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Review Article

Economical Evaluation of Cancer Types Using Intensity-Modulated Radiation Therapy Compared to 3D Conformal Radiation Therapy: A Systematic Review

Vahid Alipour [1], Aziz Rezapour [1], *Amin Adel [2], Arefeh Pourtaleb [2], Mitra Bazrafshan [2], Mozhgan Sadat Ghaem Mohammadi [2], Reza Jahangiri [2]

1. *Health Management and Economics Research Center, Iran University of Medical Sciences, Tehran, Iran*
2. *School of Health Management and Information Sciences, Iran University of Medical Sciences, Tehran, Iran*

***Corresponding Author:** Email: a-adel@student.tums.ac.ir

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Abstract

Background: Cancer is the second most common cause of death worldwide. Economic evaluation of cancer treatment to reduce costs can save the health care system millions of dollars while optimizing care. Therefore, this systematic review aimed to study the economic evaluation of cancer treatment using intermediate intensity radiation therapy (IMRT) compared to conventional 3D conformal radiation therapy (3D-CRT).

Methods: Literatures from PubMed, Embase, Cochran Library, Google scholar, Scopus and Iranian databases were retrieved since Jan 2000 to Apr 2020 for eligible English studies. The quality of the studies was evaluated using Cheers' checklist and then the textual data were analyzed manually by content analysis method.

Results: Overall, 1790 articles were retrieved, of which 12 studies were reviewed. The article quality score ranged from 14.5 to 23 out of a maximum of 24 points. Eleven studies referred to cost-effectiveness analysis and one study referred to cost-utility analysis. Studies have been conducted in the United States, Canada, Australia, Brazil, the Netherlands, the United Kingdom, and Hungary. IMRT appears to be a cost-effective treatment strategy for rectal cancer, soft tissue sarcoma, and localized carcinoma of the pharynx, and for prostate cancer in terms of prolonging survival, but it is a cost-effective treatment strategy for head cancer. In addition, the neck was not in India's cancer control program.

Conclusion: The results can help to decide whether to use radiation therapy and radiotherapy in the standard treatment path. Furthermore, they underline that IMRT treatment technique was cost effective for a long-time care service.

Keywords: Cancer; Radiation therapy; Radiotherapy; Economic evaluation

Introduction

Cancer is a major public health concern worldwide and is associated with significant healthcare costs. Rising in the incidence of various types of cancers and the number of new ones has been estimated while approximately 60% of these new cases would be in less developed parts of the world (1, 2). Even more importantly, cancer incidence is estimated to double by 2035 (3). This

disease burden exerting significant strain on populations and health systems at all income levels (4).

Up to now, radiation therapy technology has steadily improved to reduce adjacent normal organ side effects and improve therapeutic effects in tumors. Radiation therapy has evolved from conventional two-dimensional therapy to three-dimensional conformal therapy (3D-CRT).

Recently, radiotherapy technologies using intensity-modulated radiation therapy (IMRT) have been applied in most cancers (5). IMRT not only specifically targeting the tissue mass in relatively higher doses but also producing a more conformal radiation dose distribution, resulting in minimum damage to normal tissue adjacent to the targeted area (6). Intensity-modulated radiation therapy depicts a new paradigm in radiation treatment planning and delivery for treatment of cancer with enormous potential (7). Therefore, over the past decade, IMRT has become a widely accepted alternative to 3DCRT for many cancers (8); however, these advances do not come without a risk (6). IMRT may be cost effective compared with conventional RT in select patients (9) but it remains unclear whether it is cost effective generally, given its increased expense (10).

In order to provide a precise and better view on this issue, we aimed to systematically review the economic evaluation studies of cancer treatment using Intensity modulated radiation therapy (IMRT) in comparison with conventional 3D Conformal Radiation Therapy (3D -CRT). Intensity modulated radiation therapy as one of the proposed methods among other methods compared with the 3D conformal radiotherapy method and its reports can be used for cancer treatment policy making.

Methods

Database and Search strategy

A systematic review was conducted using multiple electronic databases (PubMed, Web of Science, Embase, Cochrane Library and Scopus, and reference lists) from Jan 2000 to May 2019. All English published economic evaluation studies (cost-effectiveness, cost-benefit, or cost-utility) that compared IMRT and 3D-CRT treatment technique for cancer. A specific search strategy was used for each database (Fig. 1). All studies were imported to Endnote software (version X7; Thomson Reuters)

Inclusion and exclusion criteria

All full economic evaluation studies were included (Cost-effectiveness, cost-utility analysis, cost-benefit analysis) and the PICO framework was defined as follow:

Population (P): Cancer patients treated with radiotherapy. Intervention (I): Radiation therapy with moderate intensity. Comparison control or intervention (C): Conventional three-dimensional radiotherapy with any number of samples. Primary Implications (O): Increased cost-effectiveness ratio

None full economic evaluation study was excluded such as review, letters, abstract, guidelines, editorial, protocols, poster presentation and commentary. In addition, no studies in other languages were considered. The Literature review and retrieval flow diagram is shown in Fig. 1.

Quality assessment and data extraction

All the identified papers were imported to the Endnote software (version X7; Thomson Reuters), and duplicate papers were deleted. Then, two researchers using the principles of PRISMA independently reviewed the remaining studies. If the study is relevant, in the next step, the full text of the study was carefully reviewed and the required information was extracted and summarized in a designed form. These economic evaluation studies were quality assessed by three researchers using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. This checklist includes 5 questions with 24 criteria that examine the design of each economic evaluation study in terms of title and abstract/introduction and problem statement/method/findings/and discussion and conclusion in the mentioned country. Studies with at least 15 of the 24 criteria of the CHEERS

checklist were considered to determine transfer probabilities, probability distribution of parameters, and cost dimensions of interventions (11).
For studies in final stage, a sheet was formed in the data extraction Excel file in which the basic information of the selected studies, including the author's name, year of publication, study population, effectiveness index, and viewpoints of the study, model type usage, cost-effectiveness results of the methods used and type of sensitivity analysis method were recorded.
Finally, textual data were analyzed manually by content analysis method.

Ethical approval

This study was approved by the Ethics Committee of the Research department of Iran University of Medical Sciences. (Grant IR.IUMS.REC.1398.1071)

Results

Our electronic search yielded 1790 potentially relevant publications. After automatic removal of duplicates, 1105 records were screened based on the title and abstract and 770 remained. The full text of relevant reviews was screened and finally 12 studies were selected.

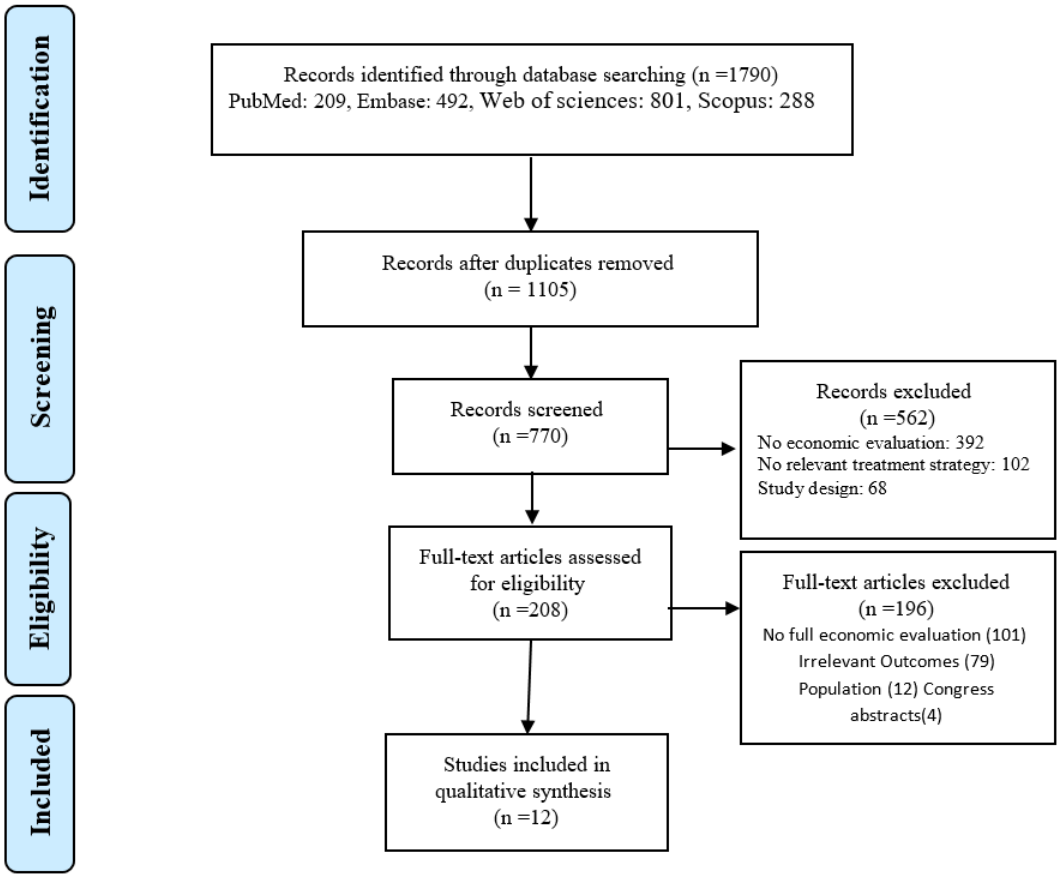

Fig. 1: PRISMA Flow diagram of literature review process

Quality scores for articles based on the Cheers checklist ranged from 14.5 to 23 out of a maximum of 24 points.

Study design

Of the reviewed studies, eleven were cost-effectiveness studies and one was cost-utility analysis (12). Regarding the viewpoint of the

studies three were from the payer's perspectives (13-15), one was from the society perspective (16), and eight studies considered health system perspective (12, 17-23). In terms of time horizon, it has been reported between 2 years to lifetime. Four studies designed for lifetime (13, 16, 18, 21), one was a 20-year study (17), one was a 5-year study (14), and two were 10-year studies (15, 22). Furthermore, one was a 2-year study (19), and one was planned for 2.5 years (23), one was a 5-10-15 year study (12), and one was a 2-15 year study (20). In terms of the effectiveness index in all studies, QALY is mentioned.

Discount rate for cost and effectiveness were reported 3% (12, 16, 19, 22), 3.7% (15), 3.5% (18), 5% (17, 21, 23) in reviewed article and it wasn't mentioned in three studies (13, 14, 20). Willingness to pay and threshold, in six studies were $ 50,000 (12-14, 17, 22, 19) and in two studies were 20,000 euros (15,18) and a study was one GDP per capita (16). However, three studies did not indicate the willingness to pay (20, 21, 23).

Setting

These studies were conducted in the India (16), USA (12-14, 22, 19), Canada (21, 23), Australia (17), Brazil (20), UK (18) and Hungary (15).

Study population

IMRT treatment technique was used for cancer patients. Specifically, one study focused on Anal cancer (13), five studies on prostate cancer (12, 15, 17, 18, 21), and three were about head and neck cancer (16, 20, 19). One study looked at soft tissue sarcoma (14) and one at oropharyngeal cancer (23), and one study looked at different types of cancer with radiation therapy (22).

Cost-Effectiveness Results

To treat head and neck cancer; according to a study in India (16), IMRT and 3DCRT are not cost effective. The costs and benefits of using IMRT for other potential symptoms (e.g. prostate, lung) need to be assessed before being introduced in India. In Brazil (20), IMRT was considered cost-effective from the perspective of the Brazilian public health system. For the treatment of anal cancer in the United States (13), IMRT was a cost-effective strategy for the treatment of anal cancer, despite the reduction in acute toxicity associated with treatment and the costs associated with managing this toxicity. In order to treat prostate cancer; in the UK (18), IMRT could be very cost-effective if it could be used to prolong survival. Otherwise, being cost effectiveness is not certain. Carter's study in Australia (17) estimated that IMRT has a long-term advantage over 3DCRT in terms of improving effectiveness and reducing costs. This result was based on clinical judgment and literature review, and for greater strength conclusions long-term clinical trial studies is required. In Canada, IMRT appears to be cost-effective compared to the equivalent dose of 3DCRT for radical irradiation (> 70 g) of prostate cancer (21). In Hungary, compared to 3DCRT, both IMRT and HF-IMRT lead to increased health at a lower cost (15). High doses of IMRT are more cost-effective compared to conventional doses of 3DCRT. Although IMRT is more expensive than 3DCRT for treating soft tissue sarcoma, it is more effective than 3DCRT in reducing severe toxicity and local recurrence and improving quality of life (14). In addition, IMRT is the preferred method in 64% of possible sensitivity analysis tests. Third-party payers should support IMRT as a cost-effective option for pre-management of soft tissue sarcoma surgeries. IMRT was cost-effective, however, at the upper limits of acceptability. Using Markov model, IMRT evaluated to be cost effective in the treatment of a 70-year-old with intermediate-risk prostate cancer (12).

Konski et al. conducted a study aimed to compare the cost and effectiveness of IMRT with 3DCRT for the treatment of locally advanced oropharyngeal cancer. In the treatment of locally advanced oropharyngeal carcinoma, the IMRT strategy appears to be cost-effective when compared with 3DCRT (22) (Table 1).

Table 1: General characteristics of included economic evaluations

Title	*authors/year/ Country*	*perspective/ Time horizon (year)*	*Evaluation technique/ index*	*Estimating resources and costs*	*Discount rate*	*sensitivity analysis*	*Threshold*
Cost-effectiveness of treating head and neck cancer using intensity-modulated radiation therapy: implications for cancer control program in India.	Chauhan AS, Prinja S, Ghoshal S, Verma R./202/India	Societal/ life time	Cost effectiveness/ QALY	From a large public sector hospital in India and existing randomized controlled trials.	3%	multivariate probabilistic sensitivity analysis (PSA)	one GDP per capita
Cost-effectiveness analysis of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for anal cancer	Hodges JC, Beg MS, Das P, Meyer J. /2014/ USA	Payer/ life time	Cost effectiveness/ QALY	Based on the final 2014 local Medicare payment schedules for free-standing facilitybased billing and based on clinical care in institutions, surgical studies, and expert opinion.	Not reported	One-way, 2-way, and probabilistic sensitivity analyses (PSA)	$50,000
A model of the cost-effectiveness of intensity-modulated radiotherapy in comparison with three-dimensional conformal radiotherapy for the treatment of localised prostate cancer	Hummel, S. R., M. D. Stevenson, et al. /2012/ UK	Payer, NHS/ life time	Cost effectiveness/ QALY	From St Bartholomew's Hospital, and clinical guideline recommendations and clinical consultation, and derived from the cost-effectiveness analysis of docetaxel chemotherapy in these patients, and chemotherapy costs, palliative care costs, and terminal care	3.5%	Univariate sensitivity analysis Probabilistic sensitivity analysis	20,000 and 30,000 pounds

				costs.			
A decision model to estimate the cost-effectiveness of intensity modulated radiation therapy (IMRT) compared to three dimensional conformal radiation therapy (3DCRT) in patients receiving radiotherapy to the prostate bed	Carter, H. E., A. Martin, et al/2014/Australia	Health System/ 20	Cost effectiveness/ QALY	From a prospective study of 28 patients. One-time transfer costs for deceased patients were determined. Unit costs were allocated to various resource use items from the public expenditure program.	5%	Univariate sensitivity analysis Probabilistic sensitivity analysis	$50,000
Cost-Effectiveness Analysis of Intensity Modulated Radiation Therapy Versus 3-Dimensional Conformal Radiation Therapy for Preoperative Treatment of Extremity Soft Tissue Sarcomas	Richard, P., M. Phillips, et al./2016/Washington	Third-party payer/ 5	Cost effectiveness/ QALY	From the 2015 Medicare annual payment schedule (CY), and the Red Book, 2010 Edition, and data from the National Inpatient Sample Database (NIS), the Health Services Cost and Utilization Project, and the Agency for Healthcare Research and Quality based on the Medicare Diagnosis Severity Related Group (MS) - DRG) code 15.	Not reported	One-way, 2-way, and probabilistic sensitivity analyses (PSA)	$50,000
Cost-effectiveness of intensity-modulated radiotherapy	Yong JH, et al./2012/Canada	Payer, Canadian Health System/ 2.5	Cost effectiveness/ QALY	The cost of radiation therapy includes the cost of	0.05	Probabilistic sensitivity analysis (PSA)	Not reported

in oropharyngeal cancer.				equipment (capital cost, specialized construction cost, maintenance and operation cost), equipment cost (immobilizer), personnel cost, and overhead costs of the radiotherapy program and the hospital.			
Cost-effectiveness of intensity-modulated radiotherapy in prostate cancer	Yong JH, et al./2012/Canada	Payer, Canadian Health System/ life time	Cost effectiveness/ QALY	Capital and equipment construction costs and equipment life expectancy were obtained from the capital planning department at the Ontario Cancer Care Center, and operating cost estimates were obtained with financial information from two experienced radiotherapy programs in Ontario. Completed. The maintenance fee is 10% of the acquisition fee. Physician fees included physician fees and basic funding from the Ministry of Health and staff salaries from Princess Margaret Hospital.	5%	Probabilistic sensitivity analysis (PSA)	Not reported

Cost-effectiveness analysis of intensity-modulated radiation therapy with normal and hypofractionated schemes for the treatment of localised prostate cancer.	Zemplenyi AT, et al./2018/Hungary	Third-party payer/ 10	Cost effectiveness/ QALY	Radiation costs, outpatient poisoning and medical equipment costs were obtained from the 2015 Medicare annual payment schedule (CY). Drug costs were obtained from the Red Book, 2010 Edition.	3.70%	Univariate sensitivity analysis - probabilistic sensitivity analysis	20000 euros
Two-year and lifetime cost-effectiveness of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for head-and-neck cancer	Kohler RE, et al./2013/North Carolina	Health System/ 2	Cost effectiveness/ QALY	Hospitalization costs, costs related to long-term side effects, initial radiation therapy costs, Medicare/single institution costs	3%	One way Probabilistic sensitivity analysis (PSA)	$50,000
Cost-effectiveness of intensity-modulated radiation therapy	Konski A./2005/Philadelphia	Payer, Medicare USA/ 10	Cost effectiveness/ QALY	The cost of hormones was calculated based on the average price obtained from the Red Book of Medicines. The amount of 100 dollars was considered for Gosserlin's administration. The average cost of all treatments in the last year of life, including chemotherapy, is estimated to be 24,000 US dollars.	3%	Monte Carlo simulation - two-way	$50,000

Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer	Konski A, et al. / 2006/USA	Payer, Medicare USA/ 5-10-15	Cost utility/ QALY	IMRT cost, cancer center reimbursement, RT cost, chemotherapy cost, hormone therapy cost	3%	Monte Carlo simulation - two-way	$50,000
Intensity-modulated radiation therapy (IMRT) versus 3-dimensional conformal radiation therapy (3D-CRT) for head and neck cancer: cost-effectiveness analysis	Marta NG, Weltman E, Ferrigno R./ 2017/ Brazil	Health System/ 2-15	Cost effectiveness/ QALY	Costs of doctor's consultation, CT simulation, IMRT mask, nursing consultation, preliminary consultation / based on the opinions of expert members of the Brazilian Society of Radiation Oncology with regard to public health	Not reported	One-way Probabilistic sensitivity analysis (PSA)	Not reported

Discussion

We aimed to systematically review the economic evaluation studies of cancer treatment using radiotherapy with adjusted intensity (IMRT) compared to conventional three-dimensional radiotherapy (3D-CRT). During the last decades, the number of studies in this field has been rapidly growing. This is not surprising because insufficient financial resources and increasing costs of the health system, health economics and especially pharmacological analysis have become an important criterion for decision-making, modern policies in health care and of course patient access (24-26). Over time, magazines and articles on cancer issue and its care are becoming more specialized (24). IMRT treatment seems to be a cost-effective method in long term. However, in terms of study perspective, time horizons, model and country hypotheses, there are inconsistencies between studies. Most studies have been conducted in the United States and different cost thresholds have been used in various studies (13, 14, 21, 27). Cost-effectiveness studies on cancer treatment methods has become one of the most important research priorities in different countries (12, 14, 15). Most retrieved studies considered cost-effectiveness in evaluation, while only one study reported cost-utility analysis. Unlike the current study, in another systematic study on the cost-effectiveness of prostate cancer screening, most economic evaluation studies has been reported cost-utility analysis, while in both studies the final outcome was presented in QALY (28). Studies in India, the United States, the United Kingdom, and Canada on the treatment of cancer with moderate-intensity radiation therapy compared with three-dimensional radiotherapy with a lifetime horizon have been found to be

cost-effective for a sustainable life cycle (13, 18, 21). The exception to this was the study by Chauhan et al. in the treatment of head and neck cancer, who stated that IMRT and 3DCRT are not cost-effective in Indian society and health systems (16).

In another study on the cost-effectiveness of IMRT in prostate cancer, the findings confirm the cost-effectiveness of this treatment without considering the time horizon compared to other older methods (29). In this regard, IMRT intervention is less costly and more effective than 3DCRT with an additional 20 QALYs gained and over $1.1 million saved per 1000 patients treated and it is the dominant option. Finally, in this study, IMRT has a long-term advantage over 3DCRT in terms of improving efficiency and reducing costs. However, this result was obtained based on clinical judgment and literature review, and long-term clinical trial studies have been proposed for stronger conclusions (17).

Most studies on the importance of cost-effectiveness evaluation have been conducted focusing on the perspective of the health system and the payer, and in most studies, indirect costs such as lost productivity are not considered. As the findings indicated the discount rate has been varied from 3% (16, 19, 22), 3.7% (15), 4% (18), 5% (17, 21) to 13% (14). Therefore, considering the importance of the discount rate in the output of the results, determining the appropriate value should be considered. The findings of this study showed that most of the economic evaluation studies that compared IMRT with 3DCRT were conducted on prostate cancer patients. In other words, the method of radiation therapy with moderate intensity is used more in the treatment of patients with prostate cancer and the evidence shows the cost-effectiveness of this treatment compared to other treatments (15, 17, 18, 21). Major studies have been conducted on the cost-effectiveness of cancer treatment interventions in high-income countries (13, 14, 18).

These studies have been designed and conducted in completely different conditions in terms of economy and health system with the conditions of low- and middle-income countries, so we should be careful in generalizing the results to low- and middle-income countries with different context. On the other hand, the fact is that these studies have been conducted in various countries and this makes it difficult to compare the results of incremental cost effectiveness (ICER) because the willingness to pay is different. Accordingly, in the present study, cost-effectiveness variable was identified based on the findings of the reported sensitivity analysis, and other complementary analyzes were performed outside the scope of this study. The present study is one of the first studies designed in systematic review. One of the strengths for the present study is that it is one of the first systematic studies on the cost-effectiveness of IMRT treatment for cancer patients, conducted using the principles of the PRISMA statement for research and reporting.

Conclusion

The results can help to decide whether to use radiation therapy and radiotherapy in the standard treatment path. Furthermore, if IMRT can be used to prolong survival, it is cost-effective. Otherwise, the cost-effectiveness is uncertain. For cancer treatment approach, there is a growing need for future economic evaluation studies. Subsequent these economic evaluation studies should use the best practice guidelines for conducting and reporting to ensure that all elements and assumptions are precisely reported. Moreover, researches in the field of economic modeling would be needed including all costs and implications related to technology which considered social perspective and appropriate time horizon. They can also be used to make a better decision about insurance coverage for treatment technology, as well as licensing. Due to the development of new methods of cancer diagnosis and treatment and because of increasing costs and limited resources, the use of economic evaluation studies is necessary for policymaking and detailed planning for the allocation and optimal use of resources. Newer treatment techniques seek to increase the quality of treatment and reduce the

side effects of treatment, so studying the costs of using new techniques and their effectiveness can help decision makers and those who pay for treatment.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that there is no conflict of interests.

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