgery in elderly patients at low risk of recurrence.¹⁰ In this prospective cohort, local recurrence rate for the low-risk cohort was <4% at 5 years. Similarly, our cohort showed a local recurrence rate of 4.6% at 6.6 years of follow up. No recurrence in the low-risk group.

Conversely, we recognize the side effects of radiotherapy. Therefore, an important strategy for the future is de-escalation of treatment in low-risk older women. Intraoperative radiotherapy (IORT) / Accelerated Partial Breast Irradiation (APBI), is a good alternative to external beam radiotherapy in our group of interest, recognized by international guidelines.

In summary, previous studies show a fairly similar local recurrence rate to our study. Due to excellent local control, there is growing evidence to de-escalate treatment by omitting radiotherapy in low-risk elderly patients.

CONCLUSION

Our study shows real-time treatment efficacy of adjuvant radiotherapy with low (4.6%) local recurrence rate, and median overall survival of 80 months. In low risk older women with T1N0 hormone positive breast cancer, the local recurrence rate is 0%. Further work in identifying low risk older women for treatment de-escalation is needed, especially in a resource-limited country such as ours.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The results of this paper have not been published previously, except in abstract format.

AUTHORS' CONTRIBUTIONS

All authors were involved in conception or design, or analysis and interpretation of data, or both. All authors approved the final version of the manuscript.

REFERENCES

1. Ageing [Internet]. Who. int. [cited 2021 Nov 8]. Available from: <http://www.who.int/health-topics/ageing>
2. Azizah AM, Nor Saleha IT, Noor Hashimah A, Asmah ZA, Mastulu W. Malaysian National Cancer Registry Report: 2007-2011. National Cancer Institute, Ministry of Health; 2016.
3. EBCTCG (Early Breast Cancer Trialists' Collaborative Group). 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. *The Lancet*. 2014; 383(9935): 2127-35.
4. Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, et al. A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. *Health Technol Assess*. 2007; 11(31): 1-149.
5. Van de Water W, Bastiaannet E, Scholten AN, Kiderlen M, de Craen AJM, Westendorp RGJ, et al. Breast-conserving surgery with or without radiotherapy in older breast patients with early stage breast cancer: a systematic review and meta-analysis. *Ann Surg Oncol*. 2014; 21(3): 786-94.
6. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol*. 2013; 14(11): 1086-94.
7. Department of statistics Malaysia official portal [Internet]. Gov.my. [cited 2021 Nov 8]. Available from: https://www.dosm.gov.my/v1/index.php?r=column/cthemeByCat&cat=116&bul_id=ROVPdE1mNEdRQms2S0M4M1ZsSlVEdz09&menu_id=LopheU43NWJwRWVSZklWdzQ4TlhUUT09
8. Baker A, Fellows C. Life expectancy in England in 2020 [Internet]. Gov.uk. [cited 2021 Nov 8]. Available from: <https://ukhsa.blog.gov.uk/2021/03/31/life-expectancy-in-england-in-2020>
9. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM, PRIME II investigators. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol*. 2015; 16(3): 266-73.
10. Kirwan CC, Coles CE, Bliss J, Kirwan C, Kilburn L, Fox L, et al. It's PRIMETIME. Postoperative avoidance of radiotherapy: Biomarker selection of women at very low risk of local recurrence. *Clin Oncol (R Coll Radiol)*. 2016; 28(9): 594-6.