Review Article

Narrative review of the utility of magnetic resonance imaging in radiotherapy for cervical cancer

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Background and Objective: In radiotherapy (RT) for locally advanced cervical cancer, high soft tissue contrast on magnetic resonance imaging (MRI) can ensure accurate delineation of target volumes (TVs) and optimal dose distribution to the RT target and organs at risk (OAR). MRI-guided adaptive RT (MRIgART) is a novel technology that revises RT plans according to anatomical changes occurring throughout the treatment to improve target coverage and minimise OAR toxicity. This review aims to assess the evidence and gaps of MRI use in RT planning and MRIgART in the treatment of cervical cancer, as well as challenges in its clinical implementation.

Methods: Ovid Medline and PubMed were searched using keywords for MRI in RT for cervical cancer. After applying the inclusion and exclusion criteria, the initial search was deduced to 32 studies. A total of 37 final studies were reviewed, including eight additional articles from references.

Key Content and Findings: In the primary studies, TVs and organ motion were assessed before, during, and after treatment. MRI was used to investigate dose distribution and therapeutic response to the treatment in association with its outcome. Lastly, rationales for MRIgART were evaluated.

Conclusions: It was concluded that MRI enables accurate target delineation, assessment of organ motion and interfraction changes, and monitoring of treatment response through dynamic parameters. Enhanced target coverage and reduced OAR irradiation through MRIgART can improve local control and the overall outcome, although its rationales against the logistical challenges need to be evaluated on further research.

Keywords: Radiotherapy (RT); cervical cancer; magnetic resonance image; motion

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Introduction

Cervical cancer is the fourth most diagnosed cancer and the fourth leading cause of cancer death in women worldwide (1). The standard curative treatment for locally advanced cervical cancer is concomitant chemoradiotherapy (CCRT), followed by brachytherapy (BT) (2). CCRT involves external beam radiotherapy (EBRT) with cisplatin as the chemotherapy agent (2). BT delivers boost of concentrated radiation doses through an applicator directly placed in the cervix and uterus (2). Magnetic resonance imaging (MRI) is considered the gold standard modality of volumetric imaging for image-guided adaptive BT (IGABT), as it enables accurate assessment of target volumes (TVs) and dose optimisation (3). Heterogeneity of disease based on tumour volume and parametrial disease, evaluated by MRI at the time of initial diagnosis and that of commencing BT is likely to influence target dosimetry in IGABT (4). The proposed advantages of MRI in IGABT are similarly relevant to EBRT.

EBRT planning is generally done through computed tomography (CT), as it is commonly available (5). Although less accessible, MRI provides superior soft tissue contrast to CT (6). It is therefore recommended that for contouring and treatment planning, MRI is acquired in the treatment position to delineate the volumes of a gross tumour and surrounding organs at risk (OAR), including the bladder, rectum and sigmoid (6). Based on the planning images, TV is defined for calculation of the radiation dose (5). However, the target and OARs are both deformable and mobile relative to each other (5). Substantial tumour regression may occur over time, further contributing to their position shift, within a fraction of treatment or between fractions (5). This poses a risk of geographical miss of the target, in which case OARs inadvertently captured in the treatment field are irradiated with higher than necessary dose (5). Predicting target motion through generating an internal TV (ITV) based on the bladder filling protocol can mitigate this risk. Intensity-modulated radiotherapy (IMRT) is one type that is often used to reduce normal tissue toxicity, as opposed to traditional conformal techniques (6,7). Furthermore, adaptive radiotherapy (ART) is utilised in clinical practice to account for the evolving anatomy during treatment (8).

ART involves modifying treatment plans under image guidance, CT and/or MRI, according to intrafraction and interfraction changes occurring throughout the treatment course (9). This may occur as 'offline' re-planning for TV changes or set-up issues, or as 'online' plan optimisation with the up-to-date anatomy on each fraction day (8). Accurate target contouring in MRI-guided ART (MRIgART) can ensure an adequate dose of radiation is delivered to sufficiently cover TV, while sparing OARs as much as practical (9). The aim of this review is to assess the evidence and gaps in the use of MRI in RT planning and ART for cervical cancer and discuss both the rationales for and challenges of its clinical implementation. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-91/rc).

Methods

A literature search was conducted in July 2021 using the electronic databases Ovid Medline and PubMed. The main topics identified were MRI in the context of RT planning for cervical cancer, as well as changes and response to the treatment with or without ART. Subject headings and keywords are listed in *Table 1*. The Boolean operator AND was used to combine different keywords within each topic. Truncation (*) was used to search for words with the common prefix. OR was used to combine different topics into one search.

Full text papers in English language published between January 2011 and July 2021 were included for screening of titles and abstracts. Upon initial screening, papers exclusively discussing cancers of other organs or distant metastasis of cervical cancer were excluded. Papers about cervical cancer outside of the context of image-guided radiotherapy (RT) as a treatment were also excluded. Review papers were excluded. A detailed search strategy of Ovid Medline is presented in *Table 2*. Eight additional publications from references were later included. Full text was then assessed for relevance to yield the final studies for this review.

Results

The initial search yielded 85 articles, 60 from Ovid Medline and 25 from PubMed. After duplicates were removed, 66 were available for screening. Upon initial screening of title and abstracts, and application of inclusion and exclusion criteria, 32 were obtained. Full text assessment based on the same criteria with the addition of eight articles from references resulted in the final 37 studies for this review. The process of identifying the studies is outlined in *Figure 1*. Out of the 37 studies, four studies evaluated RT

Table 1 The search strategy summary

Items	Specification
Date of search	28 July 2021
Databases and other sources searched	Ovid Medline, PubMed
Search terms used	"Cervical", "Cervix", "Uterine cervix"
	"Radiotherapy", "Radiation", "Radiation therapy"
	"MR*", "Functional MRI", "fMR*"
	"Motion", "Position", "Change"
	"Adaptive", "Motion"
	"Cancer", "Neoplasm", "Carcinoma", "Tumour", "Malignant*"
	"Brachytherapy"
	"Planning"
	"Response", "Clinical response", "Therapeutic response"
Timeframe	January 2011 to July 2021
Inclusion and exclusion criteria	Inclusion criteria: full text; English language; published in the last 10 years
	Exclusion criteria: distant metastatic disease; cancers of other organs; minimal discussion of RT; review papers
Selection process	The first author exclusively conducted the selection independently

*, truncation used to search for words with the common prefix. MR, magnetic resonance; MRI, magnetic resonance imaging; fMR, functional magnetic resonance; RT, radiotherapy.

Table 2 Detailed search strategy of Ovid Medline

Search number	Searches	Results
1	("cervical" or "cervix" or "uterine cervix").mp	295,849
2	("cancer" or "neoplasm" or "carcinoma" or "tumour" or "malignan*").mp	3,026,731
3	1 and 2	117,104
4	("MR*" or "functional MR*" or "fMR*").mp	1,096,983
5	("radiotherapy" or "radiation" or "radiation therapy" or "brachytherapy").mp	823,495
6	3 and 4 and 5	1,429
7	planning.mp	354,211
8	("motion" or "position" or "change").mp	1,795,888
9	("response" or "clinical response" or "therapeutic response").mp	2,603,795
10	("adaptive" or "motion").mp	430,462
11	6 and 7 and 8	63
12	6 and 9 and 10	20
13	6 and 8 and 10	36
14	11 or 12 or 13	92
15	Limit 14 to (English language and yr = "2011–current")	60

*, truncation used to search for words with the common prefix. MR, magnetic resonance; fMR, functional magnetic resonance; yr, year.

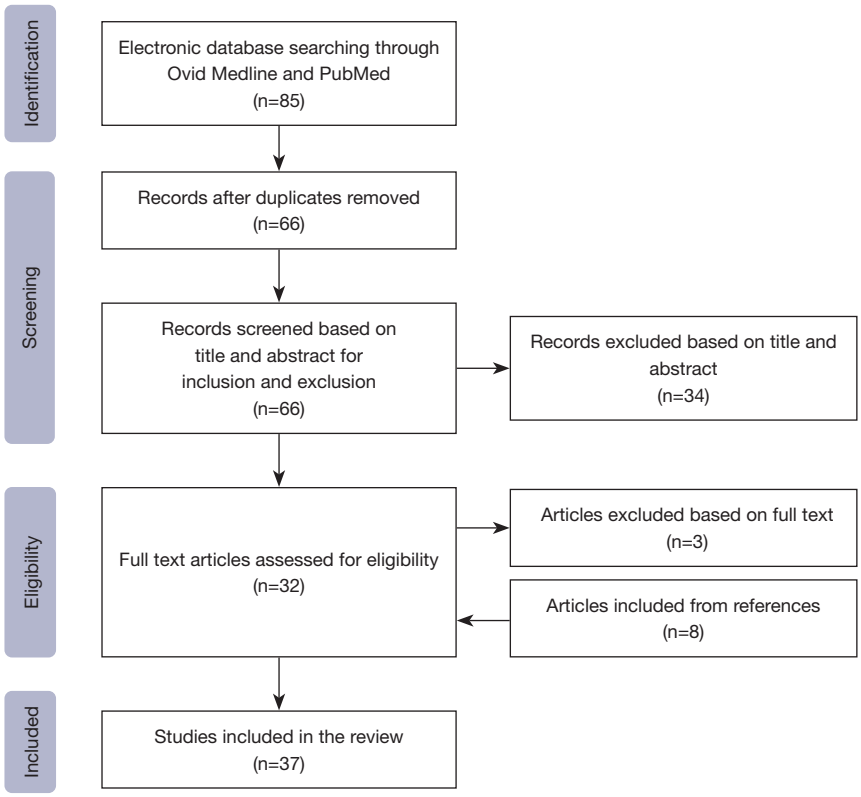

Figure 1 Diagram of the review process.

Table 3 Summary of studies by sections of discussion

Section of discussion	Number of studies [duplicates]	References
RT planning	4 [2]	(3,6,10,11)
Intrafraction changes	8 [6]	(7,8,10-15)
Interfraction changes	12 [5]	(10,14-24)
Advanced qMRI	5 [0]	(25-29)
ART	8 [6]	(7,12,14,22,23,30-32)
Challenges of clinical implementation	3 [2]	(31-33)

RT, radiotherapy; qMRI, quantitative magnetic resonance imaging; ART, adaptive radiotherapy.

planning with target contouring and dose determination, eight evaluated intrafraction changes in TV and OARs, twelve evaluated interfraction changes TV and OARs, five evaluated advanced quantitative MRI (qMRI) as a measure of treatment response and prognosis, eight evaluated roles and rationales of ART, and three evaluated the limitations of ART, including duplicates. A more detailed summary of these studies is provided in *Table 3*.

Discussion

The role of MRI in EBRT planning

RT planning involves volumetric definition and delineation of the target and other OARs under image guidance. MRI is known to provide superior soft tissue visualisation, which is required for optimal target contouring (3). Therefore, in addition to the commonly used CT with the bladder filling protocol, MRI in the appropriate treatment position is recommended at treatment simulation and planning for EBRT (6).

The evidence of MRI use in EBRT planning was discussed to a limited extent in the included studies. One study demonstrated using both MRI and CT, acquired before the treatment and fused with planning CT of each fraction, to assess the range of target and organ motion and to generate internal margin (10). Another study completed cinematic MRI prior to EBRT, then weekly during EBRT,

in 20 patients to track tumour and organ motion by selected anatomic points, and quantify margins around these points, suggesting the necessity of repeat adaptive planning (11). No studies evaluated overall dose escalation to TV in initial EBRT or BT planning at a significant level.

MRI changes during RT

Intrafraction changes and anatomical response

Image-guided strategies are used to assess organ motion within each fraction of the treatment. Organ motion is often complex and multi-dimensional, occurring in anteroposterior (AP), superoinferior and mediolateral directions (7,8,12). Individualised motion assessment and margin set-up are important, as the direction and extent to which the target and other organs shift in position can be influenced by patient characteristics, such as the cervix-uterus position, and bladder and rectal filling (5). Primary clinical TV (CTVp) typically includes the visible tumour, cervix, uterus, upper vagina and parametrium (5). The full range of motion of CTVp is measured when the bladder is full and empty, based on which an ITV is generated prior to dose calculation (9). Uterus displacement with bladder filling can be quantified, based on which patients are classified as having small or large target motion (10).

One study established a correlation between bladder inflow rate and the average length of intrafraction cervix-uterus displacement in EBRT (12). Primarily, displacement between pre-fraction and post-fraction cone-beam CT (CBCT) scans from 16 patients with large tip-of-uterus displacement (>2.5 cm) was measured (12). Movement was most significant in AP and craniocaudal (CC) directions, up to 5.8 mm posteriorly and up to 4.9 mm cranially (5th and 95th percentiles), within a mean time frame of 20.8 minutes (12). There were individual displacements that extended greater than 10 mm, again suggesting considerable inter-patient variation (12). In another study, intrafraction motion of 20 patients by selected anatomic points in cinematic MRI averaged over 5 weeks of EBRT showed the greatest movement at the uterine fundus, and progressively less at the isthmus and cervical os (11).

Bearing in mind MRI acquisition is a lengthy procedure, the change in position and volume of OARs can be magnified by the duration of treatment (34). Dosimetric impact of such change is variable for different OARs. In a prospective study of 43 patients undergoing EBRT, the bladder volume and displacement were measured in daily pre-fraction and post-fraction MRI, with a mean treatment time of 26.84 minutes (13). There was a significant average change in the bladder volume of 30 cm^3 over the fraction, with a significant mean displacement in the bladder wall in AP and CC directions (13). With consistent bladder filling protocol for each fraction, a uniform bladder volume throughout the treatment duration may be achievable, thereby having overall less impact on dose distribution (13,34).

Given the variable cervix-uterus displacement and mobility of certain OARs, as well as their dosimetric consequences, accurate TV and OAR definition is critical. Although the majority of the studies were conducted using CT or CBCT-based contouring of TV and OARs, superior soft tissue contrast and reduced interobserver variability of MRI have substantiated its role toward better intrafraction motion assessment (10,12).

Interfraction changes and therapeutic response

Significant tumour regression and OAR volume changes occur throughout the treatment which has implications for dosimetry, target coverage and OAR toxicity. Interfraction MRI plays a defined role in the assessment of tumour regression and residual disease as a measure of treatment response. GTV regression throughout the course of EBRT has been discussed in a few studies. In a study of 27 patients undergoing weekly MRI during fractionated EBRT with concurrent chemotherapy (CCT), an overall regression of 33 to 6 cm^3 in the median tumour volume occurred in all cases (16). Analysis of the weekly mean relative volume reduction indicated considerable inter-patient variability, which was attributed to complex biologic processes (16). In a different study of 81 patients undergoing a combination of EBRT and BT with or without CCT, three serial MRIs (pre-RT, mid-RT, post-RT) were performed to assess serial tumour volume regression and the regression rates at mid-RT (17). Overall, the mean tumour volume significantly decreased from 45 to 5 cm^3 in the patients receiving RT alone and from 65 to 3 cm^3 in those receiving CCRT (17). Furthermore, the mid-RT regression rate of ≥75% was associated with significantly higher 5-year local control rates in both treatment groups (17). Conversely, parametrial infiltration measured by signal intensity on MRI at diagnosis has been correlated with the rate of residual disease at the time of BT following EBRT (18).

The pattern and magnitude of the nodal position and volume changes are different from primary tumours (20). The presence of nodal disease has been associated with poor survival rates (20). On average 58% nodal regression is observed from pre-treatment to week four into IMRT (19).

Failure to account for this trend may lead to geographical omission, and suboptimal dosimetry and control of disease, permitting possible regional recurrence in the remaining undertreated tissue (19).

OAR volume and geometry changes over the course of RT directly influence target coverage and the rate of OAR-related complications. In a study of 23 patients treated with 25 fractions of volumetric-modulated arc therapy (VMAT), large rectal filling, defined as displacing the cervix position anteriorly, was found to be the most frequently associated with the lack of target coverage in EBRT (10). Although internal margins for organ motion are evaluated at treatment planning and simulation, patients are likely to be in different stages of fullness on each fraction day of EBRT. This serves as the main rationale for daily re-imaging of bladder and rectal filling in clinical practice (10,35). A bladder filling protocol with each fraction also reduces the bowel volume in the treatment field, thereby reducing rectal doses received in EBRT (10). Late rectal complications are more frequently observed than the bladder, which has a relatively consistent volume and dose (35).

The mapping of the discussed interfraction changes in accordance with disease regression, the pattern of residual disease and OAR motion can be improved by the high soft tissue resolution of MRI. MRI-guided contouring of the dynamic TV for subsequent fractions of EBRT can optimise spatial dose distribution and target coverage. This is closely associated with the precision of target irradiation and minimisation of OAR toxicity, thereby improving overall clinical outcome.

Advanced quantitative imaging techniques

While T1- or T2-weighted imaging provides anatomical information in high soft tissue resolution, advanced qMRI techniques, such as diffuse-weighted imaging (DWI) or dynamic contrast-enhance MRI (DCE-MRI), have proven potential for predicting and monitoring clinical response (25,26). Studies have recently highlighted intravoxel incoherent motion (IVIM) imaging as an extension to DWI (26,27). IVIM-DWI generates dynamic parameters such as apparent diffusion coefficient (ADC), perfusion fraction (*f*), pure diffusion (*D*), and pseudo-diffusion (*D**), which show early change during treatment and are surrogate markers of treatment response (25-28). Malignant tumours have lower ADC values at diagnosis (25,26). Significant increase in ADC values occurs throughout and beyond CCRT, as tumour regression leads to reduced tissue density and improved water motion (25-27). In the two studies assessing DWI-based parameters at four different time points (pre-CCRT, 2 and 4 weeks into CCRT, immediately post-CCRT), the average increase in ADC was 0.68 from pre-CCRT to post-CCRT in the total of 58 patients (25,27). In addition to change in ADC during the treatment, higher pre-treatment values of ADC and *D* have been associated with a worse outcome, determined by the presence of residual disease post-CCRT (25,28). DCE-MRI is also used to assess micro-perfusion and vascular permeability of tissues; however, it is more complex due to IV contrast involved (25). Inherent geometrical distortion of advanced qMRI can be corrected by deformable image registration to improve accuracy (29).

Rationales for MRIgART

The consistent aim of RT is to maintain target coverage while sparing OARs to reduce long-term gastrointestinal (GI) and haematological complications, and small planning TV margins are one such way (7,9,30). However, achieving small margins is not only difficult due to complex intrapelvic organ dynamics in cervical cancer, but it also risks target underdosing and local recurrence (30). MRIgART can mitigate these challenges with strategies that optimise RT treatment plans to the up-to-date soft tissue information provided by MRI.

There are two main streams of adaptive strategies: online automated adaptation and offline re-planning. The rationale for online ART is that the unique combination of target geometry and organ filling on each fraction day can be accounted for (8,31). The stepwise workflow of online ART is outlined in *Figure 2*. Achieving such a regimented and technical process within the limited treatment time, while patients remain on the treatment couch, may be challenging (5). Hence, offline re-planning is currently more commonly practised (33). In cervical cancer, dose-adapted re-plans has shown to be more effective in ensuring target coverage than anatomy-focused re-plans, with minimal to moderate impact on OAR doses (30). In one study of fifteen patients enrolled in 4-week IMRT, a hybrid of weekly online MRI and variable frequencies (none, single, or weekly) of offline re-planning were used in parallel (32). Geometric correction of online MRI was either done with reference to bony structures on CBCT, or on soft tissue matched to the image of planned dose distribution (32). The greatest efficacy in enhancing target

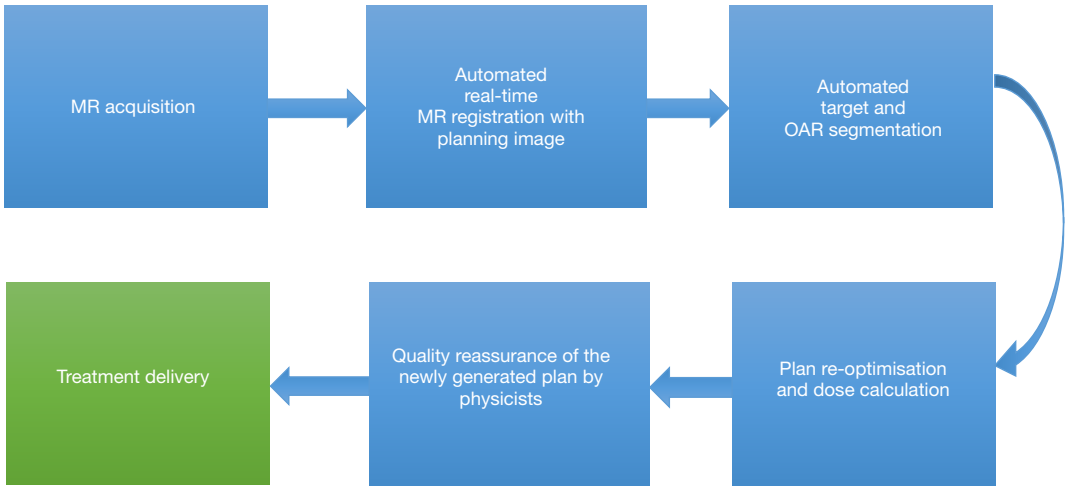

Figure 2 Workflow of online adaptive RT (5,9). MR, magnetic resonance; OAR, organs at risk; RT, radiotherapy.

coverage was seen when MRI-guided online re-planning with soft tissue matching and frequent offline re-planning were combined (32).

Challenges of clinical implementation

Current barriers to the implementation of MRIgART are predominantly logistical, especially in lower-income countries (31,32). In EBRT, the scarcity of a magnetic resonance linear accelerator (MR-linac), and intensive resources for planning and timely delivery have restricted the use of MRIgART (31). In particular, online MRIgART not only requires an appropriate software, but also the skill sets of technicians and the adoption of such a regimented multidimensional workflow at a department or institution level (31). Moreover, financial implications for staff training and equipment cannot be overlooked (33). In summary, the favourable therapeutic outcome of MRIgART is a product of longer, more expensive, and more complex processes.

Limitations of this review

Some studies from this review have small sample sizes, although a few are in larger scales. Limited periods of data collection during the treatment, ranging from one to several fractions, and the lack of post-treatment follow-up for some of them are other potential limitations of the studies. There is currently limited literature available on MRIgART as this is an emerging technology, while most of the existing data pertain to MRI-guided BT (MRIgBT). Therefore, more research of clinical application and outcome of MRIgART is needed.

Conclusions

In RT for cervical cancer, MRI enables accurate target delineation, assessment of intrafraction organ motion, as well as interfraction volume and geometry changes. Advanced qMRI can further generate dynamic parameters to predict and monitor treatment response. MRIgART offers novel individualised strategies, which ensure that treatment plans are optimised to these changes, maintaining adequate target coverage, while minimising unnecessary OAR irradiation and toxicity. Ultimately, improved local control and overall outcome can be achieved, although more research is needed to evaluate its rationales against the logistical challenges.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-91/rc

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-91/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-91/coif). The authors have no conflicts of interest to disclose.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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