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THE COMPARATIVE EFFECTIVENESS OF INTENSITY-MODULATED RADIOTHERAPY (IMRT) IN CANCER TREATMENT: SYSTEMATIC REVIEW

Naurah Nazhifah[1*], Wahyudi Nurhidayat[2]
Radiation Oncology Medical Staff Group, Dr. Mohammad Hoesin Palembang General Hospital[1,2]
[*]*Corresponding Author* : naurahnazhifah@gmail.com

ABSTRACT
Intensity-Modulated Radio Therapy (IMRT) are often used to treat cancer because of its advantages and low risks. This study aims to investigate the evidence supporting the routine use of IMRT in various cancer in the aspects of conformity and homogeneity indices, toxicity, quality of life, and life expectancy. This is a systematic review which examines articles published from 2019 – 2024 in Google Scholar, Proquest, Elsevier, Portal Garuda and local journals databases. Article searched using keywords like Radiotherapy, Intensity-Modulated Radiotherapy, Effectiveness of Intensity-Modulated Radiotherapy, and comparison of Intensity-Modulated Radiotherapy. This study found the superiority of IMRT compared to other methods in the aspects of achieving conformity and homogeneity indices, toxicity, quality of life and life expectancy.

Keyword ***:*** *radiotherapy, intensity-modulated radiotherapy, systematic review*

INTRODUCTION

Cancer is one of the most fatal diseases of recent times that causes several deaths every year.. More than 19.3 million new cancer cases were diagnosed and reported recently, causing approximately 10 million deaths in 2020 (Chhikara & Parang, 2023). In Indonesia, the number of cancer cases reaches 6% of the population and is ranked sixth in the cause of death(Anggraeni & Novianty, 2021).

Out of these total cases, the incidence of commonly diagnosed cancers worldwide were breast, lung and prostate cancer. Cancer with the highest mortality are lung, liver, stomach and breast cancer. In sex-disaggregated cancer incidences and deaths data, the most common cancers detected in men are lung, prostate, non-melanoma skin and stomach cancer, For female, it was breast, lung and cervical cancer (Chhikara & Parang, 2023). Mortality-wise, the most deaths in men occurred due to lung, liver and stomach cancer, while deaths in women are caused by breast, lung and cervical cancer (Chhikara & Parang, 2023).

According to a prediction, cancer still will be a worldwide health threat in the future(Gaidai et al., 2023)). Therefore, it is necessary to develop effective treatments for cancer (Chhikara & Parang, 2023).

One of the treatment methods used is Intensity-Modulated Radio Therapy (IMRT). IMRT is a nevolving technology. It allows the implementation of highly conformal, even concave, dose distributions. Traditional radiation therapy techniques, including three dimensional conformal radiation therapy (3-D CRT) with uniform radiation intensity and/or with simple beam fluence modifying devices like wedges, do not provide a method for sparing critical structures that push into and are partially or fully surrounded by a target or combination of targets (Vatnitsky et al., 2008). IMRT requires a treatment planning system (TPS) that allows 3D target volume and organ at risk delineation, defined dose plan objectives, formal plan assessment using 3D dose distribution and DVH criteria (as a minimum) and enhanced patient specific quality assurance (Staffurth, 2010).

Now, IMRT used in almost 60%–80% of radiotherapy (Das et al., 2020). The generally positive findings for toxic effects and quality of life are consistent with the ability of IMRT to better control the dose distribution inside (ie, dose homogeneity and simultaneous integrated boost) and outside (ie, selective sparing of organs at risk) the planning target volume. IMRT is frequently chosen over non-modulated external-beam radiation two-dimensional (2D) and three-dimensional (3D) techniques (known as non-IMRT) on the basis of computer planning studies that show better planning target volume coverage and better sparing of organs at risk. The possibility of generating concave dose distributions and tight dose gradients around the targets makes IMRT especially suitable to avoid organs at risk, such as the rectum and small bowel in prostate cancer and the spinal cord or optic structures in head and neck cancer. The tolerance of these organs at risk is often less than the prescription dose and IMRT is used in an effort to deliver a high dose of radiation to the target and to decrease the toxic effects of the treatment without compromising target coverage (Veldeman et al., 2008).

The increased numbers of beams and larger Monitor units of IMRT have raised concerns over the higher skin dose compared with 3D-CRT. However, a study on the acute skin toxicity in the breast IMRT revealed that IMRT was associated with a decrease in the severity of acute desquamation compared with a matched control group treated with conventional radiation therapy. To the contrary, another study investigated the cause of acute skin toxicity observed in the treatment of head and - neck cancer (Cho, 2018).

Another concern over IMRT is the increasing risk of radiation induced secondary cancer. Compared with 3D-CRT, IMRT involves more fields, and thus a larger volume of normal tissue is exposed to lower doses. In addition, the number of monitor units is increased by a factor of 2–5, increasing the total body exposure due to leakage radiation. Both factors will tend to increase the risk of secondary cancers. In theory, IMRT is likely to almost double the incidence of secondary malignancies compared with conventional radiotherapy, from about 1% to 1.75% for patients surviving 10 years. However, a recent study for head-and-neck cancer patients between 1992 and 2012 revealed that a comparison of the 3D-CRT period (1992–2009) with the IMRT usage period (2010–2012) showed that the annual incidence rate of secondary malignancy remained consistently below that of patients who received no radiation, indicating no evidence of an increase in secondary cancer (Cho, 2018).

In Indonesia, several hospitals have used IMRT (Alimin et al., 2024; Prasetya & Faraningrum, 2023; Putra et al., 2024). However, there has been no research that systematically investigated the evidence behind the widespread use of IMRT for various cancer sites by combining Indonesian and international contexts. Therefore, there’s a conduct an analysis of clinical studies that examine the effectiveness of IMRT and its impact on life expecxtancy, quality of life, and toxicity due to treatment.

METHOD

This research is a systematic review that used explicit and systematic methods to catalog and analyze other scientific researches(Page et al., 2021) (Page et al., 2021). PRISMA (Preferred Reporting Items for Systematic Review and Meta Analysis) was used (Stovold et al., 2014)which will examine articles published from 2019 - 2024. Search for articles using keywords in English and Indonesian. The keywords used are: Radiotherapy, Intensity-Modulated Radiotherapy, Effectiveness of Intensity-Modulated Radiotherapy, comparison of Intensity-Modulated Radiotherapy in the Google Scholar, Proquest, Elsevier and national journal databases.

The first search yielded 46 abstracts. From the first initial screening of abstracts, or from full-text articles if the abstract suggested that the report could be included or if the abstract was uninformative, 31 non-IMRT studies were eliminated. This study included clinical studies using IMRT in the inclusion criteria. Research that could be included were about effectiveness, comparisons with other methods, and testing with control groups with methods like randomised controlled trials (RCT), non-randomised controlled trials (NRCT) and case studies.

Adequate articles then selected by looking at the title and abstract of the research using Mendeley and Microsoft Excel. The next stage is a more in-depth evaluation of the article based on content. After selecting articles, 13 articles were found which will be summarized in a table that includes name, title, year, time/place where the research was conducted, study design, and research results.

RESULT

Table 2. Article Review Data

No	Tittle	Author/Year	Research Place	Study Design	Result
1.	Analisis Perbandingan Nilai Conformity Index dan Homogeneity Index pada Teknik 3D-CRT dan IMRT pada Kasus Kanker Payudara Berdasarkan Hasil TPS di RS UNAND	(Husni et al., 2021)	Indonesia	Trial-Eksperimental	The Homogeneity Index and Conformity Index scores for IMRT are more efficient when compared with IMRT
2.	Radioterapi Linac Energi 6 MV Terhadap Kanker Serviks Pada Organ Rektum Menggunakan Teknik 3DCRT dan IMRT Di RSUP Sanglah Denpasar	(Savitri et al., 2022)	Indonesia	Trial-Eksperimental	There was no significant difference between 3DCRT and IMRT. IMRT minimizes dose absorbed by OAR.
3.	Xerostomia Severity and Quality of Life after Nasopharyngeal Cancer Radiotherapy: Intensity Modulated vs Two-dimensional Radiation Therapy in Indonesia	(Gondhowiardjo et al., 2020)	Indonesia	Experimental	IMRT is significantly superior to 2DRT in preserving and sparing the salivary glands, especially the parotid glands, and improving quality of life.
4.	Comparative analysis of intensity modulated radiation therapy and volumetric modulated arc therapy techniques in brain tumor cases to minimize dosage Radiation to organs at risk	(Taufiqurrahman et al., 2023)	Indonesia	Experimental	There was no significant difference in the dose received by the target and OAR in both methods.
5.	Intensity Modulated Radiotherapy and Volumetric Modulated Arc Therapy in the Treatment of Breast Cancer: An Updated Review	(Chang et al., 2022)	International	Systematic Review	IMRT continues to advance in terms of fractionation, toxicity, and targeting of breast cancer.
6.	Comparison between Intensity-Modulated Radiotherapy and Three-Dimensional Conformal Radiotherapy for Their Effectiveness in Esophageal Cancer Treatment: A	(Bai et al., 2020)	China	Trial-Experimental	IMRT can be considered as a means of curing esophageal cancer.

	Retrospective Single Institution Study				
7.	Comparative Effectiveness Analysis of 3D-Conformal Radiation Therapy Versus Intensity Modulated Radiation Therapy (IMRT) in a Prospective Multicenter Cohort of Patients With Breast Cancer	(Jagsi et al., 2022)	International	Systematic Review	IMRT is better able to reduce toxicity in breast cancer than 3DCRT
8.	Intensity modulated radiotherapy might be effective for locally advanced esophageal carcinosarcoma: A single center's experience and review of literature	(Yang et al., 2022)	China	Sytematic Review	IMRT can be a treatment for advanced esophageal carcinoma.
9.	Xerostomia and clinical outcomes in definitive Intensity Modulated Radiotherapy (IMRT) versus three-dimensional conformal radiotherapy (3D-CRT) for head and neck squamous cell carcinoma: A meta-analysis	(De Felice et al., 2020)	Italia	Meta-Analisis	The results of the meta-analysis show the superiority of IMRT
10.	Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial	(Tree et al., 2022)	United Kingdom	Trial-Experimental	There was no significant difference between the results of IMRT and PACE-B in prostate cancer patients.
11.	Comparison of acute gastrointestinal toxicities between 3-dimensional conformal radiotherapy and intensity-modulated radiotherapy including prophylactic regions in chemoradiotherapy with S-1 for pancreatic cancer - importance of dose volume histogram parameters in the stomach as the predictive factors	(Umezawa et al., 2022)	Japan	Trial-Experimental	IMRT reduces toxicity in the gastrointestinal area significantly.
12.	Is IMRT or VMAT superior or inferior to 3D conformal therapy in the treatment of lung cancer? A brief literature review	(Afrin & Ahmad, 2022)	United States of America	Systematic Review	IMRT reduces toxicity and improves Quality of Life
13.	The effectiveness of intensity-modulated radiation therapy versus 2D-RT for the treatment of nasopharyngeal	(Du et al., 2019)	China	Meta-Analisis	IMRT correlates with higher 5-year survival and lower toxicity.

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	carcinoma: A systematic review and meta-analysis				
14.	Effectiveness of noncoplanar IMRT planning using a Parallelized multiresolution beam angle optimization Method for paranasal sinus carcinoma	(Wang et al., 2005)	China	Experimental	Parallelized multiple-resolution beam angle optimization with an optimized noncoplanar beam configuration is an effective and practical approach for IMRT treatment planning.
15.	Effectiveness and Toxicities of Intensity-Modulated Radiotherapy for Patients with Locally Recurrent Nasopharyngeal Carcinoma	(Chen et al., 2013)	China	Experimental	IMRT with 70Gy was efficient for local tumor contro
16.	Effectiveness of intensity-modulated and image-guided radiotherapy to spare the mandible from excessive radiation	(Nguyen et al., 2012)	United States of America	Experimental	Intensity-modulated radiotherapy and tomotherapy-based IGRT may significantly reduce mandibular dose because of the rapid dose falloff and may possibly reduce the risk of osteoradionecrosis
17.	Intensity-modulated radiotherapy for the treatment of prostate cancer: a systematic review and economic evaluation	(Hummel et al., 2010)	United States of America	Systematic Review	Higher doses of intensity-modulated radiotherapy (IMRT), up to 81 Gy, can improve biochemical survival for patients with localised prostate cancer
18.	Intensity-modulated radiotherapy (IMRT) in the treatment of squamous cell anal canal cancer: acute and early-late toxicity, outcome, and efficacy	(Dell'Acqua et al., 2020)	Italy	Experimental	Excellent clinical result and low acute toxicity rates, confirming the use of IMRT as standard of care for curative treatment of anal cancer patients.
19.	Haematotoxicity in IMRT/VMAT curatively treated anal cancer	(Lohynská et al., 2020)	Slovenia	Experimental	IMRT/VMAT enabled to apply a sufficiently effective dose to the tumor and elective areas and reduced not only acute skin, GI and GU toxicity, but also acute haematological toxicity.
20.	Image-guided intensity-modulated radiotherapy in patients with FIGO IIIC1 cervical cancer: efficacy, toxicity and prognosis	(Meng et al., 2023)	China	Experimental	IMRT was well tolerated with excellent survivals. T stage and number of positive lymph nodes

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					significantly influenced the survivals indicating the heterogeneity of stage IIIC1 cervical cancer patients.
21.	Evaluation of the Clinical Efficacy of Intensity-Modulated Radiotherapy Combined with Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma with Extrahepatic Oligometastasis and Prognostic Factors for Patient Survival	(Luo et al., 2023)	China	Experimental	MRT combined with TACE is safe and feasible without major toxicities for the treatment of advanced HCC patients with extrahepatic oligometastasis and results in excellent objective efficacy and a potential survival benefit
22.	Efficacy and toxicity of chemoradiotherapy using Intensity-modulated radiotherapy for unknown primary of Head and neck	(Sher et al., 2011)	United States of America	Experimental	MRT-based chemoradiotherapy for HNCUP was associated with superb overall survival and locoregional control
23.	Optimizing breast cancer treatment efficacy with Intensity-modulated radiotherapy	(Vicini et al., 2002)	United States of America	Experimental	Intensity modulation with our sMLC technique for tangential whole breast RT is an efficient method for achieving a uniform and standardized dose throughout the whole breast
24.	Efficacy of intensity-modulated radiotherapy for resected thoracic esophageal squamous cell carcinoma	(Zhang et al., 2015)	China	Experimental	Postoperative IMRT may be used as a standard treatment strategy for patients with stage III esophageal cancer or positive lymph nodes after surgery

Based on table 2, it can be seen that this research found 24 studies. 17 of them were trials within two groups, 4 systematic reviews, and 3 meta-analyses. 4 studies came from Indonesia, and the rest were international studies. 20 studies are comparative, and 3 studies are descriptive. Of the types of cancer, this study included breast, esophageal, prostate, lung, gastro-intestinal, cervical, neck-head, brain and nasopharyngeal cancers to expand the analysis. In general, IMRT is superior in reducing toxicity, raising life expectancy, and avoiding Organs at Risk (OAR).

DISCUSSION

Husni et.al found that the Conformity Index (CI) value for the IMRT had the highest value or closer to 1 as the ideal value compared to the 3D-CRT. This means that the IMRT dosage covers a more comprehensive target volume.

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The Homogeneity Index value for the IMRT technique gives the lowest value which close to 0 compared to the 3D-CRT. The ideal HI value is 0, which means the dose distribution in the cancer target volume is homogeneous. In the IMRT, the radiation beam will be segmented into smaller pieces so that each volume of cancer will receive the same amount of radiation (Husni et al., 2021).

CI and FI are two additional indicators that are often used to quantitatively assess the quality of a treatment plan. The Conformity Index helps to asses the degree of congruence between prescription isodose and planning target volume (Patel et al., 2020). Then the hemogeneity index (HI) is an objective tool to objective tool to analyz the uniformity of dose distribution in the target volume (Kataria et al., 2012). Both indices had been tested for validity and continues to be developed to be more consistent ((Arruda, 2020; Patel et al., 2020).

For many organs, IMRT studies have yielded valuable dose–volume–toxicity relations, which are now used as objectives in IMRT optimisation (Veldeman et al., 2008). Several recent studies have found that the toxicity of IMRT is lower than other therapeutic methods in several types of cancer (Afrin & Ahmad, 2022; Chang et al., 2022; Du et al., 2019; Jagsi et al., 2022; Umezawa et al., 2022).

In pancreatic cancer, the frequency of acute Gastro-Intestinal toxicity of grade 3 or higher was significantly lower in the IMRTgroup than in the 3DCRT group and IMRT including the prophylactic regions was well tolerable in CRT with fluorouracil-based oral medications for pancreatic cancer (Umezawa et al., 2022). Another study on gastro-intestinal toxicity found that after great improvements in rectal cancer treatment, late gastrointestinal toxicity after radiotherapy is experienced less frequent and less severe (Sipaviciute et al., 2020).

For lung cancer cases, compared to 3D-CRT, IMRT delivers more precise treatment, has better conformal dose coverage to planning target volume (PTV) that covers gross tumour with microscopic extension, respiratory tumour motion and setup margin. 3D-CRT has large number of limitations: low overall survival (OS), large toxicity, secondary malignancies. Although the use of IMRT to treat lung cancer is very promising; This method requires more clinical trials. This also ensures low dose delivery to surrounding organs. High-precision IMRT will increase the chances of tumor control and also the quality of life of patients undergoing treatment (Afrin & Ahmad, 2022).

In cases of head and neck squamous cell carcinoma (HNSCC), IMRT is a method often used for treatment and had superiority over 3D-CRT in terms of grade ≥2 xerostomia rates, but not on clinical outcomes. Its positive impact on tumor control and survival remains to be proven. De Felice et al., 2020). To address this, trials aiming to compare IMRT versus 3D-CRT in an adequate homogeneous HNSCC population are needed.

Based on multivariable analysis in breast cancer treatment, the odds ratio for acute toxicity after inverse-planned IMRT versus 3DCRT was 0.64 (95% confidence interval, 0.45-0.91) with conventional fractionation and 0.41 (95% confidence interval, 0.26-0.65) with hypofractionation. The study found a significant benefit from inverseplanned IMRT compared with 3DCRT in reducing acute toxicity of breast radiation therapy. However, there are still shortcomings and factors that need to be considered. Jagsi proposed that in addition to method, fractionation factors also need to be considered (Jagsi et al., 2022). Then IMRT has a risk of secondary malignancy as a form of toxicity (Chang et al., 2022). Another study evaluating the long-term risk of secondary malignancies with a follow-up period of >10 years in childhood cancer patients treated with IMRT showed that many secondary malignancies developed in the high-dose region after receiving IMRT (Tringale et al., 2022).

In general, the studies are in line with the initial research which states that IMRT has advantages in preventing the risk of acute and late toxicity. IMRT offers improved dosimetry compared with conventional non-modulated radiotherapy techniques, including two-dimensional radiotherapy (2DRT) and three-dimensional conformal radiotherapy (3DCRT) in many clinical scenarios. IMRT can create concave dose distribution and steep dose gradients, sparing normal tissue; it can also be used to improve the homogeneity of the dose distribution (Staffurth, 2010).

Based on several studies, it was found that IMRT has advantages in sparing organ-at-risk (OAR) which is defined as healthy tissue/organs placed close to the Clinical Target Volume (CTV) whose radiation can cause damage and changes to the radiotherapy treatment plan. The heart, for example, in radiotherapy with LINAC for left breast cancer, is an organ at risk (Dian Savitri et al., 2022; Taufiqurrahman et al., 2023).

The basic purpose of all techniques has been to deliver the prescribed dose safely to the target volume containing tumour and as well as to reduce dose to organs at risk (OARs). The detailed comparison between different treatment techniques is very difficult and inexplicit as well (Ansari et al., 2021).

In the context of IMRT which is driven by user-defined planning objectives. Undercontouring of the OAR leads to inferior OAR sparing with potential for increased or unanticipated toxicity; over-contouring could result in unnecessary dose compromises to the TV. In view of the growing use of sequential and multi-modality anti-cancer therapies, inaccuracies in OAR contouring and hence plan optimization risk inappropriate dose delivery to an OAR, with greater potential for "dose-dumping" in normal tissues and subsequent unanticipated toxicity during a patient's treatment pathway.

Another method used is to use RFC, RFC is a comprehensive evaluation tool encompassing a wider range of clinically relevant parameters, isodose volumes and tolerance dose of OARs. It is an advance analysing method to check both the qualitative and quantitative nature of a conformal plan, and at the same time, it assesses the degree of damage of OARs (Ansari et al., 2021).

If $RF \geq 1$, then OAR will be completely damaged as a result of irradiation.

If $RF = 0$, then OAR will remain safe totally during the course of irradiation.

The formula developed to assess degree of damage of OARs including CI of the target is risk factor conformity index (RFC) = CI + RF. In head and neck cases, for right parotid, the maximum value of RF is 1·50 and minimum value is observed as 0·97. Optic nerve, brainstem and spinal cord are completely safe as their RF values are found to be 0 on RF scale (Ansari et al., 2021).

Initial findings regarding the use of IMRT and its effect on quality of life show that IMRT is able to improve the quality of life of lung cancer sufferers by reducing toxicities such as pneumonitis and oesophagitis. The significance of the positive influence of IMRT is also felt in other types of cancer (Forster et al., 2021; Ge et al., 2020; Kawamura et al., 2020; Neibart et al., 2020). In general, the quality of life aspects referred to are functional status, respiratory symptoms, pain, constitutional symptoms, gastrointestinal symptoms, psychological stress, impact on relationships, and impact on finances (Neibart et al., 2020).

Furthermore, another study found that IMRT was correlated with higher 5-year life expectancy (Du et al., 2019). This reinforces previous research which stated that over the last decade the development of IMRT technology has increased the hope of living longer for cancer patients in general (Mondragon et al., 2023). This increase also occurred in various age groups, including elderly individuals (Pfeffer & Blumenfeld, 2017).

CONCLUSION

IMRT as a radiotherapy method has been proven to have several advantages. IMRT has an ideal Conformity Index (CI) and Homogeneity Index (HI). IMRT also has lower rates of treatment-related toxicity compared with non-IMRT treatments. In other studies, it has been proven that IMRT also has a better influence on the patient's quality of life and life expectancy.

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