

Review Article

Effect of intraoperative radiotherapy for patients with low-risk early-stage breast cancer

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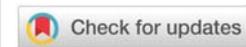
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Abstract

Introduction: External Beam Radiation Therapy (EBRT), a type of whole breast radiation therapy, has been widely used in patients with early-stage breast cancer, however it is associated with longer treatment periods and higher toxicity. Intraoperative Radiotherapy (IORT) has emerged as an alternative, reducing treatment times, however, there is uncertainty about its effectiveness and safety.

Objective: To assess the effects of IORT on low-risk early-stage breast cancer in comparison to EBRT.

Methods: We searched in Epistemonikos, a database of systematic reviews, to identify the available evidence evaluating the benefit of IORT on these patients. We extracted data of primary studies from relevant systematic reviews. Data were reanalyzed and a meta-analysis, using evidence of randomized trials, was conducted. Results are reported through a summary of findings table using the GRADE approach.

Results and conclusions: We identified eight systematic reviews including seven primary studies overall, of which two were randomized trials. We concluded that IORT slightly reduces adverse events and probably increases the local recurrence rate in comparison with EBRT.

Introduction

Breast cancer is the most common cancer and the second cause of cancer death among women in the Americas. Every year more than 462,000 new cases and almost 100,000 deaths from breast cancer occur in the region. In women from Latin America and the Caribbean, this health problem accounts for 27% of new cases and 16% of cancer deaths. Its incidence in the Americas is expected to increase by 2030, with an estimation of 572,000 new cases and 130,000 deaths [1]. In Chile, breast cancer is the most prevalent in women, accounting for 54,227 new cases and 28,584 deaths in 2020. In 75-year-old women or

younger, the risk of developing this disease and their mortality is of 16% and 8%, respectively [2].

The breast-conserving therapy combined with post-operative radiotherapy is an equivalent treatment strategy to mastectomy for patients with early-stage breast cancer. External beam radiation therapy (EBRT), a type of whole breast radiation therapy, has become a gold standard as adjuvant therapy after breast-conserving surgery, reducing the risk of local recurrence and improving survival. The results of this intervention are associated with dose-dependence, higher incidence of cardiotoxicity and lung cancer, which increases over time after exposure [3].

As an alternative to whole breast radiation therapy, the clinical practice includes the accelerated partial breast irradiation, a localized form of radiation concentrated on the tumor bed, site where most recurrence occur, which reduces the exposure to radiation from nearby organs and minimizes late adverse events [4,5].

Intraoperative radiotherapy (IORT) is one of the validated techniques of accelerated partial breast irradiation, whose greatest advantage over EBRT is that it limits the treatment to one session, which is applied to the tumor bed during surgery [4].

Despite the above, there is still uncertainty about the superiority and safety of the use of IORT over EBRT. Hence, the aim of this review is to assess the comparative effects of IORT over EBRT.

Methods

We searched in Epistemonikos, a database harboring documents from multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies evaluating the effects of IORT in patients with low-risk early-stage breast cancer in comparison to EBRT [6]. The resulting summary of the body of evidence is presented as an evidence matrix [7]. The FRISBEE methodology was used to extract, review, and analyze the available evidence [8]. The outcomes included in the summary of findings table are those considered critical for decision-making, according to the opinion of the authors, and in general they are in agreement with the systematic reviews identified. Data of relevant outcomes were extracted from the identified reviews, including local recurrence, mortality, grade 3-4 adverse events related to skin radiotherapy toxicity, complications associated with the intervention, health-related quality of life, and physician reported cosmesis (breast appearance). When the available evidence came from more than one primary study, data were reanalyzed using meta-analysis. Results are reported through a summary of findings table following the GRADE approach.

Results

We identified eight systematic reviews [3-5,9-13] including seven primary studies overall [14-22], of which two were randomized trials [14,15]. Figure 1 shows these results in the matrix of evidence elaborated using Epistemonikos database. All further analysis and the reported results are based on the extracted data from the randomized trials, since they represent the body of evidence with the highest level of certainty. Additionally, observational studies did not provide any additional relevant information.

The randomized trials, named TARGIT-A and ELIOT, included patients aged 45 years or older, all of them were women with early-stage breast cancer, harboring tumors of a size of 2.5 cm or less, and that were suitable for breast-conserving surgery. Respect to TNM classification, the largest proportion was T1c and T1ab, and N0 and N1, respectively. In

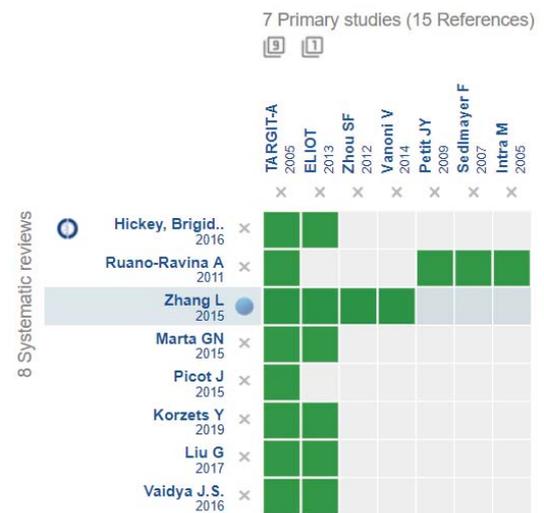


Figure 1: Matrix of evidence elaborated using Epistemonikos database. reports all the relevant evidence for the question of interest, including systematic reviews and primary studies.

both trials, the analysis of hormone receptor markers showed a higher proportion of estrogen receptor (around 90%). They compared IORT versus EBRT, with doses between 20 at 25 Gray delivered in one full dose and 40 at 45 Gray delivered in 25 fractionated doses, respectively. The TARGIT-A trial used radiotherapy with boost and the ELIOT trial used radiotherapy with or without boost [14,15].

The average follow-up of the trials was 49.3 months with a range between 29 and 69.6 months. Overall, the studies included 4,756 patients. Both measured the outcomes of local recurrence (4,860 patients), overall survival (4,756 patients), complications associated to intervention (4,327 patients), and only the TARGIT-A trial measured the outcome of adverse events (3,451 patients) and physician reported cosmesis (105 patients). Regarding health-related quality of life measurement, no review allowed the extraction of data that could be incorporated into a meta-analysis, therefore, the information on this outcome is presented as a narrative synthesis.

Relevant outcomes, together with their absolute and relative effects, are reported in table. Our results revealed that IORT reduces the risk of grade 3-4 toxicities to the skin in a 69% (95% CI 0.10 - 0.95) when comparing to EBRT. The sources of the data related to this outcome were leveled with highest certainty of evidence. Mortality and complications showed a similar tendency than adverse events; however, these results were not statistically significant. In contrast, local recurrence shows more favorable results for EBRT than IORT, represented by an increase in the risk of recurrence of 206% when treating the patient with the intervention in evaluation. Results of cosmesis were also more favorable for EBRT than IORT, but the treatment effect was not statistically significant. Regarding quality of life, no studies statistically evaluated this outcome; however, the quality-of-life parameters evaluated in the TARGIT-A study were generally favorable for the intraoperative radiotherapy arm Table 1.



Table 1: Summary of findings using the GRADE approach. Outcomes are reported in order of importance in the decision-making process.

IORT for patients with low-risk early-stage breast cancer				
Patients	Patients with low-risk early-stage breast cancer			
Intervention	IORT			
Comparison	EBRT			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITH EBRT	WITH IORT		
Difference: patients per 1000				
Local recurrence	6	19	RR 3.06 (1.23 to 7.43)	⊕⊕⊕○ ^{1,2} MODERATE
	Difference: 13 more (Margin of error: 2 to 41 more)			
Mortality	34	30	RR 0.88 (0.59 to 1.32)	⊕⊕⊕○ ^{1,3} MODERATE
	Difference: 4 less (Margin of error: 14 less to 11 more)			
Adverse Events**	8	3	RR 0.31 (0.10 to 0.95)	⊕⊕⊕⊕ ¹ HIGH
	Difference: 5 less (Margin of error: 7 less to 0 more)			
Complications associated to intervention***	540	292	RR 0.54 (0.14 to 2.01)	⊕⊕○○ ^{1,2} LOW
	Difference: 248 less (Margin of error: 464 less to 545 more)			
Health-related quality of life	One trial [15] reported favorable results in relation to quality of life in the group receiving IORT compared to the control group.			⊕⊕⊕○ ^{1,4} MODERATE
Cosmesis	260	218	RR 0.84 (0.42 to 1.66)	⊕⊕⊕○ ^{1,3} MODERATE
	Difference: 42 less (Margin of error: 151 less to 432 more)			

Margin of error: 95% confidence interval (CI).

RR: Risk ratio.

MD: Mean difference.

GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk **WITH EBRT** is based on the risk in the control group of the trials. The risk **WITH IORT** (and its margin of error) is calculated from relative effect (and its margin of error).

**Adverse events such as radiation therapy grade 3 or 4 toxicity to the skin, e.g., erythema, dryness, hyperpigmentation, and pruritus.

***Complications such as hematoma needing surgical evacuation, seroma needing more than three aspirations, infection needing intravenous antibiotics or surgical intervention, and skin breakdown or delayed wound healing.

¹ Based on the assessment of risk of bias reported in three systematic reviews, we decided not to downgrade certainty level [5], [10], [12].

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕

High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕○

Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⊕⊕○○

Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕○○○

Very Low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision.

² The certainty of evidence was downgraded in one level for inconsistency because the analysis suggests a moderate heterogeneity.

³ The certainty of evidence was downgraded in one level for imprecision because each extreme of the confidence interval implies a different decision.

⁴ The certainty of evidence was downgraded in one level for imprecision because the results do not report confidence intervals.

Discussion

The principal aim of the present study was to evaluate the effect of IORT on low-risk early-stage breast cancer in comparison to EBRT. Following the GRADE approach, our results show that the risk of local recurrence in patients could probably be three times higher in patients undergoing IORT than EBRT. The benefit in mortality is uncertain and could probably lead to a decrease for both intraoperative and external radiotherapy. Adverse events associated with radiotherapy

decrease slightly in patients undergoing IORT compared to those treated with EBRT. In the same way, IORT may slightly decrease complications associated with radiation therapy and the achievement of cosmesis compared to EBRT. Additionally, IORT probably increases quality of life in comparison with external radiotherapy.

The results obtained apply to patients with initial breast cancer, postmenopausal, with tumor of 2.0 cm or smaller, a favorable molecular histological subtype (luminal A), and suitable for breast-conserving surgery. Although some studies



included patients from other molecular subtypes, the results in terms of reported local recurrence for them are considerably higher for the intervention, therefore, the use of IORT in this context is not recommended [14].

In addition to the clinical benefits, IORT is associated with lower costs [12]. This could be due to a shorter time of treatment, which implies a reduction in the cost of professional fees and the period of medical rest (less time for medical leave of absence), an early return to work, and a decrease in costs of hospital stay and the transfer of patients who lives far from radiotherapy centers, among others. However, it is important to consider the additional costs associated to its implementation, because it requires the acquisition of the portable linear accelerator and the training of the medical and physical personnel in this technique. Regarding adherence to treatment, given that IORT is performed during surgery, the results obtained with the treatment do not depend on the patient's commitment to the treatment, as it could be for EBRT. These considerations should be noted for further analyses in the local context for implementation decisions.

Results from relevant systematic reviews are consistent with those presented in this article. Regarding international clinical guidelines recommendations, the use of IORT in women with early-stage breast cancer vary according to the age range of the patients. The American Society of Radiation Oncology (ASTRO) and the European Society for Radiotherapy and Oncology (ESTRO) suggest that patients receiving accelerated partial irradiation on the breast should be at least 50 and 60 years old, respectively. According to these recommendations, some studies have shown favorable results, even when they include patients aged 40 years and older, however, further analysis and follow-up of these studies is required to extend the indication to this population [23].

Conclusion

Our results revealed that IORT does not show an absolute superiority when compared to EBRT, in terms of the outcomes reported in this article. Thus, although IORT is associated with clinical benefits by reducing the incidence of grade 3-4 toxicity to the skin, it does not reduce the risk of local recurrences in these patients in comparison to EBRT. Further research is needed to elucidate which alternative constitute the best option for the treatment of these patients and to clarify the subgroups of patients who may benefit the most with one alternative or the other.

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