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Evidence Based Case Report

Effect of Delayed Adjuvant Radiotherapy in Early Breast Cancer on Local Control, Distant Metastasis and Overall Survival

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Abstract

Breast cancer is the second most common cancer in the world and, by far, the most frequent cancer among women with an estimated 1,67 million new cancer diagnosed in 2012 (25% of all cancers). In principle, radiation therapy is indicated in early breast cancer after breast conserving surgery or after radical mastectomy-with-positive-or-near-margin. Unfortunately, not all aforementioned indicated patients could receive immediate treatment, often due to limited radiation therapy facility. We constructed this report to investigate comprehensively, whether delayed radiation therapy for indicated-post-surgical-early breast cancer case has a significant effect to survival (either locoregional or distant metastasis-free survival). Searching was conducted on PubMed®, Cochrane®, and Scopus®. After screening for titles and abstracts, we found 25 articles, 15 of which we finally included for performing full reading. From this systematic searching, we found that time to radiation is inconsistently related to locoregional survival, overall survival, and distant metastasis-free survival.

Keywords: early stage breast cancer, delayed radiation therapy, survival, outcome

Introduction

Breast cancer is the most common cancer, and the second leading cause of death in cancer-related diseases in women.[1] Estimated incidence of breast cancer in Indonesia is 40 per 100,000 women. This number increased from 2002, with incidence of breast cancer 26 per 100,000 women.[2]

Adjuvant radiotherapy in postoperative breast cancer patients is one example of treatment modalities for cancer, where various types of therapies such as surgery, chemotherapy, radiotherapy, and hormone therapy are used together simultaneously or sequentially to achieve local and distant control of cancer and to increase patient's survival time. The clinical issue found in these therapy was when and how the therapy will be administered.[3] For radiotherapy itself, the increased use of radiotherapy modalities with limited devices is one of the factors causing increased patient waiting time after surgery until started of radiotherapy.[4]

Regarding the impact of delaying radiotherapy after surgery, there is still no conclusive data. Some studies found that there was no decreased in survival or increased local or distant recurrence,[4.5] while other studies found that there was a decreased in survival and increased local recurrence in patients who received radiotherapy more than 6 weeks.[5] Because of differences in the results of the study, we were interested to make this critical appraisal.

Case Ilustration

At a national referral hospital, a 40-year-old woman came to the Department of Radiotherapy. The patient was referred from the Department of Oncology Surgery because of malignancy found in her left breast. The patient told that she was diagnosed with stage II cancer ($T_2N_0M_0$). The oncologist surgeon has performed breast conserving surgery, and advised her to have radiotherapy after surgery.

The patient asked the Radiotherapy Resident if she could postponed adjuvant radiotherapy in about 6 months. She want to return to her hometown in NTT and want to apply health insurance first and raise funds, because she used all of her personal money that for her surgery. The radiotherapy resident would like to know if delaying radiotherapy will affect cancer recurrence and death.

Clinical Question

In patient with early breast cancer, does delayed adjuvant radiotherapy correlate with outcome (local recurrence and mortality)?

Methods

Search Strategy

The literature search was conducted on PubMed,® Cochrane,® dan Scopus® on April 8th 2017 using the search tools containing keywords "breast neoplasm", "adjuvant radiotherapy", "delay or delay waiting time or timing", and "outcome or recurrence". MesH term is applied for PubMed,® and Cochrane,® (Table 1). Search strategy, results and the inclusion and exclusion criteria are shown in a flowchart (Figure 1).

Selection

After obtaining the result, first selection was done by screening the abstract whether the journal fulfill the inclusion criteria or not. The inclusion criteria were meta-analysis of cohort studies, randomized clinical trial (RCT), cohort studies, written in English, population was women only, article published less than 15 years, delayed adjuvant radiotherapy compared with more immediate adjuvant radiotherapy, and full text available. Then for second selection was done by reading full text and discarded when the journal met exclusion criteria.

The exclusion criteria was breast cancer not in early stage, outcomes other than local recurrence, overall survival, and distant metastasis, radiotherapy was neoadjuvant or concurrent radiotherapy and other reason.

Results

Search and Selection Results

Table 1. Search terms used in PubMed, Cochrane, and Scopus (conducted on April 8th 2017)

Database	Search terms	# hit
Pubmed	"Breast Neoplasms"[Mesh] AND ("Radiotherapy, Adjuvant"[Mesh] AND (Delayed OR Delay OR Timing OR "Waiting time")) AND ("Treatment Outcome"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])	114
Cochrane	"Breast Neoplasms"[Mesh] AND ("Radiotherapy, Adjuvant"[Mesh] AND (Delayed OR Delay OR Timing OR "Waiting time")) AND ("Treatment Outcome"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh])	65
Scopus	"breast neoplasm" AND "Adjuvant Radiotherapy" AND (delay OR delayed OR timing OR "Waiting Time") AND (outcome OR recurrence)	54

After searching three database, we found 211 articles after filtering double. From 211 articles, 25 articles met inclusion criteria. Then we read full text of the articles, and 10 articles excluded based on exclusion criteria. Finally, we found 15 articles that met our eligibility criteria and would be appraised for validity, importance, and applicability.

Critical Appraisal

Fifteen article, Barbieri V et al,[6] Benchalal M et al,[7] Benk V et al,[8] Cefaro GA et al,[9] Corradini S et al,[10] Hebert-Croteau N et al,[11] Jobsen JJ et al,[12] Kim K et al,[13] Knauerhase H et al,[14] Seneviratne S et al,[15] Campos R et al,[16] Mikeljevic J et al,[17] Hershman DL et al,[18] Donato V et al,[19] Pinnaro P et al[20] were each appraised in groups by 2 authors using standardized validity criteria for prognostic research. Several aspects were critically reviewed comprising of its validity, importance, and applicability. The checklists used were obtained from www.cebm.net[21]

Fifteen articles appraised for validity, importance, and applicability. We found 4 articles with 1b level of evi-

dence (RCT, prospective cohort), and the rest were 2b (retrospective cohort). Noted that 15 articles had various outcome, but we focused on our outcome (local recurrence, overall survival, and distant-metastasis). After appraising 15 article, we concluded that all included article were valid. So, we included all 15 articles to the discussion section to answer our clinical question. The characteristic of studies were shown in Table 3.

Discussion

Local Relapse/Recurrence

From ten studies exploring the association between time to radiation and local recurrence, only four of them indicated that there was a relation between time to adjuvant radiotherapy and local recurrence rate in early stage of breast cancer patients. The different result among those study might be caused by different cut off, small number of participant, bias, and confounder in the study. For example, Kyubo et al and Knauerhause et al which reported significant results used smaller sample size compared to Benchalal et al, S Coradini et al and JJ Jobsen et al which had more than 500 participants.[13,14]

The way of applying the cut off to categorize early versus delayed time to radiation were vary among studies. In this case, study which applied the exposure in numerical variable was more reliable to quantify the time to radiation.[8] Benk et al, examined the median SRI time in patients without and with local recurrent, 8 weeks vs 14 weeks, with per additional months of delay will increase the risk of relapse by 8%. However, the association was insignificant when multivariate regression was performed. 1.13(0.96-1.33).[8]
Selecting patients regardless their chemotherapy status, which also can be a potential confounder, will lead to systematic bias which commonly occurred in observational studies. SRI in patients with chemotherapy was longer compared to those who did not received chemotherapy.[9,10] Thus, some bias occurred in studies which not stratifying chemotherapy status in the analysis. (Barbieri and Herbert-cortean) Besides patients with chemotherapy had better health status if compared to patients who had not and had better local control free survival.[19] Attempts for doing random allocation in RCT are able to prevent the selection bias, lead to more reliable results.[7]

After seeing the result of multivariate analysis from all the studies above, confounding factor may be the major factor to explain the association between SRI and high rate of local relapse. Factors such as surgical margin status, younger age, nodal positive, tumor's grade and size will increase the risk to get local control failure.[6,10] Only study form Kyobo Kim et al confirmed that SRI time (<6 weeks) lead to better local control after multivariate analysis performed.[13]

Overall Survival

There were two from nine studies reported significant difference of survival rate in patients who had earlier SRI compared to delayed.[17,18] These two studies used very big sample size, more than 7000 participants, thus a small different in two groups might resulted to a significant association. They also used same cut off to categorize the exposure group, thus they were able to quantified every difference in one month delay.
Different cut off in each study will contribute to the inconsistency of the results apart from the number of sample size. The confounders were also properly adjusted and still showed significant result after multivariate analysis performed, with HR roughly around 1.5 to 2.[17,18] The other seven studies of insignificant result varied by their cut off, analyzed confounding factors, and stratification by participants chemotherapy status. [7-9,16,20]

It can be interpreted that most of studies were unable to show a difference in overall survival between different SRI group. If there was any, the small difference in survival rate only can be detected by a big sample size.

Distant Metastasis-Free Survival

The last outcome was distant metastasis-free survival (DMFS). There were 4 study that included DMFS as outcome. There were 3 studies that stated there was no statistically significant difference in DMFS between delayed radiotherapy or not, while only 1 study stated in reversal. In Herbert-Corteau et al study, there was no significant differences in patient who had delayed radiotherapy or not.[11] In addition, Kim et al and Pinnaro et al also gave insignficant result ($p = 0.51$, $p = 0.27$) respectively.[13,20] In contrary, Jobsen et al study concluded that there was significant difference in DMFS between delayed vs non delayed radiotherapy with HR 0.3 (0.2-0.5), $p < 0.001$. Jobsen et al suggest to start radiotherapy 36 days after surgery which might be lead to 40-70% relative survival benefit. [12]

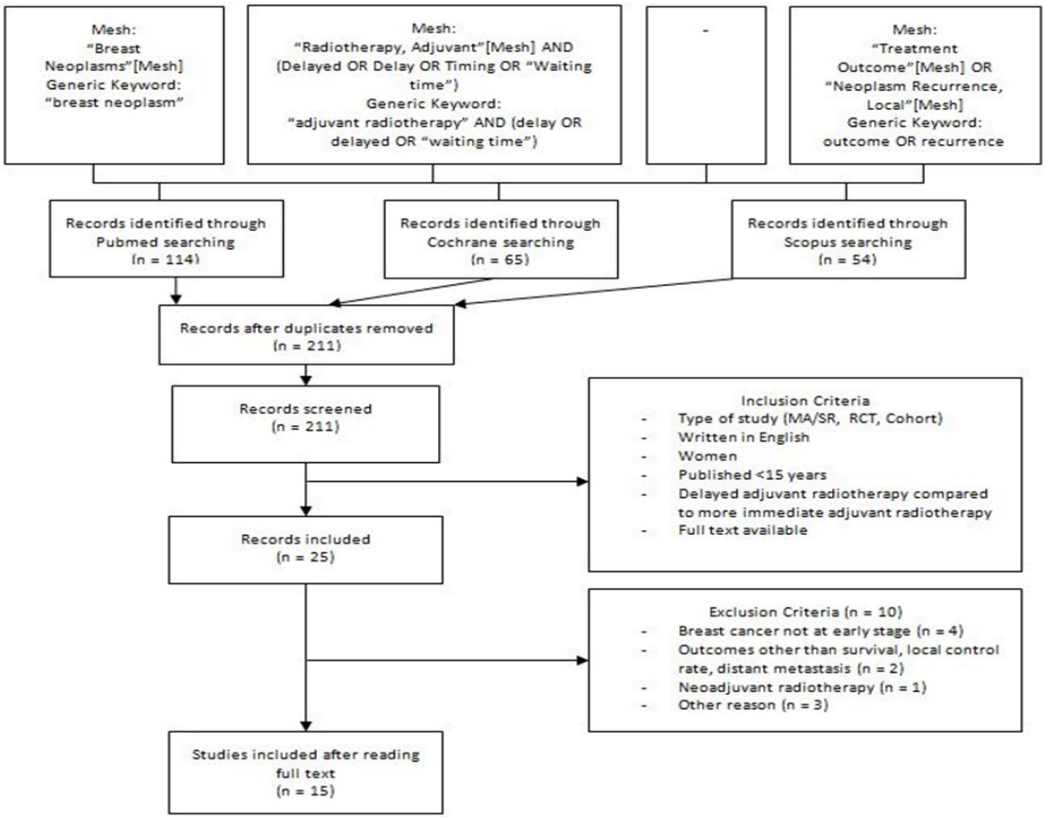

Figure 1. Search strategy flowchart

The different results of these studies might be from difference in sample size. Kim et al and Pinnaro et al study'sample size was 171 and 206 respectively,[13,20] while Jobsen et al had 1446 woman as sample, near 10-folds from two previous studies.[12] Herbert-Corteau et al's sample size was as big as Jobsen's, but these two studies had different cut-off point of delayed radiotherapy. Herbert-Corteau et al divided the group into <= 8 weeks (1-56 days), 8-12 weeks (56-84 days), and >12 weeks (>84 days),[11] while Jobsen et al divided group into 1-36 days, 37-53 days, and 54-112 days.[12] The difference of time was up to 30 days, which might be affect DMFS itself. For the adjustment for confounder, Herbert-Corteau et al study found that chemotherapy was not associated with DMFS (p = 0.84).[11] Jobsen et al and Kim et al had excluded patient with adjuvant systemic therapy. Thus, we conclude that delayed radiotherapy had inconclusive results to affect distant metastasis-free survival. Another factor that might be affect DMFS was insignificant.

Conclusion

As a conclusion, time to radiation was inconsistently found to be the risk for worse locoregional survival, overall survival and distant-metastasis-free survival. Due to possibility of bias which occur in observational studies those result have to be applied with some cautions. Other factors such as age, nodal status, margin, grading and size of the tumor might be better to predict the local control but unfortunately, they are not modifiable. Thus we better want to keep the SRI time for our patients as early as possible, as this is the best thing we can do to protect our patients from local relapse and other outcome.

Table 2. Critical appraisal of 15 articles based on criteria by CEBM[21]

Criteria	Validity				Importance				Applicability		Evidence Level
Article	Sample definition, representative, same baseline	Sufficient follow-up time	Blinded Outcome	Prognostic factor adjustment	Outcome	Suggest early adjuvant radiotherapy P value <0.05	Suggest delay adjuvant radiotherapy P value <0.05	Insignificant difference between early vs delay adjuvant radiotherapy	Patient similarity	Clinically important	Based on Oxford CEBM
Benchalal et al	+	+	-	+	9-year LRFS	yes before 3rd cycle of chemotherapy			+	-	1b
Benk et al	+	+	+	+	5 year LRFS	yes < 30 days			+	+	2b
Knauerhase et al	+	+	?	+	LRR	yes ≤ 60 days			+	+	2b
Mikeljevic et al	+	+	-	+	5 year OS	yes <140 days			+	+	2b
Hershman et al	+	+	?	+	CSFS	yes < 90 days			-	+	2b
					OS	yes < 90 days					
Jobsen et al	+	+	+	+	DMFS		yes >37 days		+	+	1b
					LRFS			yes			
Donato et al	+	+	-	-	LRFS		Yes, but p value n/a > 90 days		+	-	2b
					OS		Yes, but p value n/a > 90 days	yes, but P value n/a			
Seneviratme et al	+	+	+	-	Breast cancer specific mortality			yes	+	+	1b
Pinnaro et al	+	+	?	+	CSFS			yes	+	+	1b
					DMFS			yes			
					DFS			yes			
					OS			yes			
Barbieri et al	+	+	+	+	Mean Value of LRFS in months			yes	+	-	2b

*CSFS: Cancer specific free survival. CT: Chemotherapy. DSS: Disease specific survival. DFS: Disease free survival. DMFS: Distant metastasis free survival. HT: hormone Therapy. LCS: Local control rates. LRFS: Local recurrence free survival. LRR: local recurrence rate. OS: Overall survival. Ref.: Reference. SRI: surgery to radiation interval time.

Table 2. Critical appraisal of 15 articles based on criteria by CEBM (cont.)[21]

Criteria	Validity					Importance			Applicability		Evidence Level
Article	Sample definition, representative, same baseline	Sufficient follow-up time	Blinded Outcome	Prognostic factor adjustment	Outcome	Suggest early adjuvant radiotherapy P value <0.05	Suggest delay adjuvant radiotherapy P value <0.05	Insignificant difference between early vs delay adjuvant radiotherapy	Patient similarity	Clinically important	Based on Oxford CEBM
Cefaro et al	+	+	+	+	8 years LRR			yes	+	-	2b
Corradini et al	-	+	?	+	LRFS with CT (+)			yes	+	-	2b
					LRFS with CT (-)			yes			
					OS with CT (+)			yes			
					OS with CT (-)			yes			
Hebert Croteau et al	+	+	?	+	LRR			yes	+	-	2b
Kim et al	-	+	+	+	LCR			yes	-	+	2b
					DFMS			yes			
					OS			yes			
Campos et al	+	+	+	-	DFS			yes	+	-	2b
					OS			yes			

*CSFS: Cancer specific free survival. CT: Chemotherapy. DSS: Disease specific survival. DFS: Disease free survival. DMFS: Distant metastasis free survival. HT: hormone Therapy. LCS: Local control rates. LRFS: Local recurrence free survival. LRR: local recurrence rate. OS: Overall survival. Ref.: Reference. SRI: surgery to radiation interval time.

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