Vol 3, Issue 2, Apr 2016
Journal of Health Management & Informatics
jhmi.sums.ac.ir
Original Article

Cost-effectiveness of radiotherapy during surgery compared with external radiation therapy in the treatment of women with breast cancer

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Received 16 Nov 2015; Accepted 22 Sep 2015

ABSTRACT

Introduction: Intraoperative radiation therapy device (IORT) is one of the several options for partial breast irradiation. IORT is sent to the tumor bed during surgery and can be replaced with conventional standard therapy (EBRT). The aim of this study was to evaluate the safety and effectiveness of IORT machine compared with EBRT and to determine the dominant option in terms of the cost-effectiveness.
Method: This study was conducted in two phases; the first phase was a comprehensive review of the electronic databases search that was extracted after extraction and selection of the articles used in this article on effectiveness outcomes. Data collection form was completed by professionals and experts to estimate the cost of treatment, intraoperative radiotherapy and radiotherapy cost when using external radiation therapy process; direct costs were considered from the perspective of service provider and they were calculated in the second phase to determine the option of cost-effective ICER. Excel software was used for data analysis and sensitivity analysis was performed to determine the strength of the results of cost-effectiveness.
Results:18 studies were selected but only 8 of them were shown to have acceptable quality. The consequences like "rate of cancer recurrence", "seroma", "necrosis", "toxic", "skin disorders and delayed wound healing" and "spread the pain" were among the consequences used in the selected articles. The total costs for each patient during a course of treatment for EBRT and IORT were estimated 1398 and $5337.5, respectively. During the analysis, cost-effectiveness of the consequences of cancer recurrence, seroma, necrosis and skin disorders and delayed wound healing ICER was calculated. And IORT was found to be the dominant supplier in all cases. Also, in terms of implications of toxicity and prevalence of pain, IORT had a lower cost and better effectiveness and consequently the result was more cost effective than EBRT.
Conclusion: According to the results of this study, the difference between the two devices in terms of effectiveness was much lesser than that in terms of the cost of the two devices. According to the results of IORT machine, it is the dominant supplier compared with EBRT. From the cost-effectiveness perspective, Iran Ministry of Health can consider IORT system as an option for entering Iranian health system. But the ethical and cultural considerations in the use of the device must be taken into account.

Keywords: Health technology assessment, IORT, EBRT, Cost-effective analysis, Systematic review

►*Please cite this paper as:*
Mosalanezhad H, Keshavarz Kh, Akrami M, Sarikhani M, Kavosi Z. Cost-effectiveness of radiotherapy during surgery compared with external radiation therapy in the treatment of women with breast cancer. J Health Man & Info. 2016;3(2):33-38.

Introduction

Breast cancer is the most common cancer in women, especially in Western countries (1) and the second leading cause of death due to cancer after lung cancer in the world (2, 3). With 22.6 percent, breast cancer is the most common cancer in Iranian women (4). However, with the widespread use of mammography, more than two-thirds of breast cancers are diagnosed in the early stages (1, 5). The results significantly confirm that the death rate from breast cancer has decreased by 25% due to the amount of new diagnostic and therapeutic methods in the past two decades (6). Patients in the later stages (without metastasis) are also cured completely with adjuvant treatments such as chemotherapy, hormone therapy and radiotherapy in 30 to 50% of cases. Therefore, new therapeutic approaches for these patients seem necessary. In patients who have a high risk of local recurrence, adjuvant radiation therapy after surgery on the chest wall and lymph nodes is prescribed (3). Although the risk of recurrence has greatly reduced in recent years, 90-80% of the recurrences occur at the site of the primary tumor (7, 8).

Breast conservation surgery (BCS) is monitored by external-beam whole-breast radiotherapy (EBRT) that has become the standard of care in early breast cancer. Adjuvant EBRT, after BCS, reduces the risk for in-breast

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tumor recurrence (IBTR) and more than BCC alone improves the overall survival (9, 10). Normally, during treatment with external radiation therapy a woman should receiveGy50- 56/42 rays in 25-16 fractions in 5-4 weeks. More women also receive additional adjuvant Gy16-10 in fractions 8-4 (7, 11).

The risk of second cancer after radiotherapy is recognized by several international organizations including International Commission on Radiological Protection (ICRP), National Council on Radiation Protection (NCRP) and Measurement and American Association of Physicist in Medicine (AAPM) (12).

Radiation therapy for breast cancer in the past few decades has changed considerably according to the type of radiation treatment, during treatment and 3D dose distributions. For breast cancer at an early stage, several new techniques for accelerated partial breast irradiation (APBI) have developed: high doserate brachytherapy (HDR-BT) (13, 14), permanent breast seed implant (PBSI) (15), intraoperative radiotherapy(IORT) using 50kv X-rays (TARGIT) (11) or electrons (ELIOT) (16), and ordinary 3D radiotherapy (17).

IORT with low energy X radiation (TARGIT) is an innovative technique that can be used during the protected breast operation as the only treatment for patients with low-risk breast or to improve the tumor bed to keep track of external radiation therapy (EBRT) (11, 18). IORT is sent to the tumor bed during surgery.Typically, IORT takes 35-20 minutes and radiation dose for the tumor bed is Gy 7-5 and for the surrounding tissue it is about Gy20 (8).

IORT is a newer technique compared to the EBRT, but the question is whether this method is superior to EBRT in terms of cost and effectiveness. The decision to use this new method and introduce its technology to the market of the country should be made taking all aspects of health, including its effectiveness and cost, into consideration. One way to help the policy makers to choose a therapy is health technology assessment (HTA) (19). Health Technology Assessment has a unique potential to contribute to policy-making, strategic planning, management and implementation of technologies in health care. HTA could help transparency and guarantees accountability for government decisions and performances (20).

Unlimited and uncontrolled technologies may induce demand by service providers and consequently result in irrational and uncontrolled use of such services and the sharp increase in costs. Therefore, in some of these countries prior to the entry of this technology, it is evaluated carefully and sensitively using a systematic manner and only then the appropriate investigation and action will be taken to issue entry license of the new technology and how to use it so that the optimal use of available resources will be feasible as much as possible (21). In this study, according to the demand of the Ministry of Health, we discussed the cost effectiveness of intraoperative radiation therapy (IORT) compared with EBRT.

Methods

This study was conducted in two parts: 1) a comprehensive review of the literature 2) the analysis of the cost-effectiveness

A comprehensive review of the literature

To evaluate the effectiveness of intraoperative radiation therapy system, a comprehensive overview of studies published in English by searching electronic databases including ISI, PubMed, and Scopus Cochrane was conducted from 1997 onward.

Randomized controlled trials, published in English comparing the clinical efficacy of intraoperative radiotherapy devices with radiotherapy after surgery, were studied. Exclusion criteria included animal studies, non-controlled studies, observational studies, retrospective studies and economic evaluation studies. Lack of approval by the ethics committee was among the exclusion criteria. After the initial search, the repetitive items were eliminated and the remaining titles and abstracts were evaluated independently by two people (H.m, Z.k) so as to detect unrelated articles as well as the ones that lacked inclusion criteria; then they were removed from the study. The results obtained by these two were compared and the discrepancies were resolved with reference to the articles. In the next step, the full texts of selected articles from the previous stage were examined and those that met the basic criteria were selected.

Analysis of cost-effectiveness:

Cost effectiveness: For incremental the cost-effectiveness, the outcomes utilized in the studies were considered as a measure of effectiveness.

Cost: Data collection form was completed by asking he experts and practitioners in surgical oncology and radiotherapy department and through examining hospital records of patients in Shahid Faghihi and Nemazee hospitals in Shiraz and Tehran Shohadaye Tajrish hospital. Then, the related costs were extracted. It should be noted that indirect costs and direct non-medical costs and the cost of non-tangible costs as well as the costs shared between the two methods were excluded from this study. Concerning the cost of additional consumed materials, the price of foreign brands was used or if the material was produced domestically, the price of domestic materials was used. Cost-effectiveness analysis was carried out from the perspective of the service provider. The value of currency using the exchange rate announced by the Central Bank of Iran in 2015was converted from Iranian Rial (IRR) to America dollars (USD). America dollar, according to the Central Bank of Iran, was £ 29956.

Incremental cost-effectiveness ratio (ICER):

Based on the results of cost effectiveness and collected costs, the incremental cost-effectiveness ratio was calculated. ICER was calculated based on the following formula to each of the outcomes.

$$ICER = \frac{CostA - CostB}{OutcomeA - OutcomeB} = \frac{CostIORT - CostEBRT}{OutcomeIORT - OutcomeEBRT}$$

The obtained cost-effectiveness ratio was compared with the threshold value and if it was less than the threshold, the process was found to be cost effective. In order to calculate the threshold, the method used by the World Health Organization was utilized. This means that if ICER index was lower than 3*GPD per capita, the program was cost-effective (22). According to the Central Bank of Iran, GDP per capita was $ 4670;therefore, the threshold was three times as high as this amount, i.e. US $ 14,019.

One-way Sensitivity Analysis:

After calculating the ratio of increasing cost-effectiveness to case-based economic evaluation, the relative strength of the assessment is necessary. Strength indicates the sensitivity of the cost-effectiveness to the uncertainty of data and alternative approaches in analysis. If the results remain unchanged when you change the parameters, this result can be considered very strong.In this study, to assess the strength of the results obtained from the calculated ICERs, a one-way sensitivity analysis was employed. The cost and effectiveness of the device IORT increased by20%, separately. And at every step, the new ICER was calculated.

Results

From the initial search, 6268 articles were identified, from which 18 articles were recognized appropriate, only after investigation and comparison with the study inclusion and exclusion criteria. After evaluating the quality by the authors, of the 18 studies only 8 cases entered into cost-effectiveness analysis.

In the mentioned 8 articles, six outcomes, including "cancer recurrence, pain prevalence, necrosis prevalence, seroma prevalence, skin disorders and delayed wound healing and toxicity prevalence ", were extracted as measures of effectiveness (23-29) (Table 1).

The outcome of cancer recurrence for each of the devices IORT and EBRT was extracted from 5 studies so that to measure the effectiveness of the devices, the average ratio of the effectiveness of 5 studies (IORT = 0.0125, EBRT = 0.0106) was calculated. The consequence of the spread of necrosis for each of the devices IORT and EBRT was extracted from 3 studies and then in order to assess the effectiveness of a device, the average ratio of the effectiveness of 3 studies (IORT = 0.2081, EBRT = 0.061) was estimated. The aftermath of the spread of pain for each of the devices IORT and EBRT was extracted from 2 studies and in order to evaluate the effectiveness of a device, the average ratio of the effectiveness of 2 studies(IORT = 0.226, EBRT = 0.2475) was evaluated. The outcome of skin disorders and delayed wound healing for each of the devices IORT and EBRT was extracted from 2 studies and in order to estimate the effectiveness of a device, the average ratio of the effectiveness of 2 studies (IORT = 0.0235, EBRT = 0.0095) was calculated. The consequence of the spread of toxicity for each of the devices IORT and EBRT was extracted from 2 studies and then in order to assess the effectiveness of a device, the average ratio of the effectiveness of 2 studies(IORT = 0.025, EBRT = 0.048) was calculated. The total cost per patient over a period of treatment with IORT was $1398 dollars and with EBRT equals to $5/5337 dollars. The cost of treatment with IORT was higher than that of EBRT as much as $ 5/3939 (Table 2). With respect to the information on the effectiveness and cost for each outcome, ICER was calculated (Table 3).

The results showed that the incremental cost-effectiveness ratio for the consequences of cancer recurrence, seroma, necrosis and skin disorders and delayed wound healing was negative which represented the smaller cost of IORT compared with that of EBRT.

Concerning the studied outcomes, the less the effective unit, the better. As you can see, the device IORT reduces the cost by $3,939.5 compared with that of EBRT and consequently increases the return of cancer to 0.0019; therefore, the calculated incremental cost-effectiveness indicates that for every single cancer return, IORT device reduces the cost by $2073421 compared with EBRT. This means that because ICER value is lower than the threshold, IORT device is considered as cost-effective. In relation to the consequences of the spread of necrosis, IORT device reduces the cost to $3939.5 compared with EBRT and necrosis spread increases to 0.1471; as a result, the calculated incremental cost-effectiveness indicates that for every single unit of necrosis prevalence, IORT device reduces the cost by $26,781.1 compared with EBRT. This means that because ICER value is lower than the threshold, IORT device is considered as cost-effective. Regarding the consequences of the spread of pain, IORT device reduces the cost to $3939.5 compared with EBRT and the spread of pain decreases to 0.0215. Since IORT device costs less than EBRT and pain prevalence in it is less than in EBRT, so there is no need to calculate ICER and IORT device is more cost-effective than EBRT. Concerning the outcome of the prevalence of seroma, the device IORT reduces the cost to $3939.5 compared with EBRT and the spread of seroma increases by 0.1;therefore, the calculated incremental cost-effectiveness indicates that per unit more seroma outbreak, IORT device reduces the cost by $ 5337.5compared with EBRT. This means that because ICER value is lower than the threshold, IORT device is considered as cost-effective. With respect to the consequences of skin disorders and delayed wound healing, IORT device reduces the cost to $3939.5 compared with EBRT and necrosis spread increases to 0.014; as a result, the calculated incremental cost-effectiveness indicates that for every single unit of skin disorders and delayed wound healing, IORT device reduces the cost by $281,392.8 compared with EBRT. This means that because ICER value is lower than the threshold, IORT device is considered as cost-effective. In relation to the consequences of toxicity prevalence, IORT device reduces the cost to $3939.5 compared with EBRT and necrosis spread decreases to 0.0215. Since IORT device costs less than EBRT and toxicity prevalence in it is less than in EBRT, there is no need to calculate ICER, and IORT device is more cost-effective than EBRT (Table 3).According to the findings of the present study, IORT device is more cost-effective than EBRT.

The results of the One-way sensitivity analysis show that a 20 percent increase in the cost and efficacy of IORT device does not cause a change in the results of the study and IORT is still the dominant option (Table 4).

Table 1. Indicators of effectiveness and safety of treatment with IORT and EBRT investigated in elective studies

Study (Author)	Consequences					
	Pain	Necrosis	Seroma	Skin disorder or delayed wound healing	Toxicity	Rate of cancer recurrence
Dubois (1997)	-	-	-	No significant difference between groups	-	A: 0 B: -
Reitsamer (2004)	-	A: 2 (1%) B: -	-	very low and comparable in both groups	-	A: 0 B: 8 (4.3%)
Jayant S Vaidya. (2010)	-	-	A: 23 (2.1%) B: 9 (0.8%)	A: 31 (2.8%) B: 21 (1.9%)	A: 37 (3.3%) B: 44 (3.9%)	A:6 (1.2%) B: 5 (0.95%)
B. Elsberger (2014)	-	-	-	-	-	A:0 B: 0
Kenneth Geving Andersen (2012)	A: 31 (24.6%) B: 38 (33.9%)	A: 1 (1.6%) B: 0	-	-	-	-
M. Ruch (2009)	-	A:31 (57%) B: 8 (17%)	A: 12 (22%) B: 2 (4%)	-	-	-
Umberto Veronesi (2013)	-	A: 22 B: 10	-	-	A: 11 B: 37	A: 35 (4.4%) B: 4 (0.4%)
Elena Sperk (2012)	A: 7 (20.6%) B: 8.6 (15.7%)	-	-	A: 0.648(1.9%) B: 0	-	A: 0 B: 0

Table 2. Calculation of the cost per patient over a period of treatment using any device (costs are in dollar)

Cost of Capital	EBRT	IORT
Annual Depreciation Expense	168812.6	153558.6
Annual Depreciation Expense for setting up the Necessary Infrastructure	552647.6	33762.5
Upkeep and Repair Cost	66764	55000
Current Cost		
Annual Personnel Costs	24028	24028
Annual Cost of Consumables	72000	2078.08
Total Price	884252.2	268427.18
Number of Sessions Per Year	720	192
Cost Per Session	1228.01	1398
Average Number of Sessions For a Patient	25	1
Cost For Each Patient During a Course of Treatment	5337.5	1398

Table 3. Calculation of ICER and the results of the cost-effectiveness of IORT compared with EBRT

Parameter ranges / Outcomes	IORT		EBRT		ICER ($/Effectiveness)	Cost-effectiveness results
	Effectiveness	Cost($)	Effectiveness	Cost($)		
Rate of cancer recurrence	0.0125	1398	0.0106	5337.5	-2073421	IORT Dominant
seroma	0.125	1398	0.025	5337.5	-39395	IORT Dominant
necrosis	0.2081	1398	0.061	5337.5	-26781.1	IORT Dominant
Skin disorder or delayed wound healin	0.0235	1398	0.0095	5337.5	-281392.8	IORT Dominant
pain	0.226	1398	0.2475	5337.5	-	IORT Dominant
Toxicity	0.025	1398	0.048	5337.5	-	IORT Dominant

Table 4. One-way sensitivity analysis in relation to reviewed outcomes

Sensitivity analyses / Outcomes	ICER (20% increase in the effectiveness of IORT)	ICER (20% increase in the cost of IORT)	Cost-effectiveness results
Rate of cancer recurrence	-895272.7	-1926263	IORT dominated
seroma	-31516	-36599	IORT dominated
necrosis	-20844	-24880	IORT dominated
Skin disorder or delayed wound healing	-210668	-261421	IORT dominated

Discussion

This study was carried out aiming at providing suggestions to policy makers to select the most cost-effective radiation therapy device for the treatment of patients with breast cancer; the total cost per patient over a period of treatment with IORT was $1398 and with EBRT it was $5337.5, which reflects the higher cost of using EBRT machine compared with that of IORT in a course of treatment. In a study conducted by Michel and colleagues (2013), IORT technology was identified as more cost-effective than EBRT (30). In a study to compare the cost of the use of IORT and EBRT, Holmes et al. (2012) reached the conclusion that preferring IORT over EBRT resulted in cost savings of $8.6 (31).

The results obtained from the analysis of cost-effectiveness showed that, from the service provider's perspective, although the EBRT is more effective than IORT device concerning the consequences of cancer recurrence, seroma, necrosis and skin disorders and delayed wound healing, since the difference between the price of these two devices equals to $3939.5, ICER calculations showed that given the negligible difference in their effectiveness and dramatic differences in the cost of the two devices, IORT option is preferable. As to the consequences of the prevalence of toxic and the prevalence of pain, IORT device was more cost effective and less costly compared to the EBRT device. This issue, thus, indicates that the IORT device is more cost-effective compared with EBRT. According to the results obtained from cost-effectiveness analysis in the present study, IORT device is the dominant option compared with EBRT and can be used instead of it. In a study on the cost-effectiveness of intraoperative radiotherapy device in patients with breast cancer, Michel and colleagues (2013) concluded that IORT is more cost-effective than EBRT. In this study, IORT was introduced as a unique example of new technology that is less expensive than regular treatments. However, in terms of effectiveness both devices are very close together. The results of the present study confirmed the substitution of radiation therapy with IORT treatment in patients with breast cancer in the first place (30).

In their study, Esposito et al. reported that IORT could be used instead of EBRT, but it must be used with the controller (32).

The above results substantiate the superiority of IORT compared to EBRT device. However, in addition to the results of this study, there are other reasons for the replacement of IORT for EBRT; due to delivering a low dose of radiation to cancerous tissue and concentrating radiation at the tumor site and reducing radiation reaching other tissues, the IORT device is preferred over the EBRT device (33). In a study on cancer recurrence after IORT, Aziz et al. (2011) concluded that since IORT emits far smaller radiation dose to the target tissue and surrounding, it is dominant over the two other options of APBI and EBRT in this respect (33). From a patient's perspective, the IORT system can have many advantages; since IORT is executed during the operation, it is no longer necessary for the patient to waste his time coming to the radiotherapy center on several occasions, or to wait hours to receive radiation; it causes cost saving opportunities and indirect economic issues as well (34). Another advantage of IORT machine from the service provider's vision is reducing the workload of radiotherapy, because the patient needs only a few sessions to go to the center to get radiotherapy (34). According to the results obtained in this present study, the IORT device is a more cost-effective option compared with the EBRT device and can be used instead of it. However, more clinical studies, yet more accurate ones, and especially clinical local studies on this device are required to make more appropriate decisions regarding the use of IORT so that policy makers can make decisions based on more realistic results. The study faced some limitations, the first of which being limited access to electronic data bases and internal and external resources. The second limitation was lack of sufficient clinical studies about the real effectiveness of IORT device on native conditions due to the novelty of this technology. Third, since IORT was a new device, commuting to Tehran for collecting the cost information was difficult. Finally, it would better if all the consequences resulting from the use of devices be involved in decision-making that requires further clinical trials in this field (IORT device) in Iran.

Conclusions

Generally, the study showed that the use of IORT in comparison with EBRT device in patients with breast cancer is more economical.

Competing Interest

None declared.

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