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REVIEW

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Clinical application of MR-Linac in tumor radiotherapy: a systematic review

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Abstract

Recent years have seen both a fresh knowledge of cancer and impressive advancements in its treatment. However, the clinical treatment paradigm of cancer is still difficult to implement in the twenty-first century due to the rise in its prevalence. Radiotherapy (RT) is a crucial component of cancer treatment that is helpful for almost all cancer types. The accuracy of RT dosage delivery is increasing as a result of the quick development of computer and imaging technology. The use of image-guided radiation (IGRT) has improved cancer outcomes and decreased toxicity. Online adaptive radiotherapy will be made possible by magnetic resonance imaging-guided radiotherapy (MRgRT) using a magnetic resonance linear accelerator (MR-Linac), which will enhance the visibility of malignancies. This review's objectives are to examine the benefits of MR-Linac as a treatment approach from the perspective of various cancer patients' prognoses and to suggest prospective development areas for additional study.

Keywords Radiotherapy, MR-Linac, MRgRT, Tumor, Cancer

Introduction

One crucial method of treating tumors is radiotherapy (RT). Statistics show that radiotherapy is required for more than 50% of cancer patients [1]. Therefore, the advancement of radiation will be crucial in enhancing patients' prognoses and minimizing adverse effects. Both volumetric modulated arc therapy (VMAT) and intensity-modulated radiotherapy (IMRT) are currently used in conventional radiotherapy techniques that achieve uniform radiation dose distribution. However, image guidance is required to achieve correct dose transmission and increase treatment accuracy [2]. Cone beam computed tomography (CBCT) is the most common image-guided radiation (IGRT) technique used in radiotherapy [3]. However, there are some drawbacks to CBCT imaging, including excessive scattering, poor image quality, ionizing radiation, and more [4, 5].

Magnetic resonance imaging (MRI) has the benefits of high soft tissue contrast [6–8] and no ionizing radiation compared to computerized tomography (CT) and CBCT, which can improve the accuracy of tumor target delineation and obtain biological information and functional data of tumor and normal tissues. MRI has developed into a crucial tool for identifying clinical targets and organs in danger. MR and linear accelerator have currently been coupled to create a magnetic resonance accelerator (MR-Linac) [8], a novel piece of radiation equipment that is directed by MR [9, 10]. In addition to offering superior target pictures than CBCT, MR can raise the target dose and improve the robustness [11] of adaptive radiotherapy to obtain a high tumor cure rate. According to several studies [12, 13], MR-guided radiation (MRgRT) is possible, effective, and considerably improves patient prognosis when used to treat tumors [14]. This article mostly reviews the development of

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MRgRT research in the management of various cancer types.

Clinical practice

The most common cancers that are currently being treated with MR-Linac are listed in Table 1, together with information about the treatment, patient count, median follow-up period, overall survival rate, and advanced toxicity. There is a discussion of the thorough descriptions of several malignancies.

Head and neck tumors

As opposed to the chest, abdominal, and pelvic organs, which are more susceptible to motion errors, MR images have advantages in identifying brain tissue, muscle, and nerve. As a result, the target area can be defined using the MRI's superior soft tissue contrast [15, 16]. In a comparison of patients with retropharyngeal lymph node (RPLN) metastases, MRI was found to be more sensitive to detect lymph nodes than CT (74% vs. 65%) [17]. MRI was useful for evaluating dura mater, intracranial, and orbital invasion in nasopharyngeal cancer, and it considerably improved the detection rate of intracranial and pterygopalatine fossa invasion compared to CT [18, 19]. Particularly crucial for radiation for head and neck malignancies, MRI has a high rate of detection for distant metastases associated with poor prognosis. The size, shape, and number of targets [20], which correlate to the tumor stage and have a direct impact on the effectiveness of radiation, are the primary factors that determine how malignant a tumor is. By repeating MRI, the use of MR-Linac during radiotherapy can more clearly demonstrate the tumor response and target changes and enhance the therapeutic impact [21]. The frequency of persistent dysphagia in oropharyngeal cancer (OPC) patients treated with MRgRT fell by 11% compared to intensity-modulated radiation, and the average dosage to the parotid gland was reduced by 3.3 Gy [22], effectively protecting OARs and minimizing adverse effects. According to Ding et al., 50% of OPC patients who had MRgRT experienced complete remission [23, 24]. Another study found that patients with nasopharyngeal cancer (NPC) treated with MRgRT had a 2-year disease-free survival rate of 93.6%, compared to intensity-modulated radiotherapy's 87.5%. Acute toxicity did not differ significantly [25]. As a result, it is possible to apply MRgRT to head and neck malignancies [26, 27], which can not only successfully control the growth of tumors but also lessen the side effects that patients experience [28, 29]. The intra- and inter-fractional movement of head and neck tumors are, however, rather limited when compared to other lesions [30], therefore a proper benefit ratio analysis is crucial to gauge the effectiveness of the current and future treatments for MR-Linac in head and neck tumors.

Chest tumors

Radiotherapy for chest malignancies is primarily influenced by respiratory exercise. Respiratory gating, abdominal control, and employing a CT simulator (4D-CT) to monitor the overall amplitude of the goal movement are the main techniques for controlling respiratory movement in different fractions [31]. The inability of 4D-CT to show intra- and inter-fraction anatomical changes of the target in real-time during treatment makes target

Table 1 Main types of cancer treated with MR-Linac

Tumor sites	Author	Time period	Reference	Treatment	No. of patients	Median follow-up (months)	Overall survival	Toxicity rates (≥ 3) (%)
Nasopharyngeal carcinoma	Fu S et al	4/2018–1/2020	[25]	70.4 Gy/32F	130	25	100% (2 years)	1.5
Lung tumor	Finazzi T et al	2016–2018	[41]	60 Gy/8F (n = 28), 55 Gy/5F (n = 23), 54 Gy/3F (n = 2), 60 Gy/12F (n = 1)	54	21.7	88.0% (1 years)	8
Breast cancer	Nachbar M et al	1/2019	[50]	40.05 Gy/15F	1	3	–	0
Pancreatic cancer	Chuong MD et al	2018–2021	[62]	50 Gy/5F	62	18.6	40% (2 years)	4.8
Cholangiocarcinoma	Luterstein E et al	5/2015–8/2017	[69]	40 Gy/5F	17	15.8	46.1% (2 years)	5.9
Prostatic cancer	Bruynzeel AME et al	10/2019–1/2020	[78]	35 Gy/5F	25	–	–	0

F fractions

definition more challenging. The error in the treatment process is increased for low-fractionated or ultra-low-fractionated stereotactic radiation (Stereotactic Body Radiation Therapy, SBRT), hence accuracy is a requirement for radiotherapy [32, 33]. The target coverage and OARs dose limitation can be greatly enhanced by utilizing the real-time gating technology of MR-Linac and SBRT, which allows for a more precise evaluation of intra- and inter-step changes in anatomy and function [34]. The accuracy of radiation can be considerably improved by MRgRT, which is more useful for chest cancers that are most impacted by respiratory movement. It can both shrink PTV and enhance dose [35]. The PTV delineated with gating and online adaptation on MR-Linac was found in a study of early peripheral non-small cell lung cancer (NSCLC) lesions to be 53.7% smaller than that based on 4DCT [36], demonstrating that MRgRT can not only lower the dose to normal tissue but also improve the accuracy of target coverage when compared to CT-guided radiotherapy. In 22 patients with lower lobe lung cancer, a retrospective analysis revealed that MRgRT was superior to VMAT in terms of target dosage uniformity and OARs dose limiting [37]. Chest malignancies respond well to MRgRT in terms of toxicity and side effect reduction, and the radiation dose to OARs is also greatly reduced [38]. The likelihood of toxic events will be considerably raised when radiotherapy for a chest tumor is administered because the bronchus, esophagus, heart, and main blood vessels, as well as the brachial plexus, spinal cord, phrenic nerve, and recurrent laryngeal nerve, are nearby structures [39]. According to Machtay et al.'s meta-analysis report, the biologically effective dose (BED) has a 4% survival advantage with each increment of 1 Gy [40], Other research revealed that the MR-Linac treatment for lung cancer had 12-month local control rates of 95.6%, overall survival rates of 88.0%, and disease-free survival rates of 63.6%. There were no toxicities rated 4–5 found [41]. It is indicated that MR-Linac is a potent tool for treating locally progressed diseases that can safely raise the effective dose.

When used in breast cancer radiotherapy, MR-Linac is superior to a traditional accelerator in terms of displaying breast tissue, targets, and postoperative changes [42, 43], clearly displaying carcinoma in situ, reducing radiation exposure, quickly adjusting the daily schedule, and offering patients individualized treatment plans [44]. However, the Lorentz force of the magnetic field will deflect the secondary electrons, alter the distribution of the tissue dose, increase the dose in the skin and chest wall of the radiation field, cause adverse reactions like skin radioactive ulcers, and lower the quality of life for patients [45–47]. Studies have demonstrated that MRgRT is more efficient at irradiating breast cancer before surgery because it uses the signal difference between the tumor and the surrounding glandular tissue to more precisely define the target [48, 49]. A 1.5 T Elekta MR-Linac investigation of adjuvant partial breast irradiation (PBI) revealed only grade 1 toxicity in the breast [50]. Another study contrasted the MR-Linac and VMAT's differing dosimetric properties. The outcomes demonstrated that MR was more successful in defending the ipsilateral breast and chest wall [51]. There are, however, not many reports on the use of MR accelerators in radiotherapy for breast cancer. The effect of the electron cyclotron effect in breast cancer radiation should be taken into consideration by MR accelerators due to the influence of magnetic fields on electrons, and steps should be taken to avoid extra side effects.

Abdominal tumors

Pancreatic cancer is difficult to detect early and has a low survival rate [52]. Although surgical resection is a crucial component of early pancreatic cancer treatment, more than 80% of patients already have advanced pancreatic cancer at the time of their diagnosis [53]. One of the treatments for pancreatic cancer that cannot be operated on is neoadjuvant radiation. But the pancreas inhabits a very intricate anatomical setting, and its vital organs move considerably when breathing. The common bile duct and the duodenum are both close to the head of the pancreas. The jejunum, stomach, kidney, spleen, and major blood arteries are close to the pancreas' neck, body, and tail. Patients' intestines and stomachs may react poorly to high-dose radiation [54]. To prevent severe toxic effects, the acceptable dose of the surrounding tissues and organs should be taken into account when planning and administering radiation. The MR-Linac is appropriate for dose enhancement of tumor targets because of its high picture quality and online adaptive planning capability [55], especially for tumors with significant abdominal and pelvic mobility [56]. The adaptive plan may be noticed in the MR imaging of the MR-Linac, which not only optimizes the target coverage area but also successfully lowers the dose of OARs [57, 58]. In a study using MR-Linac, the toxicity was found to be significantly reduced in patients with locally advanced pancreatic cancer. Over the median follow-up of 13 months, only one incident of grade 1 toxicity and no advanced toxicity were recorded, which was a significant reduction from the usual criterion [59]. Since other retrospective investigations have produced comparable findings, using adaptive radiation can reduce adverse effects and enhance patient prognosis [60, 61]. Chuong MD et al. discovered that the 2-year local control rate and 2-year OS rate of patients getting high-dose treatment in MRgRT were, respectively, 87.8% and 45.5% via a median follow-up of 17 months for pancreatic cancer patients who received radiotherapy. The 2-year overall survival rate was statistically higher compared to other cohorts [62]. MRgRT is utilized to modify the radiation plan in real-time for more precise dose distribution to lower toxicity, increase efficacy, and lower the likelihood of recurrence in the treatment of pancreatic cancer.

The similarity of the electron density in the abdominal cavity makes it more challenging to use CBCT for radiation planning because of the movement of the diaphragm and changes in organ volume during the course of liver cancer treatment [63, 64]. MRI has excellent soft tissue resolution [65], which makes it useful for locating tumor targets and delivering more precise and effective care. The target dose might be impacted by the mobility of OARs in the abdominal cavity. Through real-time viewing, MRgRT can improve the flaws in present abdominal radiation [66, 67]. MR imaging meets the standards for dose transfer precision and provides a better display effect on 77% of abdominal tumor targets and OARs than normal CBCT imaging [68]. A patient with acute grade 3 gastrointestinal toxicity was detected in the trial of 17 patients with unresectable locally advanced cholangiocarcinoma treated with MRgRT, which was much better than the 10–26% grade 3 gastrointestinal toxicity shown by meta-analysis [69, 70]. MRgRT has dosimetric advantages in target coverage and OAR protection for primary or metastatic liver lesions [71, 72]. All things considered, MRgRT is safe and practicable for patients with abdominal malignancies.

Genitourinary system tumors

External radiation therapy for prostate cancer commonly causes dysuria, frequent urination, diarrhea, and rectal urgency among its acute adverse effects. Urinary stricture, cystitis, proctitis, and sexual dysfunction are long-term adverse effects [73, 74]. Therefore, the key to raising patients' quality of life following radiotherapy is to lessen the toxicity and side effects of prostate cancer. When treating prostate cancer, MR-Linac can adjust to structural changes as the disease progresses and reduce movement-related errors following intestine and bladder filling [75, 76]. According to a study, prior to actual radiation treatment, the pelvic organs would shift as a result of the course of image acquisition and planning adjustments, changing the PTV. As a result, it is required to modify the radiotherapy plan to take into account the altered anatomical structure. Therefore, an essential method of ensuring the use of an exact dose to decrease toxicity during radiation is the motion monitoring mechanism of the MR-Linac [77]. The incidence of grade 2 or higher acute genitourinary toxicity was found to be 23.8% in a prospective study [78] of 101 patients with moderate or high risk localized prostate cancer treated with MRgRT. This is significantly less frequent than the likelihood of toxic reactions when using conventional accelerators [79, 80]. The findings from a different study were comparable. Early prostate cancer patients experienced 5% grade 2 gastrointestinal toxicity, but no grade 3 toxicity [81]. When compared to CT-guided radiotherapy, Ma TM et al. discovered that MR-guided radiotherapy for prostate cancer dramatically reduced acute genitourinary toxicity and improved urine and intestinal function [82]. These findings support the notion that MRgRT can be used to treat prostate cancer more effectively clinically [83]. We can lower the dose of OARs and further reduce side effects for patients by responding to the changes in intestinal and bladder position by using the changes of target and OARs observed on daily MRI and the online adaptive therapy offered by MR-Linac [84]. Overall, radiation advantages can be increased by safe, efficient treatment with a low hazardous burden. Daily adaptive Mr-guided SBRT is a viable and accurate treatment strategy for prostate cancer [85].

MRI offers superior soft tissue contrast to conventional imaging techniques [86] and has taken over as the primary way of staging cervical cancer [87]. The use of MRI in extracorporeal radiation (EBRT) for gynecological malignancies can prevent missing beams in the target area [88]. Numerous experimental findings have demonstrated that IGRT can enhance patient prognosis, increase survival rate, and decrease therapeutic toxicity [89–92]. In order to create a breakthrough in the treatment of gynecological malignant tumors, MRgRT combines the benefits of both approaches. The goal of MRgRT is to reduce therapeutic toxicity and optimize treatment by performing online adaptive radiotherapy based on the anatomical structure of the day, shrinking the scope of GTV, monitoring anatomical changes during treatment, and increasing the target dosage. Compared to CBCT-guided radiation, the daily online adaptive plan employing MR-Linac can increase the target dose [93]. In their investigation, Cree An et al. discovered that the combined therapy had a reported incidence of adverse events (grade 3) as low as 3.7% and a 5-year survival rate of 78.5% for 1322 patients with endometrial cancer [94]. As a result, MRgRT is secure and successful in treating gynecological cancers.

Prospect

The clinical use of MRI in conjunction with radiotherapy is discussed in this study for the treatment of cancer. Radiation oncology is using MR-Linac as one of its key instruments. The use of MRgRT, which combines the imaging benefits of MRI with RT and has significant potential for treating tumors, advances the field of radiation. Large amounts of imaging data acquired during

MRgRT can be used to extract a variety of data sources, which can then be coupled with machine learning and artificial intelligence to incorporate new MRI features [95, 96]. The development of radiation dosage individualization and re-irradiation can be accelerated by the use of MRI in the future [97]. It can also be used to measure patients' risk classification and prognosis, enhance patient prognosis, lower complications, and boost overall survival. It can qualitatively enhance the therapeutic impact on cancer patients [98].

Given the clinical and technical issues raised, MRgRT's future research should concentrate on advancing imaging technologies and bolstering the high-dimensional quantization of pictures. Biomarkers of pictures are utilized to direct the intensification or de-enhancement of radiation, systemic, and surgical techniques in regions like the abdomen and pelvis. To get better results, it would be ideal if this study used a multicenter approach to general data analysis. Clinical investigations should be carried out following pre-treatment evaluation in order to make sure that the edge of the target that should be included in the conventional PTV will not be missed, even though MRgRT can increase treatment accuracy and decrease PTV. Since PET/MRI imaging is still in its infancy, it is possible to examine the potential synergy of the two in the use of MRgRT technology by using better imaging techniques. Radiomics can be used to enhance the clinical outcome of patients receiving MRgRT by enhancing image guidance methods and utilizing functional imaging biomarkers [99].

Artificial intelligence (AI) advancement has altered our lives in recent years. With the help of AI, radiomics has benefited from significant advancements, including the ability to automatically draw regions of interest (ROI), the introduction of neural networks (NN) that can directly infer image features from ROI, and the advancement of machine learning (ML) and deep learning (DL) algorithms [100] to streamline predictive models to inform treatment decisions [101, 102]. The widespread use of AI in RT has enormous promise and can significantly advance numerous processes, from diagnosis to treatment [103, 104]. The effectiveness of the MR-Linac online adaptive program is hampered by the lengthy treatment times, hence there is an urgent need for manual process automation to reduce the treatment times [105, 106]. The field of RT is undergoing revolutionary changes as a result of the development of AI. To reach the goal of a reduced treatment time, it offers a DL-based system that can produce electronic density (ED) maps one by one voxel [107, 108]. In order to increase the precision of dose distribution, AI is expected to work in collaboration with MR-Linac to make a significant contribution to the study of dosage augmentation. Nearly 90% of the cases in the study of 203 individuals with nasopharyngeal cancer utilizing the DL approach didn't require expert manual re-editing [109]. Chen et al. processed the magnetic resonance images of 20 patients with abdominal tumors using a type of automated deep learning-based abdominal multi-organ segmentation (ALAMO). The outcomes demonstrate that most organs can be segmented accurately, and the therapy takes around 18 s, which is completely compatible with online operation [110]. All things considered, the incorporation of AI may considerably raise the level of MRgRT treatment over the course of the next few years and be crucial to the development of customized cancer treatment. However, the proper use of AI in radiation oncology is also a significant problem, and all participants must learn new procedures while receiving irradiation under the supervision of experts [111, 112].

As of right now, this technology is still in its infancy, the full potential of AI has not yet been realized, the clinical data are not yet mature, and there are still certain issues, including the standard of MRgRT workflow, that need to be further resolved by academics. In the future, we'll investigate the true potential of online adaptive radiotherapy, gradually advance the clinical use of MR-Linac, demonstrate the viability of MR-based radiotherapy, and identify the patients who will profit from it the most.

Conclusion

In conclusion, MRgRT has played a significant role in the evolution of radiotherapy. The clinical outcomes of MR-guided radiotherapy will be closely monitored throughout the coming years, which will advance the new knowledge of tumor therapy.

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Author contributions
XL selected the references, wrote the text, and approved the final version of this manuscript. ZL, and YY contributed to discussing the content, review and editing of the manuscript before submission. All authors read and approved the final manuscript.

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Declarations

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Competing interests
The authors declare that they have no competing interests.

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