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Safety, effectiveness and economic evaluation of intra-operative radiation therapy: a systematic review

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Abstract

Background: Intra-operative radiation therapy (IORT) is the transfer of a single large radiation dose to the tumor bed during surgery with the final goal of improving regional tumor control. This study aimed to investigate the safety, effectiveness and economic evaluation of intra-operative radiation therapy.

Methods: The scientific literature was searched in the main biomedical databases (Centre for Reviews and Dissemination, Cochrane Library and PubMed) up to March 2014. Two independent reviewers selected the papers based on pre-established inclusion criteria, with any disagreements being resolved by consensus. Data were then extracted and summarized in a structured form. Results from studies were analyzed and discussed within a descriptive synthesis.

Results: Sixteen studies met the inclusion criteria. It seems that outcomes from using intra-operative radiation therapy can be considered in various kinds of cancers like breast, pancreatic and colorectal cancers. The application of this method may provide significant survival increase only for colorectal cancer, but this increase was not significant for other types of cancer. This technology had low complications; and it is relatively safe. Using intra-operative radiation therapy could potentially be accounted as a cost-effective strategy for controlling and managing breast cancer.

Conclusion: According to the existing evidences, that are the highest medical evidences for using intra-operative radiation therapy, one can generally conclude that intra-operative radiation therapy is considered as a relatively safe and cost-effective method for managing early-stage breast cancer and it can significantly increase the survival of patients with colorectal cancer. Also, the results of this study have policy implications with respect to the reimbursement of this technology.

Keywords: Intra-Operative Radiation Therapy, IORT, Health Technology Assessment, Cancer.

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Introduction

Cancer is commonly used for great group of diseases that can influence any part of the body. One of the specifications defining cancer includes fast reproduction of abnormal cells beyond their regular duplication that can attack their neighborhood sides and diffuse to other organs of the body. This is called metastasis. Metastasis is the main cause of death from cancer. Cancer is the main reason for mortality worldwide, there were over than 8.3 million mortalities in 2012. Main types of cancer include: lung cancer (1.59 million deaths per year), liver cancer (74500 deaths per year), stomach (72300 deaths per year), colon (694000 deaths per year), breast cancer (521000 deaths per year) and esophageal

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cancer (400,000 deaths per year). Some of the most prevalent kinds of cancer such as breast, cervix, mouth and colon cancers, when diagnosed early and treated by best methods could have high therapeutic success. Some types of cancers including leukemia and lymphoma in children can have high improvement rate even after diffusion with proper treatments. Cancer treatment needs accurate selections of one or more of some interventions such as surgery, radiation therapy and chemotherapy. It comes with this goal that while improving the quality of life in the patient, it can also increase their life years through treating the disease (1).

Radiation therapy as an important part of combination therapy of cancer has been considerably attended during recent decades; its philosophy includes attaining to higher and more effective dosages of radiation without increasing the prevalence of its complication (2). For improving the clinical consequences of cancer, various radiotherapeutic methods are used including External Beam Radiation Therapy (EBRT), Intensity-Modulated Radiation Therapy (IMRT), 3-Dimensional Conformal Radiation Therapy (3D-CRT) and Intraoperative radiation therapy (IORT) (3). One of these techniques which were mentioned above, called IORT, is a technique to deliver a high dose of radiation to a locally advanced tumor to protect the neighboring normal tissues at the time of surgery (3). During IORT, the normal tissues are not exposed to radiation because they are removed or shielded from the treatment field (4,5). Therefore, by the advent of the technology in Iran and considering the fact that recently there has been a high demand for reimbursing such a technology by insurance companies, this study aimed to review the safety, effectiveness and economic evaluation of IORT for the treatment of patients with different cancer types.

Methods

Scientific literature was searched in the main biomedical databases up to March 2014: Centre for Reviews and Dissemination (Health Technology Assessment, Database of Abstracts of Reviews of Effectiveness, and NHS Economic Evaluation Database), Cochrane Library and PubMed. Mesh and free text were used in the search strategy (Table 1). Duplicated and non-relevant studies were removed. The titles and abstracts of the remaining studies were investigated and unrelated studies were excluded. The full texts of the remaining articles were checked against the inclusion criteria to select studies for the review (Fig. 1). Two independent reviewers checked the selected studies in accordance with inclusion criteria, with any disagreements being resolved by consensus. A structured form was used to collect data from the included studies. The criteria were as follows: (1) The study design, systematic reviews, meta-analysis, health technology assessment and economic evaluations; (2) Treatment type: patients who received intraoperative radiotherapy (IORT) or other prevalent methods used for radiotherapy; (3) Patient type: patient diagnosed with cancer in any stage; (4) Language: only publications in English or English abstracts were included; (5) Outcome: Overall survival, complications, expected life years, doses of irradiation, costs and surgical time were considered as outcome. Because this was a rapid review study, the quality of papers investigated in this study was not critically assessed; however, because the studied papers have been provided from Cochrane library and Centre for Reviews and Dissemination (CRD), it could be stated that these databases can provide highest level of quality for medical papers based on evi-

Table 1. Search Strategy

No.	Search strategy
#1)	"Intraoperative Radiation Therapy"
#2)	"IORT"
#3)	(#1 or #2)
#4)	"Health Technology Assessment"
#5)	"Systematic Review"
#6)	"Cost*"
#7)	(#3 and #4)
#8)	(#3 and #5)
#9)	(#3 and #6)
#10)	(#7 or #8 or #9)

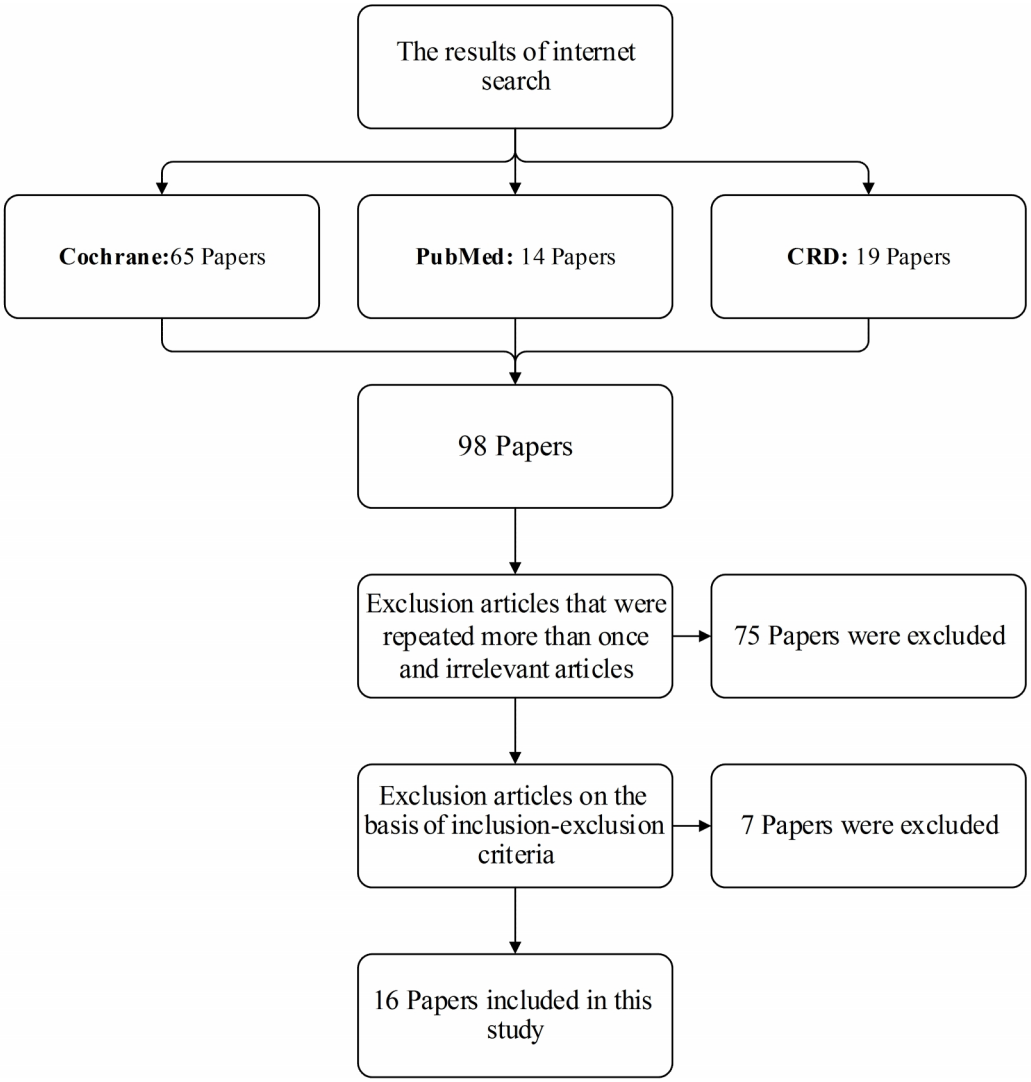

Fig. 1. Flow of papers through the study

dences. Finally, qualitative analysis was done using thematic synthesis.

In this study, the search strategy was as Table 1.

Results

Sixteen studies met the inclusion criteria and comprised 9 systematic reviews (2, 3, 6-12), one health technology assessment (13), one literature review (14), four economic evaluation (15-18) and one health technology horizon scanning (19). Two studies were published in 2014 (16, 18), three in 2013 (2, 10, 15), three in 2012 (3, 6, 13), two in 2011 (8, 12), one in 2010 (17), one in 2009 (7), one in 2008 (11) and three in 2004 (9, 14, 19) (Table 2). Results were presented in six sub-categories including survival rate, complications, life expected years, irradiation rate, costs and surgical times. Also, included studies on the basis of cancer types were as follows: ten on breast cancer (2,6,7,9,12,13,15,16,18, 19), three on colorectal cancer (7,8,10), one on pancreatic cancer (11), one on pelvic gynecologic malignancies (14), one on prostate cancer (3), one on liver cancer (17). Table 2 reflects the main characteristics of the studies.

A-Safety

A-1- Complications

In the study conducted by Cucins- Hearn et al. on using IORT in breast cancer, less complications after operation was reported; therefore, one cannot determine the relative

Table 2. List of included papers

Author, Location, Publication Date	Paper Title	Comparing Methods	Study Type
Alvarado et al. (15) USA, 2013	Cost-Effectiveness Analysis of Intraoperative Radiation Therapy for Early-Stage Breast Cancer	WB-EBRT	Economic Evaluation
Bahadur et al. (6) Saudi Arabia, 2012	Tumor bed boost radiotherapy in breast cancer: A review of current techniques	EBRT, HDR, IMRT	Systematic Review
Cantero Muñoz et al. (7) Spain, 2009	Radioterapia intraoperatoria en cáncer de mama y cáncer colorectal/ Intraoperative radiotherapy in breast and colorectal cancer	External Radiotherapy	Systematic Review
Cantero-Muñoz et al. (2) Spain, 2013	Radioterapia intraoperatoria en el tratamiento del cancer de mama/ Intraoperative radiation therapy in the treatment of breast cancer	External Radiation	Systematic Review
Cantero-Muñoz et al. (8) Spain, 2011	Efficacy and safety of intraoperative radiotherapy in colorectal cancer: A systematic review	Conventional Treatment	Systematic Review
Commonwealth Of Australia (19) Australia, 2004	Intraoperative Radiation Therapy	BCT	Horizon Scanning
Cuncins-Hearn et al. (9) Australia, 2004	A systematic review of intraoperative radiotherapy in early breast cancer	BCT	Systematic Review
Esserman et al. (16) USA, 2014	Application of a decision analytic framework for adoption of clinical trial results: are the data regarding TARGIT-A IORT ready for prime time?	EBRT	Economic Evaluation
Glujovsky (14) Argentina, 2004	Radioterapia intraoperatoria (IORT) en cánceres ginecológicos pelvianos/ Intraoperative radiation therapy in pelvic gynecologic malignancies	Conventional Treatment	Literature Review
LU et al. (17) China, 2010	Study of intra-operative radiotherapy in primary liver cancer	3D-CRT	Economic Evaluation
Marchioro et al. (3) Italy, 2012	Radical Prostatectomy and Intraoperative Radiation Therapy in High-Risk Prostate Cancer	Conventional EBRT	Systematic Review
Mirnezami et al. (10) UK, 2013	Intraoperative radiotherapy in colorectal cancer: Systematic review and meta-analysis of techniques, long-term outcomes, and complications	no IORT	Systematic Review, meta-analysis
Ruano-Ravina et al. (11) Spain, 2008	Intraoperative radiotherapy in pancreatic cancer: A systematic review	External radiotherapy	Systematic Review
Ruano-Ravina et al. (12) Spain, 2011	Efficacy and safety of intraoperative radiotherapy in breast cancer: A systematic review	EBRT	Systematic Review
Shah et al. (18) USA, 2014	Evaluating Radiotherapy Options in Breast Cancer: Does Intraoperative Radiotherapy Represent the Most Cost-Efficacious Option?	APBI and WBI	Economic Evaluation
Xie et al. (13) Canada, 2012	Single-dose Intraoperative Radiotherapy Using Intrabeam® for Early-stage Breast cancer: A Health Technology Assessment	Conventional External Beam Irradiation	Health Technology Assessment

safety and effectiveness of using IORT compared to BCT (9). Ruano- Ravina et al. concluded that there were less occurrence of chronic and acute complications when using combined therapy with IORT and EBRT for breast cancer in early stages (12). In a study, Cantero- Munoz et al. indicated that using IORT in treating breast cancer is a relatively safe method because its observed complication is similar to that of external radiotherapy (7). In another study, Cantero- Munoz et al. concluded that acute complications from the use of IORT in colorectal cancer was mainly of gastrointestinal type, and IORT technology is a safe method with no increase in the toxicity resulted from conventional treatment (8). In another study by Cantero- Munoz et al. it was found that using IORT individually for breast cancer may not considerably improve the toxicity of conventional treatment (2). Mirnezami et al. did not report any increase in general side effects whether urologic or anastomotic when using IORT in colorectal cancer. Also, their results revealed that IORT may improve the onco-

logical outcomes in advanced and recurrence colorectal cancer (10). Xie et al. concluded that in breast cancer, the rate of main complications for using IORT is similar to conventional treatment by external radiotherapy (13). Marchioro et al. indicated that Intraoperative Electron Radiation Therapy (IOERT) is a preferred method with minimum toxicity (3).

B- Effectiveness

B-1- Survival Rate

Cuncins- Hearn et al. showed that short-term outcomes for both treatment methods, IORT and Breast Conserving Therapy (BCT), in the early-stage breast cancer were similar in term of local recurrence, disease-free survival and overall survival. However, the existing evidence base for using IORT in early breast cancer is poor (9). Ruano-Ravina et al. found that IORT may cause a slight increase survival among patients with pancreatic cancer in localized stages. However, the results were not in favor of IORT in the case of pancreatic cancer in the locally advanced and metastatic stages (11). Bahadur et al. concluded that the difference in the overall survival, disease-free survival and disease-free distant survival among 4 interventions including External Beam Radiation Therapy (EBRT), High Dose Rate (HDR), Intensity-Modulated Radiation Therapy (IMRT) and IORT in breast cancer is not significant (6). Ruano- Ravina et al. found that in combined therapy with IORT and EBRT in early-stage breast cancer, local control was over 95% for 1 and 4 years of follow-up, and the 5-year overall survival was 99%. TARGIT-A(TARGeted Intraoperative radioTherapy Alone) study found a similar survival for IORT compared to standard treatment (12). Cantero- Munoz et al. indicated that using IORT in breast cancer causes slight improvement in their survival rate than patients treated by other treatments (7). Cantero- Munoz et al. in another study concluded that the use of IORT for colorectal cancer, five-to-six-year local control was over 80% and 5-year overall survival was close to 65%. For recurrences, the 5- year overall survival was 30%. Also, their study showed that adding IORT to conventional treatment reduces the incidence of local recurrences within the radiation area over 10%(8). In another study conducted to assess the effectiveness of IORT as a replacement treatment for current standard treatment of breast cancer, Cantero- Munoz et al. found that results from studies assessing the IORT as a replacement for a dosage promoting the external radiation indicate that this combination may not increase the effectiveness and overall survival. Using IORT individually may have recurrence and metastasis similar to conventional treatment (2). Mirnezami et al. concluded that using IORT in colorectal cancer may have a significant effect on improving the localized control, overall survival and disease-free survival (10). Australian Horizon scanning Report declared that according to the existing evidences, the safety and relative effectiveness of IORT to maintain the breast with post-operative radiation therapy has not been yet clear compared to surgery (19). Glujovsky et al. indicated that intra-operative radiation therapy in the gynecology cancers should be only considered in terms of clinical protocols and tests. Extended usage of this method may not be recommended in daily clinical practice. It seems that IORT may be potentially effective for patients with localized recurrence in their pelvic wall (14). Xie et al. concluded that in breast cancer, the localized recurrence rate for inter-operative radiation therapy is similar to traditional treatments with external radiation therapy (13).

B-2- Life Expected Years

Esserman et al. found that in breast cancer, by using IORT during primary stages and with increase in the rate of localized recurrence of IORT more than 10% during 10 years, only less than 0.002 life expectancy (less than one day) can be expected compared to EBRT (16). Alvarado et al. in their study indicated that in early stages of

Table 3. Effectiveness outcomes and cost aspects in the studies

	Comparator	Type of cancer	Overall Survival	Complications	Expected Life Years	Doses of Irradiation	Costs	Surgical Time
Alvarado et al. (15) USA, 2013	WB-EBRT	Breast Cancer	Slightly higher in local recurrence rate.	-	Slightly less effective (a difference of 0.062 days)	-	Dominant (less costly and more QALYs)	-
Bahadur et al. (6) Saudi Arabia, 2012	EBRT, HDR, IMRT	Breast Cancer	no significant difference regarding the overall survival, disease free survival, and distant disease free survival	-	-	-	-	-
Cantero Muñoz et al. (7) Spain, 2009	External Radiotherapy	Breast and Colorectal Cancer	Slightly better survival rate	Relatively safe technique. Adverse effects is similar.	-	-	-	-
Cantero-Muñoz et al. (2) Spain, 2013	External Radiation	Breast Cancer	incidence of recurrences and metastasis is similar	similar toxicity	-	-	-	-
Cantero-Muñoz et al. (8) Spain, 2011	Conventional Treatment	Colorectal Cancer	5-6-year local control: 80%. 5-year overall survival: 65%. For recurrences, the 5- year overall survival: 30%. IORT to reduce the incidence of local recurrences within the radiation area over 10%.	The main acute complications were gastrointestinal	-	-	-	-
Commonwealth Of Australia (19) Australia, 2004	BCT	Breast Cancer	-	Minor complications in the short-term and the cosmetic outcome were similar. The relative safety and efficacy is still uncertain.	-	Has potential to minimize irradiation of normal tissue	-	Has potential to shorten the course of radiotherapy treatment
Cuncins-Hearn et al. (9) Australia, 2004	BCT	Breast Cancer	similar Short-term outcome in terms of local recurrence, disease-free and overall survival	Minor postoperative complications	-	-	-	-
Esserman et al. (16) USA, 2014	EBRT	Breast Cancer	-	similar frequency of major toxicities	At an local recurrence rate of 10%, only 0.002 fewer expected life years	-	$1.7 billion opportunity cost of waiting an additional five year. Offer similar life expectancy, but cost less. Reduce $1467 in	-

							indirect costs per patient.	
Glujovsky (14) Argentina, 2004	Conventional Treatment	Pelvic Gynecologic Malignancies	Has higher benefit for patients with local recurrence involving the pelvic wall.	-	-	-	-	-
LU et al. (17) China, 2010	3D-CRT	Primary Liver Cancer	-	-	-	Effectively protect the neighboring sensitive organs and improve the absorbed dose in the tumors and the local control rate.	The cost was significantly lower	-
Marchioro et al. (3) Italy, 2012	conventional EBRT	Prostate Cancer	-	Minimal toxicity	-	-	-	Acceptable
Mirnezami et al. (10) UK, 2013	no IORT	Colorectal Cancer	A significant effect favoring improved local control ,disease free survival and overall survival.	No increase in total, urologic or anastomotic complications. Increased wound complications.	-	-	-	-
Ruano-Ravina et al. (11) Spain, 2008	External radiotherapy	Pancreatic Cancer	Slightly increase survival among patients with pancreatic cancer in localized stages.	-	-	-	-	-
Ruano-Ravina et al. (12) Spain, 2011	EBRT	Breast Cancer	Local control was over 95% for 1 and 4 years of follow-up and the 5-year overall survival was 99%. The similar survival comparing IORT with standard treatment. no differences in survival for IORT treated patients versus standard treatment	The incidence of acute and chronic complications was scarce. Acute and late toxicities are low.	-	-	-	-
Shah et al. (18) USA, 2014	APBI and WBI	Breast Cancer	-	-	-	-	More costs per QALY	-
Xie et al. (13) Canada, 2012	Conventional External Beam Irradiation	Breast Cancer	the rates of local recurrence is similar	the rates of major complications is similar	-	-	For 100 patients per year the budget impact of IORT would be a saving of $146,300.	-

breast cancer, single dosage IORT has lower effectiveness than 6 weeks Whole-Breast External Beam Radiation Therapy (WB-EBRT) (15).

B-3- Radiation Rate

Xie et al. concluded that using IORT in breast cancer may reduce the workload of oncological radiation team. In the patients' point of view, using IORT may considerably reduce the troubling weekly external radiation as well as waiting time for radiation therapy patients (13). Lu indicated that using IORT in primary liver cancer may effectively protect from adjacent sensitive tissues with improving the dosage absorbed in the tumors as well as local control rate (17).

C-Economic Evaluation

C-1- Cost of Treatment

Xie et al. concluded that using single dosage IORT in breast cancer may slightly reduce or increase in the budget expenditures based on the patients' turnover (13). Esserman et al. found that there will be an opportunity cost amounted to 1.7 billion USD for using IORT during a 5 year period for low risk females, hormone receptor- positive and postmenopausal females (16). Alvarado et al. indicated that single dosage IORT during operation in early stage breast cancer is considered as a dominated treatment with a more cost effective strategy by providing more life expectancy based on quality of living together with reduced costs compared to 6 weeks of administrating the WB-EBRT. Compared to WB-EBRT, IORT has lower cost and higher QALY with valuable strategy. IORT is an example of new technology with cost lower than existing treatment standard but with similar clinical effectiveness (15). Lu concluded that cost of using IORT in primary liver cancer is considerably lower than 3-Dimentional Conformal Radiation Therapy (3D-CRT) (17). Shah et al. in their study indicated that for treating 1000 patients affected by breast cancer, the cost savings for using IORT compared to WB-3D-CRT, APBI-IMRT, APBI-SL, APBI-ML and APBI-I is 3.6-4.3 million dollars, 1.6-2.4 million dollars, 3.6 to 4.4 million dollars, 7.5 – 8.2 million dollars and 2.8 to 3.6 million dollars, respectively and compared to APBI 3D-CRT, it saves costs up to 1.6 to 2.4 million dollars. The cost per QALY for WBI-3D CRT, APBI-IMRT, APBI-SL, APBI-ML and APBI-I compared to IORT was 47990 to 60002 dollars, 17335 to 29347 dollars, 49019 to 61031 dollars, 108162 to 120173 dollars and 36129 to 48141 dollars, respectively. According to the results of this study, APBI and WBI were cost-effective compared to IORT. They concluded that according to the analysis of costs minimization, IORT has the potential for cost savings in managing early-stage breast cancer; however, considering the additional medical and non- medical costs, WBI and APBI are cost-effective modalities based cost-per-QALY analyses and will be yet remained as standard of treatment (18).

C-2- Surgery Time

Xie et al. concluded that using IORT technology may result in increase of operation room load with increase in waiting time for surgery (13). Marchioro et al. indicated that IOERT is considered as a method with acceptable surgery time (3).

Discussion

According to the studies, it seems that in this case, using this method for colorectal cancer could only significantly increase the survival rate with no significant effect on other types of cancer (6-8,10-12,15). Because of the complications of using this kind of radiation therapy, the studies generally focused on post-operative complications and toxicity from using intra-operative radiation therapy, and it seems that such complications are slight and this technology can be safely used in all types of cancer (2, 6-10, 12, 13, 16, 19). For life expectancy, in breast cancer, if IORT localized recurrence rate was high about 10% per 10 years and IORT is applied in early

stage of disease, we will expect 0.002 fewer life years (less than one day) compared to EBRT. Also, in primary stages of breast cancer, single dosage IORT is less effective compared to 6-week WB-EBRT, with the rate of 0.062 days (15, 16). By IORT, one can attack the site of neoplasm with higher accuracy without damaging the intact tissues by radiation (17,19). Studies indicate that using intra-operative radiation therapy may be potentially accounted as a cost-effective strategy for controlling and managing breast cancer (15-17). Using IOERT may be conducted during an acceptable surgical time. However, this aspect has heterogeneity because it has also been pointed that using IORT technology may increase the load of operation room by increasing the waiting time for surgery operation (3, 13). Based on the current level of evidence, that are the highest level of evidence on the Evidence Base Medicine pyramid for using intra-operative radiation therapy, it can be generally concluded that IORT is a relatively safe and cost-effective treatment method for managing the early-stage breast cancer and it can also significantly increase the survival of colorectal cancer patients. In addition, the results of this study have implications with respect to reimbursement of this technology. Given that the results of economic evaluation studies in other countries cannot be generalized to other contexts, an economic evaluation study on IORT needs to be undertaken in our country.

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Conflict of Interest

The authors have no conflict of interest in this article.

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