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Health technology assessment of image-guided radiotherapy (IGRT): A systematic review of current evidence

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Abstract

Background: Image-guided radiotherapy used multiple imaging during the radiation therapy course to improve the precision and accuracy of health care provider's treatment.
Objectives: This study aims to assess the safety, effectiveness and economic aspects of image-guided radiation therapy for decision-making about this technology in Iran.
Methods: In this study, the most important medical databases such as PubMed and Cochrane Library were searched until November 2014. The systematic reviews, health technology assessment reports and economic evaluation studies were included. The results of included studies were analyzed via the thematic synthesis.
Results: Seven articles were included in the study. The results showed that image-guided radiation therapy, regardless of the imaging technique used in it, is associated with no major toxicity and has the potential to reduce the symptoms of poisoning. Using image-guided radiation therapy for prostate cancer resulted in substantial improvement in the quality of the received dose and optimal therapeutic dose of radiation to the targeted tumor while the radiation dose to the surrounding healthy tissues was minimal. Additionally, image-guided radiation therapy facilitated the diagnosis and management of exception deviations, including immediate changes and gross errors, weight loss, significant limbs deformity, systematic changes in the internal organs and changes in respiratory movements. Usage of image-guided radiation therapy for prostate cancer was associated with increased costs.
Conclusion: Current available evidence suggests that the image-guided radiation therapy can reduce the amount of radiation to healthy tissue around the tumor and the toxicity associated with it. This can enhance the safe dose of radiation to the tumor and increase the likelihood of destruction of tumor. The current level of evidence required conducting further studies on the costs and effectiveness of this technology compared with conventional technology.

Keywords: Image-Guided Radiotherapy, Health Technology Assessment, Systematic Review.

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Introduction

Radiotherapy is a type of therapy that uses a high dose radiation for destruction and stopping the cancer cells growth. Interventional radiotherapy is done under guide of an image and this imaging is involved in each key phase of procedure, including patient staging, simulation, therapy planning and radiation of beam until follow-up of patient (1). The purpose of radiotherapy is improvement of survival, control of tumor progression, attention to symptoms and im-

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provement of the quality of life of cancer patients throughout the world (2). Image-guided Radiotherapy (IGRT) is a new form of radiation therapy that uses X-ray imaging for determination of tumor location and proper focusing of the radiation to the tumor. Low controllability of tumor location reduces the accuracy of beam radiated to the tumor sustaining tissue. IGRT with the purpose of imaging in operating room guides the radiation to target area and makes change in the tumor volume during the therapy process (3).

IGRT may be defined as below: Increasing the accuracy by repeated imaging of target and/or healthy tissues before the therapeutic action and matching the image with the therapy (4). IGRT is repeated 2D or 3D imaging during a radiotherapy course. In this method, computer is used for making an image of tumor in order to guide the radiation during the radiation therapy. The purpose of IGRT process is improvement of accuracy in radiation therapy area for reduction of healthy tissues exposing to radiotherapy. In other word, in IGRT, radiation therapy is more precise and lower loss is incurred to the surrounding tissues (5).

IGRT measures the changes of tumor location, size and shape during the therapy course and applies a few settings for maximizing the accuracy of angle of radiation and reduction of healthy tissue under radiation. These actions increase the probability of tumor control, reduce the risk of infecting with poisoning after treatment and facilitate the development of shorter radiotherapy courses (6).

IGRT is used for treatment of tumors within regions of body that are exposed to motion such as lungs (under impact of respiration), liver and prostate gland as well as the tumor located in proximity of vital organs and tissues. This technique often together with Intensity-Modulated Radiation Therapy (IMRT), Proton Beam Therapy, stereotactic radiosurgery or Stereotactic Body Radiotherapy (SBRT) that are advanced modes of radiation therapy with high accuracy and for providing precise doses of radiation to malignant tumor or specific regions in the tumor, uses X-ray accelerators under control of computer (7).

Research Questions

This article addressed the question 'what is safety, effectiveness and economic aspects of image-guided radiation therapy compared to the other radiation therapy methods for treatment of cancer patients in the light of pre-specified outcomes?

Study Objectives

This study aims to assess the safety, effectiveness and economic aspects of image-guided radiation therapy for decision-making about this technology in Iran.

Methods

Literature Search

The most important medical databases including Cochrane Library and PubMed were searched using two search strategies via Mesh to find relative articles without limitation, until Nov. 2014 (Appendix 1). Fifty-one articles were retrieved from Cochrane and 460 ones from PubMed. Duplicated articles and unrelated ones were removed and 361 articles remained. The full text of articles obtained from previous stage were considered based on the inclusion and exclusion criteria determined by the researchers, and finally based on consistency to these criteria, 8 articles included in final phase of study (figure 1; tables 1 and 2). The articles were considered independently by two reviewers and a structured form was used for collection of data from included studies. Data of studies was collected by one researcher and controlled by a second researcher.

Scope

Safety, Effectiveness and Overview of Economic Aspects of this technology.

Inclusion criteria

Study design

Whereas this study is a health technology assessment by an accelerated method, crite-

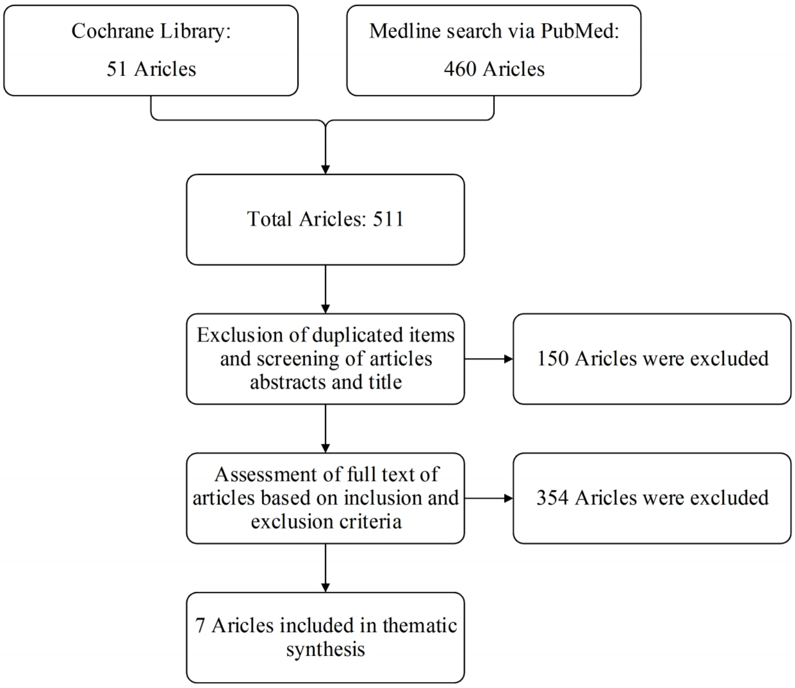

Fig. 1. The Flowchart of Articles Process

rion of study type based on clinical evidences pyramid included systematic review studies and health technology assessment studies, economic evaluation studies, health technologies horizon scanning studies were included in the study.

Intervention
Image-guided radiation therapy

Population
Population of cancer patients

Comparators
Other radiation therapy methods

Outcomes
The outcomes of the review are: toxicity, contraindications, dosimetry quality, radiation therapy quality and tumor destruction period, effectiveness on patients' consequences, treatment costs and cost-effectiveness.

Exclusion criteria
The studies conducted on the population of healthy humans, animal, phantom and cadaver, were removed.

Quality Appraisal Method
Although most of included studies had a desirable quality (using CASP checklist), quality of study was not used as a tool for exclusion of articles.

Synthesizing Method
Results obtained from included studies were analyzed qualitatively based on thematic synthesis.

Results

Literature Search Results
Out of seven included articles, three articles were economic evaluations (8-10), three ones were systematic review studies (2,11,12), and one was health technology horizon scanning (13). Of these articles, one article had been done in 2013 (8), three in 2012 (2,10,11), two in 2009 (9,13), and one in 2007 (12) (Tables 1 and 2).

Summary of Safety, Effectiveness and Economic Aspects Results

1. *Safety*
Results obtained for safety of this technology was analyzed and classified in toxicity rate subgroup.

Table 1. The List of Included Articles

No.	Study type	Article title	Publication year
1	Economic evaluation	Cost of prostate image-guided radiation therapy: Results of a randomized trial	2013
2	Economic evaluation	Prospective economic evaluation of image-guided radiation therapy for prostate cancer in the framework of the national program for innovative and costly therapies assessment	2012
3	Systematic review	Image-guided Radiotherapy for Rectal Cancer*:* A Systematic Review	2012
4	Systematic review	Image-Guided Radiotherapy: Has It Influenced Patient Outcomes	2012
5	Horizon scanning	Image-guided intensity-modulated radiotherapy	2009
6	Economic evaluation	A cost-outcome analysis of Image-Guided Patient Repositioning in the radiation treatment of cancer of the prostate	2009
7	Systematic review	Review of image-guided radiation therapy	2007

Table 2. The Characteristics of Included Articles

No.	Authors	Country/ publication year	Study design	Cost analysis method	Therapeutic techniques	Consequences
1	Perrier et al (8)	France/ 2012	RCT economic evaluation- two intervention groups received IGRT (daily or weekly) in patients with local prostate cancer	Calculation of costs based on micro costing from hospital approach	IGRT methods (CBCT and EPI-FM) and control times (daily or weekly)	Therapy fraction period, average of additional cost for each patient
2	Ploquin et al (9)	Canada/ 2009	Economic evaluation- two intervention groups received IMRT and 3DCRT in prostate cancer	Activity based Costing	3DCRT and IMRT in patients with localized cancer by KV, MV and CBCT imaging processes	Analysis of cost, consequence of adding IGPR as main part of IGRT to 3DCRT and IMRT
3	Gwynne et al (11)	USA/ 2012	Systematic review including 9 studies related to rectal cancer patients	-	Electronic portal imaging device (EPIDs) -CBCT -Tomography based kilovoltage -Megavoltage computed tomography scan	Internal and intra fractional motion, gross weight of tumor
4	Bujold et al (2)	Canada/ 2012	Systematic review of IGRT used on clinical and economic consequences	-	Ultrasound Plain kv Plain MV Kv CBCT Mv CBCT KV FBCT Mv FBCT	Quality of radiotherapy Consequences of patients
5	Jaffray et al (12)	USA/ 2007	Systematic review	-	EPIDs CBCT IMRT Megavoltage computed tomography scan	Value of radiation to tumor tissue and healthy tissue
6	Pommier et al (10)	France/ 2013	RCT economic evaluation- two intervention groups received IGRT (daily or weekly) in prostate cancer	Calculation of costs based on micro - costing from hospital viewpoint	EPIDs for control group CBCT for intervention group	Additional cost of daily control, quality of patient position in comparison to weekly control of additional cost of 3D imaging in comparison to 2D in portal imaging for controlling the patient position
7	Zamura et al (13)	Australia/ 2010	Horizon scanning	-	FBCT IMRT IGRT And other IGRT modes	Safety, effectiveness, cost-effectiveness and ethical aspects

1-1. *Toxicity Rate:* In general image-guided radiotherapy, regardless of its imaging technique, is not associated with a major toxicity; and in one of the studies, it was proved that the prescribed dose is not associated with toxicity consequences. IGRT has the potential of reducing the poisoning symptoms (13). One of potentially negative aspects of IGRT is its additional radiation dose (2).

2. *Effectiveness*

Results obtained for effectiveness of this technology was analyzed and classified in quality of radiation therapy subgroup:

2-1. Quality of Radiation Therapy: Use of image-guide radiotherapy for treatment of prostate cancer results in relative improvement of dosimetric quality (9). IGRT radiates a desired therapeutic dose of radiation to the targeted tumor, whilst the radiation dose to the healthy surrounding tissues is minimized. This technology with better targeting of cancer tissues, increases the safety and effectiveness of radiation dose. This method has the potential of improving the quality of radiation therapy, reducing the time of tumor destruction as well as reducing the poisoning symptoms. This technology is currently used in Australia in limited capacity (13).

Although there are many instructions for guaranteeing the quality of IGRT equipment, only a few has focused particularly on the effect of IGRT as quality assurance or potential of IGRT for reduction of patient's therapeutic events (2).

Various papers indicate that IGRT is an effective quality control process that reduces the diversity (systematic and random uncertainty) in process outputs (patient position). Computer simulation of these uncertainties shows that the reduction may affect the final clinical areas. Also, IGRT facilitates the diagnosis and management of exceptional deviations, including prompt or false changes such as gross position errors, weight loss, considerable deformation of organs, systematic change in internal organs, changes in respiratory motions, and etc. (2). IGRT increases the probability of applying radiotherapy based on planning so that respective dose is offered to the targets (2).

In a study by Jaffray et al, evaluation of 5-year perspective of this technology, demonstrated that despite of limited data in this field, IGRT indicates a high confidence level of radiotherapy control comparing to other conventional approaches and currently this approach tends to combining 3D or 4D technologies to the therapies with high conical radius. Easier perception of therapeutic goals of abnormal tissue without tumor controllability, is one of the important achievements in this field (12).

In a study by Gwynne et al (11), nine studies were reviewed on internal and intrafractional motion of tumor's gross volume in rectum and mesorectum and clinical target volume using all kinds of imaging methods. An important motion existed in the upper mesorectum. Also, a strong relationship existed between rectal filling and mesorectal motion. This difference was reported based on gender and body mass index. The study indicated enough doses for rectum despite of rectal motion and deformation. The current marginal instructions may not be used in the deformation structures. The margins recommended for clinical target volume to target volume promotion planning are within 1 to 3.5 cm. Reimaging and re-planning may be needed during a therapy period. According to the available data, electronic portal imaging devices must be used to be conformed to the bone anatomy. Further information about internal motion may be obtained from cone beam computed tomography or tomotherapy and if available, use thereof shall be taken into consideration. Individualized anisotropic margins may also be required. Further work is needed for assessment of optimal imaging method including conformity to the bone or soft tissue and to assess if internal motion affects the result of therapy or not (11).

Control of dose distribution to the tumor seems to be studied in many included studies and desirable symptomatic relief of disease progression was found. Comparison between different imaging techniques indicated that megavoltage of CBCT and intraprostatic Seed Maker provide better imaging accuracy than ultrasound-based approaches (13).

3. *Economic Evaluation*

Results obtained for economic evaluation of this technology was analyzed in the therapeutic costs subgroup:

3-1. *Treatment Costs:* Daily use of IGRT and 3D imaging for controlling the patient's position in prostate cancer therapy results in a significant additional cost in comparison to 2D imaging and weekly control (10).

Use of IGRT in prostate cancer treatment increases the costs. Cost-outcome analysis of addition of IGPR as main part of IGRT to 3DCRT and IMRT indicated that if image guiding is only used for changing the patient position in prostate cancer it will relatively increase the costs; particularly through reducing the margin, it is expected that cost-outcome ratio to be reduced (9).

Study conducted by Perrier et al. indicated that the average additional cost for each patient for daily and weekly control was equal to 679 and 187 Euros ($P< 0.0001$), respectively. In comparison to weekly control for CBCT and EPI-FM, daily control strategy was more expensive than weekly control (8). In addition, total mean of fraction period was 21 min for daily CBCT and 18.3 min for EPI-FM. Increase of control frequency from weekly to daily was followed by increase of mean therapy fraction period for 7.3 min (+53%) for CBCT and 1.7 min (+10%) for EPI-FM. In comparison to weekly control, daily control considerably takes more time from oncologist and intervention time of radiologist as well as occupation of operating room for both IGRT methods (CBCT and EPI-FM) (8).

Discussion

This study was applied in Iran aiming to assess safety, effectiveness and economic aspects of image-guided radiotherapy technology for proper decision making. Logical thinking for execution of IGRT is following a "no damage" approach. IGRT may be used as a quality assurance instrument. IGRT may facilitate the execution of new radiotherapy techniques (e.g. SBRT of lung and liver) and in the selected areas and reduce the toxicity and improve local control (2). The current available evidences recommend that IGRT may reduce the radiation to healthy tissue around the tumor and its related toxicity. It can increase the safe dose radiation to tumor and increase probability of tumor destruction (13). Currently, IGRT in clinical operations is a perfect instrument for solving the problems of radiotherapy accuracy. The last achievements of IGRT may reduce the uncertainty of localization so that 1-2mm margin of PTV that is often enough for considering this uncertainty, particularly if motionlessness and enough motion management is provided. Nonetheless, due to other error resources (such as determination of target), PTV margin for many radiotherapy processes must be bigger than 2mm (2). IGRT provides the requirements for radiation of beam dose carefully and using imaging techniques during the therapy to the tumor (13). Most of available evidences about use of radiotherapy during surgery had a low level of evidence and reported consequences are referred to prostate (13).

This study shows low benefits about dosimetry of using IGRT in prostate cancer patients' repositioning states, but lower radiation to the areas around lesion without increasing the costs is assumed as clinical benefits of IGRT utilization. Generally, benefits of its cost effectiveness consequences in comparison to non-image guided option is higher and use of weekly radiation therapy with the 3DCRT technique in EPID form has the best position in terms of effective cost consequence.

Additional costs for various strategies of IGRT of prostate are relatively average. Daily IGRT combining with IMRT is recommended for patients prescribed to receive high radiotherapy dose for prostate. Economic studies applied on limited range of patients concluded that IGRT is essentially expensive due to the longer therapy period with imaging; however, this subject is associated with IGRT type. Yet, the desirable times for IGRT have not been confirmed that may be due to cost impacts of IGRT. Daily control groups are recommended for regular or random prostate repositioning. Control of days 1, 2, 3 and weekly control is recommended for regular prostate repositioning (mean prostate displacement during therapy).

Conclusion

Overally, it is concluded that IGRT may reduce the radiation to healthy tumor surrounding tissue and related toxicity. It can also increase the safe dose of radiation to tumor and probability of tumor destruction. Moreover, current levels show the need to applying further studies on comparison of effectiveness and costs of this technology in comparison to conventional technologies.

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Appendix 1

In this study, two search strategies were used:

Search strategy for Cochrane library

#1)	Image near/2 guide*	365
#2)	radiation near/2 therapy	3999
#3)	#1 and #2	45
#4)	IGRT	13
#5)	#3 or #4	51

Search strategy for Medline via PubMed

#1)	Search "image guided radiation therapy"	460
#2)	Search "image-guided radiation therapy"	460
#3)	Search ((#1 or #2))	460