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Magnetic resonance image-guided radiotherapy in patients with cancer in thorax, abdomen, pelvis or head and neck

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VÄSTRA GÖTALANDSREGIONEN
SAHLGRENSKA UNIVERSITETSSJUKHUSET

Magnetic resonance image-guided radiotherapy in patients with cancer in thorax, abdomen, pelvis, or head and neck [MR-guidad strålbehandling av patienter med cancer i thorax, abdomen, pelvis eller huvud och hals]

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1. Abstract

Background: A key challenge in radiotherapy is to reach a critical exposure of radiation to the tumour and at the same time avoid potentially harmful exposure of adjacent tissues and organs. Thus, the exact position of tumour and healthy tissues during radiotherapy is crucial. Currently, x-ray and/or low-dose CT images are used to verify patient positioning in conjunction with radiotherapy. Magnetic Resonance image guided radiotherapy (MRgRT) offers an opportunity to perform imaging with MR during radiotherapy. MR provides superior imaging of soft tissues, tumours, as well as organs at risk. In MRgRT images are used to guide and adjust radiation during treatment sessions which may provide an opportunity to reduce the dose to normal tissue – especially in tumours that change position during and between treatment sessions (fractions).

Objectives: The objective of this Health Technology Assessment (HTA) was to assess whether MRgRT improves treatment results of radiotherapy (RT) in patients with cancer in thorax, or abdomen/pelvis, or head and neck compared to current methods. Overall survival and health related quality of life (HRQL) were considered critical outcomes for decision making. Important outcomes were toxicity, progression-free survival, treatment time (in machine), target coverage, proportion of cases with replanning of treatment, organs at risk constraint violations (ie exceeding specified exposure limits for organs at risk during a treatment session), patient treatment experience, and partial / complete response.

Methods: A systematic literature search was conducted in January 2019 with an update in November 2019 in PubMed, Embase, and the Cochrane Library. The certainty of evidence was assessed using the GRADE approach.

Main results: The search identified 22 case series using MRgRT. The case series included a total of 806 patients with cancer in head and neck, thorax, abdomen or pelvis.

Critical outcomes: None of the included studies provided comparative data for the critical outcomes ***overall survival*** or ***HRQL***.

Important outcomes: For the important outcomes ***toxicity***, ***progression-free survival***, ***treatment time***, ***proportion of cases with replanning of treatment***, ***patient treatment experience*** and ***partial or complete response***, only case series were available. However, several publications provided within-subject comparisons for the intermediate outcomes ***organs at risk constraint violation*** (7 studies) and ***target coverage*** (8 studies). Here, the initial non-adapted plan for each patient and the MR-guided adapted plan for the same patient were calculated and compared regarding the calculated target coverage and avoidance of dose to organs at risk. These studies had no problems regarding directness, but some limitations in study quality and precision. A key limitation was that the new technique of adaptive MR-guidance was the "reference standard" in the comparison, which implies that only differences in favour of the new technique could be detected. Accordingly, analyses showed that organs at risk constraints were violated less often in the MR-guided adapted plan than in the non-adapted plans. In the context of the above limitations it is concluded that MRgRT when used as reference standard may be associated with a lower number of organs at risk constraint violations compared to RT without MR-guidance. (Low certainty of evidence, GRADE ⊕⊕◯◯).
The same studies also consistently showed better target coverage for the MRgRT than RT without MR-guidance. Considering the same limitations as above, it is concluded that MRgRT when used as reference standard may be associated with a higher proportion of treatment sessions reaching planning target volume coverage goals compared to RT without MR-guidance (low certainty of evidence, GRADE ⊕⊕◯◯).

Costs: Investment cost for a linear accelerator with integrated MR (MR-Linac) was approximated at 50 million SEK compared to 25 million SEK for the currently used Linac (excluding potential costs associated with alterations to facilities). Further, MRgRT requires additional staff (in addition to current staff, one oncologist, one physicist, and one specialized nurse) and 3-4 times longer treatment sessions compared to the present technique. The cost per treatment is dependent on the number of patients treated per year. Assuming MRgRT treatment of 40 patients annually, the added cost per treatment session with the MR-Linac is about 7,000 SEK, and about 95,000 SEK per patient, which is about 2-2.5 times higher than with the currently used Linac.

Ethics: Critical clinical outcome data to evaluate the benefit risk balance of MRgRT compared to current treatment are missing. In addition to high investment costs it has been noted that MRgRT requires longer time and more staffing resources than present treatments which may lead to displacement effects.

Concluding remarks: For critical clinical outcomes - overall survival and HRQL - no comparisons of MRgRT with current methods are available. This also holds for the important outcomes toxicity, progression-free survival, treatment time, patient treatment experience and partial or complete response. For two intermediate endpoints within-subject comparisons of treatment plans based on both methods – using the new technique as reference standard - are available: the new technique may be associated with a higher proportion of treatment sessions reaching target coverage goals and a lower number of treatment sessions with violations of organs at risk constraints. However, the extent of improvement varied substantially between studies and the certainty of evidence is low. It remains to be seen, whether, and for which patient population the reported advantage in intermediate endpoints may translate into an improved benefit risk balance of the new compared to the present technique. Treatment sessions with MRgRT are presumably 3-4 times longer than with current methods, and the need to stay in the same body position during extended times may be difficult for elderly as well as patients in pain. Economic aspects including high investment costs and the considerable increase in time and clinical staff needed for MRgRT are further challenges and imply a risk for displacement effects.

2. Svensk sammanfattning – Swedish summary

I denna HTA-rapport har vi utvärderat frågeställningen:
”Förbättrar MR-guidad strålbehandling behandlingsresultaten för patienter med cancer i bröstkorg, buk, bäcken, eller i huvud- och hals?”

Slutsatser
Vår genomgång av det vetenskapliga underlaget visar att det saknas avgörande kliniska data för att bedöma risk och nytta av MR-guidad strålbehandling jämfört med nuvarande behandlingsmetoder. Det finns inga studier som har jämfört MR-guidad strålbehandling och nuvarande metoder avseende patienternas *överlevnad*, eller *hälsorelaterad livskvalitet*, *biverkningar, progressionsfri överlevnad, behandlingstid, andel fall där omplanering av behandling gjordes, patienternas upplevelse av behandlingen,* eller *lokalt* respektive *fullständigt behandlingssvar*. För två intermediära variabler finns inom-individuella jämförelser baserad på behandlingsplaner framtagna med båda metoderna. I jämförelsen har MR-guidad strålbehandling används som referens-standard så att endast fördelaktiga effekter för den nya tekniken har kunnat fångas upp. Resultaten visar att den nya tekniken möjligen kan vara associerad med en högre andel behandlingstillfällen där den planerade täckningen av det avsedda tumörområdet uppnås. Den nya tekniken kan även vara associerad med färre behandlingstillfällen där exponeringsgränser för intilliggande organ överskrids. Det är dock inte undersökt, ifall dessa skillnader - som varierar betydligt mellan olika studier - kan leda till klinisk nytta för patienten.

Varje behandlingstillfälle med MR-guidad strålbehandling tar ungefär 3 – 4 gånger längre än nuvarande behandlingstillfällen. För patienter med smärta och/eller äldre patienter kan det vara svårt att ligga stilla under den förlängda behandlingstiden. Ekonomiskt medför MR-guidad strålbehandling avsevärda kostnadsökningar för både utrustning och personal. Speciellt med tanke på rådande personalbrist innebär detta en risk för undanträngningseffekter.

Bakgrund
En central utmaning vid strålbehandling är att uppnå den nödvändiga strålexponeringen av tumörvävnaden och samtidigt undvika skadlig exponering av intilliggande frisk vävnad och organ. Således är den exakta positionen av tumör och frisk vävnad under strålbehandlingen avgörande. För närvarande används slätröntgen bilder och/eller CT-bilder för att verifiera patientens position i samband med strålbehandlingen. MR-guidad strålbehandling innebär att magnetresonansbilder används som bildinformation direkt inför och under strålbehandlingen. Magnetresonansbilderna ger förbättrad information om tumörvävnad och intilliggande organ. Förhoppningen är att tekniken kan möjliggöra en minskning av strålbelastningen till frisk vävnad framförallt vid behandling av tumörer som är rörliga under och mellan behandlingstillfällena (fraktionerna).

Metod
Systematiska databassökningar i PubMed, Embase, och the Cochrane Library genomfördes i januari 2019 med en uppdatering i november 2019 för att identifiera vetenskapliga artiklar som kunde bidra till att besvara den aktuella frågeställningen. För att veta hur pålitliga studiernas resultat är, granskades kvaliteten av de studier som redovisar inom-individuella jämförelser av behandlingsplaner framtagna med versus utan guidning av MR bilder, och en bedömning gjordes av den vetenskapliga kvaliteten på det sammanlagda underlaget.

Resultat
Denna rapport baseras på 22 fallserier som inkluderade 835 patienter med cancer i bröstkorg, buk, bäcken, eller i huvud och hals.
Ingen av studierna jämförde effekten av MR-guidad och nuvarande strålbehandlingsteknik avseende patienternas *överlevnad* eller *hälsorelaterad livskvalitet*, *biverkningar, progressionsfri överlevnad, behandlingstid, andel fall där omplanering av behandling gjordes, patienternas upplevelse av behandlingen,* eller *lokal* respektive *fullständigt behandlingssvar*.
Det fanns ett flertal studier som för varje patient och behandlingstillfälle beräknade och jämförde den MR-guidade adapterade planen med den initiala, icke-adapterade planen som inte använde MR-guidning. Sju studier visade att de MR-guidade planerna innebar färre tillfällen där exponeringsgränser för intilliggande organ överskreds, och i åtta studier rapporterades en högre andel behandlingstillfällen som uppnådde målen för täckningen av det avsedda tumörområdet. Studierna inkluderade en patientpopulation som motsvarade frågeställningen, men studierna var små och hade vissa begränsningar i kvaliteten. En viktig begränsning är att MR-bilderna av den nya tekniken användes som referensstandard i beräkningarna vilket innebär att enbart skillnader till fördel av den nya tekniken kan upptäckas i analysen.

Kostnader
Kostnaden för en linjäraccelerator som stödjer MR-guidad behandling (MR-Linac) uppskattas till 50 miljoner SEK jämfört med 25 miljoner för Linac tekniken som används idag (exklusive eventuella kostnader för ombyggnationer). MR-guidad strålbehandling kräver dessutom runt 3– 4 gånger längre behandlingstider och mer personal (en läkare, en onkolog, samt en specialistsjuksköterska utöver nuvarande bemanning). Kostnaden per behandling är beroende av antalet patienter som behandlas årligen. Om 40 patienter skulle erhålla MR-guidad strålbehandling årligen istället för behandling med den nuvarande tekniken, skulle det medföra en extrakostnad på ca 7,000 SEK per behandlingstillfälle med MR-guidad strålbehandling, och ca 95,000 SEK per patient.

För 40 patienter skulle behandlingen med MR-Linac därmed vara ungefär 2 – 2,5 gånger dyrare än strålbehandlingen med Linac som används för närvarande.

Etiska aspekter
Det saknas avgörande klinisk information för att bedöma risk och nytta av MR-guidad strålbehandling jämfört med behandlingsmetoden som används idag. Utöver en hög kostnad för själva utrustningen noteras att MR-guidad strålbehandling tar längre tid och kräver mer personal vilket kan leda till undanträngningseffekter i cancervården.

The above summaries were written by representatives from the HTA-centrum. The HTA report was approved by the Regional board for quality assurance of activity-based HTA. The abstract is a concise summary of the results of the systematic review. The Swedish summary is a brief summary of the systematic review with a concluding summary.

Christina Bergh, Professor, MD
Head of HTA-centrum of Region Västra Götaland, Sweden, March 25th 2020

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DDS Doctor of dental surgery
MD Medical doctor
PhD Doctor of Philosophy
OD Odontology doctor
PT Physiotherapist
RN Registered Nurse

3. Summary of findings MR-guided radiotherapy

Outcomes	Study design Number of studies	Relative effect	Certainty of evidence GRADE[1]
Critical outcomes			
Overall survival	No studies with comparative information identified		NA
HRQL	No studies with comparative information identified		NA
Important outcomes			
Toxicity	No studies with comparative information identified		NA
Progression-free survival	No studies with comparative information identified		NA
Partial and complete response	No studies with comparative information identified		NA
Patient reported treatment experience	No studies with comparative information identified		NA
Target coverage	9 case series, of which 8 provide cross-sectional comparison[1]	Higher PTV coverage in the MR-guided adapted than in the non-adapted RT in all studies. Increase in % fx achieving coverage goal: 1.5% to 84%.	⊕⊕◯◯[2]
OAR constraint violations	9 case series of which 7 provide cross-sectional comparison[1]	Lower % fx with constraint violations in MR-guided adapted vs non-adapted plan in 6 of 7 studies. Difference range 3% to 88%. One study without any constraint violations in MR-guided adapted or non-adapted plan.	⊕⊕◯◯[2]
Proportion of cases with replanning of treatment	11 studies	Proportion of fx with replanning based on MR guidance: range 28% to 100%	NA
Treatment time	3 studies with analysis of time for adaptation	Median treatment time for MRgRT ranged from 48 to 79 minutes in the 3 studies. Time needed for re-segmentation and replanning (minutes) Study 1: median 19 (range 4-48) Study 2: mean 16.5, (SD 6) Study 3: mean 15	NA

fx: fractions, HRQL: Health related quality of life, MR: Magnetic resonance, NA: Not applicable, OAR: Organ at risk, PTV: Planning target volume, SD: standard deviation

[1]These studies included patients with cancer in thorax, abdomen or pelvis.

[2]Evaluated outcomes in cross-sectional studies started from ⊕⊕⊕⊕, downgraded for some study limitations (no blinding, limitations in description of patient selection, methods, analyses, and results), and uncertain precision (small studies, analyses in terms of fx rather than patients). Note, MRgRT was used as reference standard in the comparisons. Thus, only differences in favour of MRgRT could be detected.

Certainty of evidence

High certainty ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⊕⊕⊕◯	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⊕⊕◯◯	Confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⊕◯◯◯	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

4. Abbreviations/Acronyms

ART	Adapted radiotherapy
CB-CT	Cone beam computed tomography
Co	Cobalt
CT	Computed tomography
CTV	Clinical target volume
FFF Linac	Flattening filter-free linear accelerator
fx	fractions
GTV	Gross tumour volume
H&N	Head and neck
HRQL	Health Related Quality of Life
IMRT	Intensity modulated radiotherapy
kV/kV	kiloVolt-kiloVolt
Linac	Linear accelerator
MR	Magnetic resonance
MR-Linac	Linear accelerator combined with magnetic resonance imaging
MRgRT	Magnetic Resonance Image-guided radiotherapy
NA	Not applicable
NTCP	Normal tissue complication probability
OAR	Organs at risk
OBI	On-board imaging
OS	Overall survival
PET-CT	Positron emission tomography CT
PFS	Progression-free survival
PTV	Planning target volume
QA	Quality assurance
RT	Radiotherapy
RTT	Radiation treatment therapist
SABR	Stereotactic ablative radiotherapy
SBRT	Stereotactic body radiotherapy
SD	Standard deviation
SVF	Standardized treatment flow
VMAT	Volumetric arc therapy
3D-CRT	3-dimensional conformal radiotherapy
4D-CT	4-dimensional computed tomography

5. Background

Disease/disorder of interest and its degree of severity

Every year, more than 60,000 patients in Sweden are diagnosed with cancer - a potentially life-threatening disease. The most common sites are prostate, breast, lung and colon. Cancer can be treated in different ways, such as surgery, chemotherapy or radiotherapy. These modalities may also be used in combination.

This analysis focuses on patients treated for cancer in the thorax, abdomen, pelvis, or head and neck (H&N). About half of these patients will receive radiotherapy as part of their treatment, either as part of their primary treatment with a curative intent or in a palliative setting. Treatment response varies between different cancers.

Radiotherapy is an "intense" treatment with the ability to harm as well as heal. When the radiation passes through the body it will affect both the tumour and the surrounding healthy tissue. This will result in side effects that in some cases will become permanent. Over the last decades there has been substantial work in order to decrease the side effects. Risk for permanent illness or disability after radiotherapy still remains an issue, and so does reduced quality of life.

Prevalence and incidence

The overall population in Region Västra Götaland (VGR) in 2016 was approximately 1.7 million, corresponding to 17% of the total Swedish population. According to a publication by Cancerfonden (2018) an incidence of 64,107cases with cancer was registered in the Swedish Cancer registry in 2016. Presuming an even distribution over the country, about 10,900 of these cases occurred in VGR. The total prevalence in Sweden in 2016 was 524,349 (Cancerfonden, 2018) indicating a prevalence in VGR of about 89,000.

Present treatment

Patients treated with radiotherapy at Sahlgrenska University Hospital today are treated with linear accelerators (Linacs). Depending on cancer site, size and treatment intent, volumetric modulated arc therapy (VMAT), 3-dimensional conformal radiotherapy (3D-CRT) technique or stereotactic body radiotherapy (SBRT) technique are used. Both VMAT and SBRT techniques aim at sparing adjacent non-cancerous tissues. SBRT is mainly used for smaller (below 5 cm) lung cancer, liver and brain metastases.

In all techniques, the tumour, i.e. gross tumour volume (GTV), is delineated on dedicated computed tomography (CT) images. 4-dimensional-CT, magnetic resonance (MR) images, and /or Positron emission tomography-CT (PET-CT) is frequently used as complementary information. An extra margin, clinical target volume (CTV), is added to the GTV delineation to compensate for microscopic spread in 3D-CRT and VMAT. An extra margin to compensate for technical uncertainties is then added (PTV).

After the delineation process, dose planning takes place. Dose prescription, i.e. dose/fraction, field angles, length and position of arcs, avoidance areas, and total dose are registered in a dose planning software and dose is calculated. The plan is approved by a physician and a physicist and quality assurance (QA) is approved by a physicist.

Daily treatment is administered by nurses specialised in radiotherapy. 3D-CRT and VMAT treatment (including verification of positioning of the patient) takes approximately 15 minutes and SBRT treatment (including verification of positioning of the patient) for patients with lung cancer takes about 20 minutes. Portal images to verify patient positioning, on-board imaging (OBI), is done daily and patient position is changed accordingly.

The normal pathway through the healthcare system and current wait time for medical assessment/treatment

The majority of patients diagnosed with a potentially curable cancer in VGR are presented at a multi-disciplinary conference. If a decision on radiotherapy is made, the patient is referred to the oncology department who refers to the radiotherapy department. Current waiting time differs between patients depending on cancer site, size and treatment intent. Patients treated according to a standardized treatment flow (SVF) usually have a waiting time from the date of the multi-disciplinary conference to treatment start of 2-3 weeks. Others may have to wait between 4-10 weeks.

Number of patients per year who undergo current treatment regimen

In VGR, 4,582 patients were treated with radiotherapy in 2018. Approximately half of these were treated with curative intent. The demand for radiotherapy treatment is estimated to increase 5 % annually. With todays' standard of treatment, we presume that only a minority of patients would be considered for treatment with the new MR-Linac technique, which could be beneficial especially for targets where tumours as well as organs at risk change position during treatment.

Present recommendations from medical societies or health authorities

In Sweden, there are presently no recommendations from medical societies or health authorities in VGR concerning the use of MR-Linac.

6. Health Technology at issue: Magnetic resonance image-guided radiotherapy

Today, radiotherapy is administered at the Department of Oncology at Sahlgrenska University Hospital with a Linac and validation of tumour positioning/treatment is done daily with kV/kV or cone beam computed tomography (CB-CT) imaging (so called on-board imaging (OBI)). Many tumours change position during treatment. This can be due to movements during an individual treatment session - for example lung tumours that move during breathing, or changes between treatment sessions – for example when the tumour position or size changes in the course of treatment. In order to take these movements into account, safety margins are added to the tumour volume in the dose-planning.

MRgRT – e.g. using an MR-Linac system - offers the opportunity to perform MR during radiation. As MRI is superior in imaging soft tissue, tumours, as well as organs at risk (OAR), this might give an opportunity to reduce the extra margins that in the present technique are added to the clinical tumour volume delineation (CTV) to compensate for movements and technical uncertainties. Reducing these extra margins may decrease the dose to normal tissue which could lead to decreased toxicity.
Today, worldwide there are mainly three MRgRT systems in clinical use:

- The MRIdian with a 0.35 Tesla magnet and 3 Cobalt 60 source was introduced in 2014.
- The cobalt source was replaced by 6 MV Flattening filter-free linear accelerator (FFF Linac) in 2018 (Mutic et al., 2014).
- The Unity system with a 1.5 Tesla magnet and 7 MV FFF Linac was introduced in clinical treatment in 2017 (Winkel et al., 2019).

In contrast to kV/kV and CB-CT, imaging with MR does not imply any extra radiation dose to the patient. Thus, prolonged imaging is possible to visualise organ movements.

The question at issue is whether MR-Linac results in an optimised treatment of moving targets - tumour as well as vital OAR - that are difficult to identify during treatment.

7. Focused question

Does magnetic resonance image-guided radiotherapy (MRgRT) improve the results of radiotherapy of patients with cancer in thorax or abdomen/pelvis, or head and neck compared to conventional image-guided radiotherapy?
If so - which patient population would benefit and to what extent?

PICO: P= Patients, I= Intervention, C= Comparison, O=Outcome

P: Patients with cancer in thorax or abdomen /pelvis or head and neck who are eligible for radiotherapy. *(Including both curative and palliative treatment, however the health economic analysis will focus curative treatment)*

I: Magnetic resonance image-guided radiotherapy (MRgRT), (eg. MR-Linac, MR during the treatment session)

C: Conventional image-guided radiotherapy (on board imaging (OBI), kiloVolt-kiloVolt (kV-kV), Cone Beam computed tomography (low dose CT, or CB-CT)

O:

Critical for decision making

- Overall survival (OS)
- Health related quality of life (HRQL)

Important for decision making

- Toxicity (adverse effects, complications)
- Progression-free survival (PFS)
- Overall treatment time (in machine)
- Target coverage (Planning target volume (PTV), Clinical target volume (CTV), Gross tumour volume (GTV))
- Proportion of cases with replanning of treatment
- Normal tissue complication probability (NTCP), Organ at risk (OAR) constraint violation
- Patient reported treatment experience
- Partial / complete response

8. Methods

Systematic literature search (Appendix 1)

During January 2019 with an update in November 2019 one author (TS) performed systematic searches in PubMed, Embase and the Cochrane Library. Reference lists of relevant articles were also scrutinised for additional references. Search strategies, eligibility criteria and a graphic presentation of the selection process are presented in Appendix 1. At least two authors independently of one another assessed the obtained abstracts. Any disagreements were resolved in consensus. All authors independently read the full text articles and it was decided in a consensus meeting which articles should be included in the assessment.

Critical appraisal and certainty of evidence

The results of each included study have been summarised per outcome in Appendix 4. The included studies that contain cross-sectional data have been critically appraised using a checklist from the Swedish Agency for HTA and assessment of social services (SBU) for assessment of observational studies. Cross-sectional data were only available for two outcomes – OAR constraint violations and target coverage.
When possible, data have been pooled for meta-analysis in RevMan 5.3 using a random effects model. Where applicable, certainty of evidence for an outcome was assessed using the GRADE approach

(Atkins et al., 2004; GRADE Work group). Intermediate outcomes (accuracy measurements) from cross-sectional designs were managed as diagnostic studies, which means that the GRADE assessment starts at the ⊕⊕⊕⊕ level. Summary results per outcome and the associated certainty of evidence are presented in a Summary-of-findings table (page 7).

Ongoing research

A search in Clinicaltrials.gov (2019-06-07) using the search terms ((magnetic resonance OR MRI OR MR) AND guided AND (radiotherapy OR radiation OR radio therapy)) OR (((mr OR mri) AND linac) OR mrilinac OR mrlinac OR mrigrt) identified 259 trials.

9. Results

Search results and study selection (Appendix 1)

The literature search identified 2,912 articles after removal of duplicates. After reading the abstracts 2,851 articles were excluded. The remaining 61 articles were read by all participants of the project group, and 22 articles were finally included in the assessment (Appendix 2).

Included studies

A total of 22 studies fulfilled our PICO criteria. Studies included a total of 835 patients with cancer in head and neck, thorax, abdomen or pelvis – a population that is considered relevant for the current HTA analysis.

Only one cohort study had a control group (Kim et al., 2018). All other studies were case series. This implies that comparative information is lacking for all but two outcomes – target coverage and OAR constraint violations. For these two outcomes, a within-subject comparison of MR-guided adapted and non-adapted plans was provided in several publications (El-Bared et al., 2018, Finazzi et al., 2019a, Finazzi et al., 2019b, Henke et al., 2018b, Henke et al., 2018d, Kim et al., 2019, Palacios et al., 2018). As the assessment of these two outcomes is based on within-subject comparisons similar to diagnostic analyses the GRADE assessment started at the highest level of ⊕⊕⊕⊕, and applies to the diagnostic accuracy level in the standard hierarchy for HTA of tests (level 2 in Figure 1)**.**

Figure 1: Hierarchy for appraisal of literature on tests (Fryback and Thornbury, 1991)

1. **Technical quality of the test**
2. **Diagnostic accuracy**
3. **Change in diagnostic thinking**
4. **Change in patient management**
5. **Change in patient outcomes**
6. **Societal costs and benefits**

Reasons for downgrading were some study limitations as material, methods, and results were incompletely described in several publications. Furthermore, six of these studies retrospectively analysed adaptive treatment plans which does not reflect the feasibility of treatment optimisation in a clinical setting. Another limitation is that MRgRT is considered the intervention in the PICO of this HTA, and current methods are the comparator. The publications, however, present MRgRT as reference standard in the analysis of target coverage and OAR constraint violations.

Also, it is noted, that for 17 out of 22 publications, at least one of the authors reported grants or personal fees from a company developing MRgRT equipment. No or only minor problems were found regarding the directness of the included studies regarding the type of cancer and population treated. It should be noted that – given the early stage of clinical development of MRgRT - the question in the present HTA spans across different types of cancer. However, the benefit risk balance for the new method may differ between different types of cancer.

Most studies were based on small sample sizes with corresponding limitations in precision. Exceptions were four publications that collected information from somewhat larger study groups on the outcomes treatment time, proportion of cases with re-planning of treatment, and patient experience of the treatment.

Results per outcome

9.1 Outcomes, critical for decision-making

None of the included studies provided any comparative information regarding the outcomes considered critical for decision-making – overall survival, and HRQL. No conclusions regarding the impact of MRgRT compared to current radiotherapy on these outcomes can be drawn from available data.

Overall survival (Appendix 4.1)

Six observational studies (three studies in patients with cancer in the abdomen, two studies in patients with head and neck cancer, and one study in patients with lung cancer) reported data on overall survival in a total of 144 patients treated with MRgRT, yet without any comparative information. The follow up time for overall survival varied in the included studies ranging from 1 to 2 years.

For the two small studies in patients with cancer in head and neck, the overall survival one year after treatment was 96% in one study, and 61% in the other study – which included patients with recurrent head and neck cancer.

Two small studies in patients with cancer in abdomen, reported overall survival of 75% and 69%, respectively. The study on pancreas cancer reported an overall survival of 40%. The study in lung cancer patients reported a Kaplan Meier estimated overall survival at one year of 96%.

HRQL and patient reported treatment experience (Appendix 4.2)

Three observational studies reported data on HRQL in a total of 139 patients. One study in 101 patients with prostate cancer, one study in 18 patients with cancer in head and neck, and one study in 20 patients with cancer in the abdomen.

Patient reported treatment experience of MRgRT was recorded in two studies – one study including 140 patients with prostate cancer and one study in 150 patients with cancer from several sites.

None of the studies provided any comparative information.

9.2 Outcomes, important for decision-making

Toxicity (Appendix 4.3)

Nine studies provided information regarding toxicity within six months after treatment in 277 patients treated with MRgRT. Two studies including a total of 31 patients with head and neck cancer reported severe toxicity (NCCTC grade 3+) in 42%, and 44%, respectively. Of the four studies in a total of 100 patients with different types of cancer in the abdomen, three studies reported no cases with severe toxicity and the fourth study reported severe toxicity in 7%. One study in patients with lung cancer reported severe toxicity (CTCAE grade 3+) in 4% and in a study on patients with rectal cancer, rectum severe toxicity (CTCAE grade 3+) was reported in 27%. In the study of 101 patients with prostate cancer mild to severe gastrointestinal and/or urinary tract toxicity in 20% was reported within six months of treatment. None of the studies provided any comparative information.

Progression-free survival (Appendix 4.4)

Seven studies reported data on progression-free survival in 153 patients treated with MRgRT, yet without comparative information (six of these also report data on overall survival). Progression free survival after one year was 65-95% in patient with cancer in head and neck and 89% in lung cancer. For patients with cancer in the abdomen, the PFS at one year was 45% and 35%, and in patients with pancreas cancer 67%. None of the patients with spinal metastases had local recurrence.

Treatment time (Appendix 4.5)

Treatment time is important from a patient perspective as it can be difficult for elderly as well as patients in pain to endure long treatment times in the same body position.

Nine studies provided data regarding time per treatment session in a total of 418 patients treated with MRgRT. The median time for adapted MRgRT ranged between 48 to 79 minutes in these studies.

In three studies, detailed information on the time needed for the process of adaptation (re-segmentation, re-planning) was provided. This time amounted to a median 19 (range 4-48) minutes in a study in patients with cancer in the abdomen, a mean (SD) of 16.5 (6) minutes in another small study in patients with adrenal metastases, and approximately 15 minutes in a study in patients with cancer in lung, pancreas, or adrenal glands.

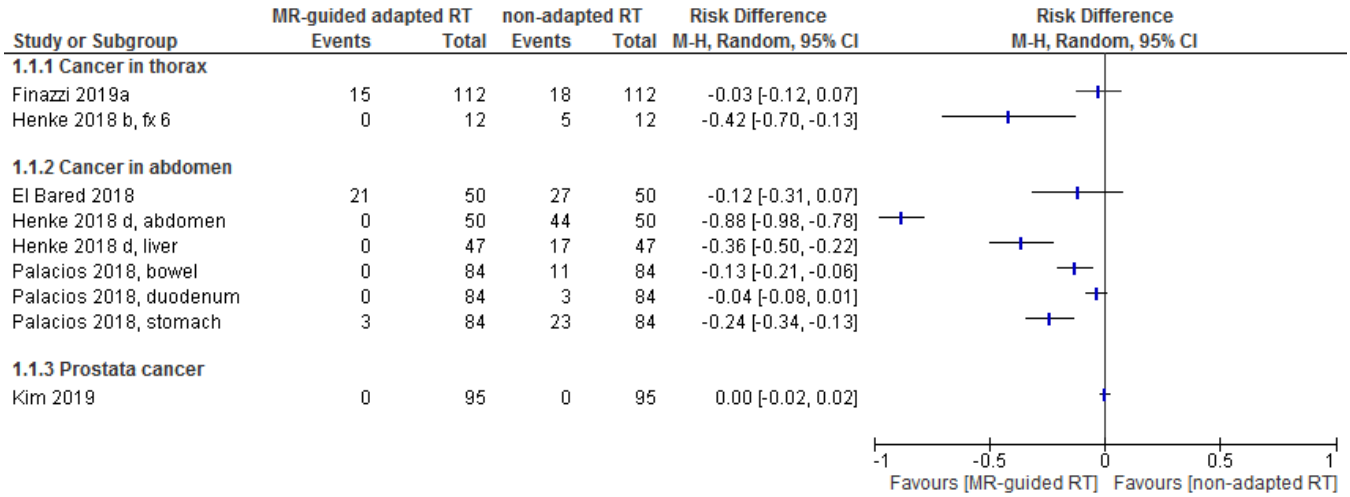
Normal tissue complication probability, Organ at risk (OAR) constraint violation, (Appendix 4.6)

Nine case series reported data regarding OAR constraint violations. Of these, seven studies provided the proportion of fractions with OAR constraint violation when using MR-^{60}Co guided adapted radiotherapy compared with non-adapted radiotherapy for a total of 126 patients with cancer in abdomen, thorax or prostate.

In five of these studies MR-guided adapted plans were produced and retrospectively compared to the non-adapted treatment plans. In the remaining two studies patients were treated with MR-guided adapted RT and the OAR violations were compared with the initial non-adapted plan (Henke et al., 2018d, Palacios et al., 2018). Consistently in all studies, the proportion of fractions with OAR violations was higher in the non-adapted plan than in the MR-guided adapted plan. The difference ranged from 3% to 88% more fractions with OAR constraint violations in the different analyses.

One retrospective cohort study (Kim et al., 2018) in 16 patients with lung cancer treated with stereotactic ablative radiotherapy (SABR) compared the doses in MR-guided cobalt treatment with Linac VMAT, without any treatment plan adaption in either group. The study showed that the mean radiation dose was lower both in the ipsi- and contralateral lung in the conventional Linac VMAT treatment group than in the MR-guided cobalt treatment group. This finding is expected as cobalt-60 treatment gives wider penumbra/dose spread than Linac.

Figure 2: Forest plot of risk difference of fractions with OAR constraint violations when using MR-guided adapted RT compared with non-adapted RT



In this figure Finazzi 2019b is not included as it reports the number of OAR constraint violations rather than the number of fractions with OAR constraint violations. Yet the results in this study are in line with those shown in the figure.

In summary, OAR constraints were violated less often in the new technique with adapted plan of the day than in the non-adapted conventional plans. The degree of reduction in number of fractions with OAR constraint violation varied considerably between studies – ranging from a reduction by 3% of fractions (from 18 to 15 of 112 fractions reported in a group of patients with cancer in thorax in Finazzi 2019a) to a reduction by 88% of fractions (from 44 to none of 50 fractions with OAR constraint violations in a group of patients with cancer in the abdomen in Henke 2018d).

Starting the GRADE evaluation at the highest level of ⊕⊕⊕⊕ given the within-subject comparisons, the following limitations have to be considered in the interpretation of these results:

The comparisons are made in a reverse way assessing the conventional method against the new technique of adaptive MRgRT as the "reference standard". This implies that only difference to the disadvantage of the conventional technique can be detected.

Furthermore, the analysis of OAR constraint violations is reported in terms of fractions and not per patient which may limit the clinical relevance of the OAR assessment.

> ***Conclusion: MRgRT when considered as reference standard may be associated with a lower number of OAR constraint violations compared to RT without MR guidance. Low certainty of evidence (GRADE ⊕⊕◯◯).***

Target coverage (PTV coverage, GTV coverage) (Appendix 4.7)

Nine observational studies provided data regarding target coverage. All but one study provided information regarding target coverage in terms of PTV coverage. Results in these studies were reported in different measures, yet they consistently showed higher PTV coverage in the adapted than in the non-adapted RT. In the studies reporting the proportion of fractions reaching PTV coverage goals, increases ranged from 1.5% (coverage defined as 95% of PTV covered by 95% of dose) in a study in patients with prostate cancer to 84% (coverage defined as 100% of PTV covered by 90% of dose) reported in a study in patients with pancreas cancer.

Only one study reported GTV coverage with an increase in median GTV coverage of 4.6% after adaptation.

In the interpretation of the results regarding target coverage, the same limitations as described regarding data on OAR violations apply – ie adaptive MRgRT was used as "reference standard" implying that only differences to the disadvantage of the conventional technique can be detected.

> ***Conclusion: MRgRT when considered as reference standard may be associated with a higher proportion of treatment sessions reaching PTV coverage goals compared to RT without MR guidance. Low certainty of evidence (GRADE ⊕⊕◯◯).***

Partial / complete response (Appendix 4.8)

Four studies included in this report presented data on partial and complete response yet none of the studies provided comparative information. Two of these studies provided data on patients treated with MRgRT. Follow-up time varied from end of treatment up to 18 months and in one study it was not stated.

Percentage of cases with re-planning of treatment (Appendix 4.9)

Ten studies presented data on the proportion of fractions in which an adapted rather than the non-adapted plan would have been chosen. One of these studies provided retrospective analyses, i.e. patients were treated with non-adapted RT, yet the proportion of fractions that would have been re-planned was calculated. In this study, the proportion of re-planning was 57%. The remaining nine studies actually delivered adapted RT, in these studies the proportion of re-planned fractions ranged from 28% to 100%.

10. Ethical aspects

Studies of the critical outcomes - overall survival and HRQL - to evaluate the benefit and risk of MRgRT compared to conventional technique are missing. So far, case series have shown that MRgRT treatment of different types of cancer is feasible and there is low certainty of evidence that MRgRT may improve the intermediate endpoints target coverage and avoidance of dose to organs at risk.

Treatment sessions with MRgRT are presumably 3-4 times longer than with current methods, and certain patient groups as for example patients in pain as well as elderly patients may not be able to stay in the same position during these extended times.
In addition to the longer treatment sessions, it is also noted that MRgRT requires more staffing resources than present treatments. This may lead to displacement effects. Already with the currently used Linac technique, there are concerns about the scarcity of radiation treatment therapists (RTTs) as well as radio-oncologists in Sweden. Introducing MR-Linac with increased staffing needs may imply that regular Linacs would have to close down which would lead to longer waiting times. Considering the astounding development in systemic cancer treatments as well as the prolonged life expectancy during the last decade, the number of patients living with a cancer disease is expected to increase. This will possibly lead to a growing demand for radiotherapy and it is therefore crucial to find time- and resource-effective treatments.

11. Organisational aspects

Time frame for the putative introduction of the new health technology

Not applicable at the time of this health technology assessment.

Present use of the technology in other hospitals in Sweden

Currently, there is one MR-Linac in Sweden, situated in Uppsala, which during the last months has been introduced in clinical routine.

Consequences of the new health technology for personnel

The treatment requires increased staffing – especially increased need for oncologists, physicists and RTTs for treating the patients. Furthermore, the staff will have extensive need for education and training.

Consequences for other clinics or supporting functions at the hospital or in the Region Västra Götaland

The number of patients who could benefit from treatment with on-board MRgRT is currently unclear.

12. Economic aspects

The investment costs for MR-Linac is approximated at 50 million SEK compared to 25 million SEK for Linac (excluding potential costs associated with alterations to facilities). Further, a life-length of 10 years was assumed and a discount rate of 3%.

The cost per treatment is dependent on the number of patients treated per year. In 2018, a total of 4,582 patients were treated with radiotherapy in VGR. Only a small share of these are assumed to be relevant for potential MR-Linac treatment (instead of Linac). The analysis here assumes 40 patients annually with 500 treatment sessions (fractions).

It is further assumed that the treatment time with a Linac is 15 minutes, and with the MR-Linac that treatment time is 3-4 times higher, i.e. 45-60 minutes. The Linac treatment is assumed to require two specialized nurses during treatment, while MR-Linac is assumed to require additionally 1 oncologist, 1 physicist, and 1 specialized nurse.

Present costs of currently used technologies

Based on the above-mentioned assumptions, the cost per treatment session with Linac is approximately 6,000 SEK (including capital investments and salary costs required for treatment). The associated cost per patient is approximately 73,000 SEK.

Expected costs of the new health technology

Based on the above-mentioned assumptions, the cost per treatment session with MR-Linac is approximately 13,000 SEK (including capital investments and salary costs required for treatment). The associated cost per patient is approx. 165,000 SEK.

Total change in costs

Based on the above-mentioned assumptions, the added cost per treatment session with the MR-Linac is about 7,000 SEK, and about 95,000 SEK per patient, i.e. the treatment cost with the MR-Linac is about 2-2.5 times higher. The total budget impact is dependent on the total number of treatments per year and whether the new technology replaces Linac treatments 1:1 or if it increases the total number of treatments at the clinic level.
If the number of treatments is increased with 40 patients treated with MR-Linac, the added cost would be approx. 6.5-7 million SEK per year. If MR-Linac treatment replaces Linac treatment for 40 patients, the added cost would be approx. 3.5-4 million SEK per year.

Possibility to adopt and use the new technology within the present budget

There is no possibility to adopt and use the new technology within the present budget. Investing and implementing MR-Linac treatments will require additional budget funds, or it will displace currently offered health care.

Available economic evaluations or cost advantages/disadvantages

The search did not identify any health-economic literature on the topic.

13. Discussion

The treatment approach in radiotherapy is that a critical exposure of the tumour to radiation, together with avoidance of harmful doses to adjacent healthy tissues improves clinical outcomes including overall survival and progression free survival (deVita et al 2019). Treatment with MRgRT is appealing based on the theorem of optimal target definition and minimizing radiation to healthy tissue. If the treatment makes it possible to construct CTV/PTV with smaller margins and thereby lessen the dose to adjacent critical structures the method will have beneficial effects on most patients irrespective of age and/or gender. The new method may, however, also have risks – for example, a decrease in currently used extra margins may imply a risk for unintentional under-treatment. Given the lack of comparative data regarding the critical clinical outcomes it is neither possible to evaluate the potential clinical benefit risk balance of MRgRT compared to currently used technique, nor to answer the question which patient groups may potentially benefit from treatment with the new technique in the near future.

The currently available literature comprises several case series, showing that it is feasible to use MRgRT in patients with cancer in different sites – including head and neck, thorax, abdomen or pelvis. Critical clinical data on overall survival, and HRQL comparing MRgRT with present methods are not available.

This also holds for the outcomes toxicity, progression-free survival, treatment time, patient treatment experience and partial or complete response. However, the effect of adapting treatment plans based on MR compared to non-adapted plans has been studied regarding intermediate endpoints – target coverage and avoidance of OAR constraint violations. In these comparisons plans based on MRgRT were used as reference standard implying that only differences in favour of the new technique could be detected. In the comparisons, advantages of the adapted plans were reported. However, the extent of improvement varied substantially between studies and the certainty of evidence is low. In principle, the intermediate endpoints target coverage, and OAR constraint violation correspond to the general theorem of optimal target exposure and minimizing exposure of healthy tissue described above. However, these endpoints are assessed per treatment session, whilst the clinical effect depends on the precision across all treatment sessions. It remains to be seen, whether, and for which patient population the reported advantage in intermediate endpoints may translate into an improved benefit risk balance of the new compared to the present technique.

Studies are currently focusing on technical aspects and feasibility of the treatment procedure. Several sites have published in-house, prospective case series. No randomised clinical studies are available and outcomes considered critical for decision making have not been evaluated in any controlled studies. Randomised trials with clinically relevant endpoints such as overall survival, toxicities and HRQL are warranted.

One of the challenges will be to select the patient groups who may benefit most from MRgRT. Currently, a key issue is the prolonged treatment time when using MRgRT. According to currently available literature, the new technique is quite time consuming and there are concerns whether elderly as well as patients in pain will be able to endure staying in the same body position during an extended treatment time in the machine. This may hamper the quality of treatment. For the time being, most studies are performed with hypofractionated schedules, i.e. few treatments with higher dose per fraction. This means shorter treatment periods and that more patients may be treated within a given time frame. Our conclusion is that treatment on an MR-Linac would preferably be given with a hypofractionated scheme. However, stereotactic lung RT is a common treatment at most radiotherapy centres already. Applying MR-Linac to these treatments would take more time and require more personnel than before.

Key issues for clinical applicability at our centre will be the treatment time and treatment staff needed, as these resources are scarce and an increase in time and staffing needed may lead to displacement effects.
These key questions cannot be evaluated based on currently available publications and need to be addressed based on larger clinical studies. Of note, research in the area of MRgRT is highly dynamic - updating our literature search after less than one year lead to a doubling of included publications.

Chin et al (2019) highlighted many of the discussed challenges and their conclusions are similar to ours. To our knowledge this is the only systematic review regarding MRgRT published.

There is also a need for clinically applicable cost-effectiveness analyses on this new technology.
It takes time and effort to prospectively evaluate the introduction of new medical techniques in clinical practice. Nonetheless, it will have to be addressed in the near future since treatment options regarding medical oncology as well as radiotherapy are rapidly increasing. Eventually, this will have economic impact on the health care systems and the ability to treat patients.

14. Future perspectives

Scientific knowledge gaps

There is a need for controlled clinical studies that document outcomes critical for decision making – overall survival, and HRQL.
We need studies to ensure that decrease in extra margins does not negatively affect recurrence and overall survival due to unintentional under-treatment. Of special interest are studies focusing on patients where organ motion (inter- as well as intra-fraction) create a therapeutic challenge as currently used kV-kV/CB-CT imaging imply a lack of soft tissue contrast.

Ongoing research

A ClinicalTrialGovs search was conducted 31st May 2019. Of 259 abstracts identified in the search, four studies were ongoing and of interest for this HTA report. Two studies are focusing on liver/pancreas malignancies (**NCT02683200, NCT03621644**), one is focusing on lung cancer (**NCT03916419**), and one is focusing on breast cancer (**NCT03936478**).

NCT02683200 conducted in USA, aims to recruit 20 patients with adult hepatocellular carcinoma or metastatic malignant neoplasm in the liver in a single-arm phase 1 study. The patients will be treated with SBRT. Primary objectives are to assess the feasibility of utilizing an MR-guided tri-60Co teletherapy system for liver SBRT, as determined by the treating radiation oncologist's ability to accurately visualize and align to the target lesion(s) and to assess the feasibility of using a three versus five fraction scheme, for one versus multiple (i.e., ≤ 5) target lesions. Secondary objectives will be local control, DFS, and OS.
The study started recruiting in June 2015 and is expected to be completed in June 2021.

NCT03621644 conducted in USA is planning to recruit 133 patients with locally advanced pancreatic cancer in a single-arm phase 2 study. The patients will be treated with SBRT, delivered with MRgRT delivery system (ViewRay MRIdian or MRIdian Linac). The prescribed dose will be 50 Gy in 5 fractions. On-table adaptive re-planning will be used when clinically indicated.
Primary outcome will be gastrointestinal toxicity (CTCAE) and secondary outcomes will be OS (time frame two years), distant progression free survival (time frame six months) and patient-reported quality of life (time frame 12 months).
The study started recruiting in August 2018 and is expected to be completed in January 2026.

NCT03916419 conducted in USA are planning to recruit 27 patients with inoperable stage IIB and IIIA non-small cell lung cancer, in a single-arm phase 2 study. Patients will be given concurrent radio-chemo-therapy. Radiotherapy will be given on an MR-guided apparatus (View-Ray). Primary outcome will be safety of hypofractionated MR-guided adapted radiotherapy and dose limiting toxicity. Secondary outcomes are acute/late toxicities, tumour response rate, distant recurrence rate, incidence of brain metastases and PFS, DFS and OS.
The study started recruiting in June 2019 and is expected to be completed in December 2024.

NCT03936478 conducted in USA is planning to recruit 30 patients with early breast cancer in a single-arm phase 2 study. Patients will be given a 3-fraction radiation regimen with MRI-guided radiotherapy (MRIdian). The hypothesis is that 3-fraction radiation therapy can be delivered safely without compromising the therapeutic ration. Primary outcome is Physician reported cosmesis, secondary outcome is patient-reported quality of life, acute/late toxicities, tumour recurrence, regional node recurrence, DFS, and OS. The study was started in May and suspended in August 2019 due to protocol modification.

15. Participants in the project

The question was nominated by
Johanna Svensson, Head of Department, MD, PhD, Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden

Participating healthcare professionals
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Participants from the HTA-centrum
Annika Strandell, MD, associated professor, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden
Constanze Wartenberg, psychologist, PhD, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden
Mikael Svensson, health economist, professor, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden
Therese Svanberg, librarian, Medical Library, Sahlgrenska University hospital, Gothenburg, Sweden

Administrative support
Pernilla Rönnholm, project coordinator, HTA-centrum, Region Västra Götaland, Gothenburg, Sweden

External reviewers
Due to prioritization and workload related to COVID-19, the nominated external reviewers could not contribute to this HTA report.

Declaration of interests
None of the authors had any conflicts of interest to declare.

Project time
The HTA was accomplished during the period of 2018-12-05 – 2020-05-11.
Literature searches were conducted in January 2019 and updated in November 2019.

Appendix 1: PICO, study selection, search strategies, and references

Question(s) at issue:
Does magnetic resonance image-guided radiotherapy (MRgRT) improve the results of radiotherapy of patients with cancer in thorax or abdomen/pelvis, or head and neck?
If so - which patient population would benefit and to what extent?

PICO: (*P=Patient I=Intervention C=Comparison O=Outcome*)

P: Patients with cancer in thorax or abdomen (eg. prostata, pancreas, lung) or head and neck who are eligible for radiotherapy. *(Including both curative and palliative treatment, however the health economic analysis will focus curative treatment)*

I: Magnetic resonance image-guided radiotherapy (MRgRT), (eg. MR-Linac, MR during the treatment session)

C: Conventional Image-guided radiotherapy (on board imaging (OBI), kiloVolt-kiloVolt (kV-kV), Cone Beam computed tomography (low dose CT, or CB-CT)

O: Critical for decision-making:

- Overall survival
- Health related quality of life (HRQL)

Important for decision-making:

- Toxicity (adverse effects, complications)
- Progression-free survival (PFS)
- Overall treatment time (in machine)
- Target coverage (Planning target volume (PTV), Clinical target volume (CTV), Gross tumour volume (GTV))
- % cases with re-planning of treatment
- Normal tissue complication probability (NTCP), Organ at risk (OAR) constraint violation
- Patient treatment experience
- Partial / complete response

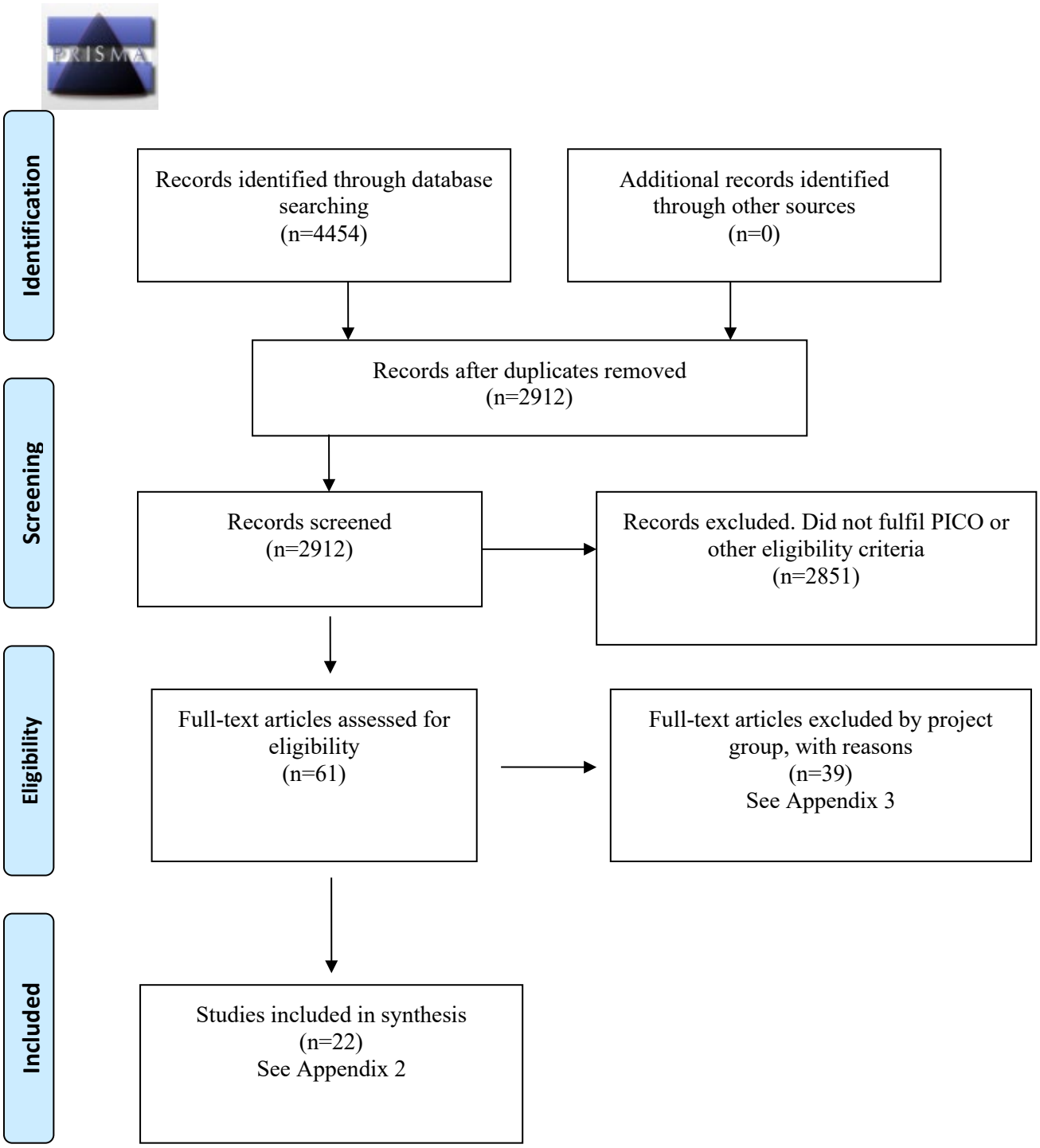
<u>Eligibility criteria</u>

Study design:
Systematic reviews
Randomised controlled trials
Non-randomised controlled studies
Case series if ≥ 5 patients

Language:
English, Swedish, Norwegian, Danish

Publication date: 2010 -

Selection process – flow diagram



Search strategies

Database: PubMed
Date: 11 Jan 2019
No. of results: 1765
Search updated: Nov 21, 2020. 373 results

Search	Query	Items found
#17	Search #8 NOT #9 Sort by: Author Filters: Publication date from 2010/01/01; Swedish; Norwegian; English; Danish	1765
#16	Search #8 NOT #9 Filters: Swedish; Norwegian; English; Danish	2392
#10	Search #8 NOT #9	2532
#9	Search animal[ti] OR animals[ti] OR rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR dog[ti] OR dogs[ti] OR cat[ti] OR cats[ti] OR hamster[ti] OR hamsters[ti] OR rabbit[ti] OR rabbits[ti] OR Swine[ti]	1715084
#8	Search #6 NOT #7	2547
#7	Search ((animals[mh]) NOT (animals[mh] AND humans[mh]))	4534809
#6	Search #4 OR #5	2640
#5	Search ((mr[tiab] OR mri[tiab]) AND linac[tiab]) OR mrilinac[tiab] OR mrlinac[tiab] OR mrigrt[tiab]	360
#4	Search #1 AND #2 AND #3	2410
#3	Search "Radiotherapy"[Mesh] OR "Radiotherapy, Image-Guided"[Mesh] OR "radiotherapy"[Subheading] OR radiotherapy[tiab] OR radiation[tiab] OR radio therapy[tiab] OR "Radiation Oncology"[Mesh]	559460
#2	Search guided	138401
#1	Search "Magnetic Resonance Spectroscopy"[Mesh] OR "Magnetic Resonance Imaging"[Mesh] OR magnetic resonance[tiab] OR MRI[tiab] OR MR[tiab]	805736

Database: Embase 1974 to 2019 January 10 (OvidSP)
Date: 11 Jan 2019
No. of results: 1729
Search updated: Nov 21, 2020. 413 results

#	Searches	Results
1	*nuclear magnetic resonance/	33914
2	exp *nuclear magnetic resonance imaging/	219492
3	*nuclear magnetic resonance spectroscopy/	23896
4	(magnetic resonance or MRI or MR).ab,kw,ti.	718211
5	1 or 2 or 3 or 4	774805
6	exp *radiotherapy/	188131
7	exp *radiotherapy equipment/	8132
8	*radiotherapy planning system/	521
9	*radiation oncology/	887
10	*cancer radiotherapy/ or *adjuvant radiotherapy/	43736
11	radiotherapy.fs.	298147
12	radiotherapy.fx.	298147
13	(radiotherapy or radio therapy or radiation).ab,kw,ti.	587647
14	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	771887
15	guided.af.	195354
16	5 and 14 and 15	4894
17	(animal not (animal and human)).sh.	1023333

18	(animal or animals or rat or rats or mouse or mice or dog or dogs or cat or cats or hamster or hamsters or rabbit or rabbits or Swine).ti.	1794521
19	17 or 18	2594092
20	16 not 19	4813
21	limit 20 to (embase or medline)	2520
22	**limit 21 to ((danish or english or norwegian or swedish) and yr="2010 -Current" and (article or article in press or conference paper or note or "review"))**	**1729**

Database: The Cochrane Library
Date: 11 Jan 2019
No. of results: 165
Cochrane reviews 2
Trial 163
Search updated: Nov 21, 2020. 9 results

ID	Search	Hits
#1	MeSH descriptor: [Magnetic Resonance Spectroscopy] explode all trees	638
#2	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	7430
#3	("magnetic resonance" or MRI or MR):ti,ab,kw (Word variations have been searched)	26922
#4	#1 OR #2 OR #3	26950
#5	(guided):ti,ab,kw (Word variations have been searched)	24137
#6	MeSH descriptor: [Radiotherapy] explode all trees	5774
#7	MeSH descriptor: [Radiotherapy, Image-Guided] explode all trees	71
#8	MeSH descriptor: [Radiation Oncology] explode all trees	42
#9	(radiotherapy or "radio therapy" or radiation):ti,ab,kw (Word variations have been searched)	33891
#10	#6 OR #7 OR #8 OR #9	34207
#11	**#4 AND #5 AND #10 with Cochrane Library publication date Between Jan 2010 and Jan 2019**	**165**

Reference lists
A comprehensive review of reference lists brought no new records

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Reference lists

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Project: MR-Linac
Appendix 2 – Characteristics of included studies

Author Year Country	Study Design	Duration of follow-up	Study Group MRgRT system	Patients (n) Type of cancer	Age Years (range)	Men (%)	Outcome variables
Acharya 2016b USA	Case series	No FU	0.35 T ^{60}Cobalt	30 Breast	Mean (range) 58 (42-77)	0%	Target coverage
Bertelsen 2019 Denmark	Case series	No FU	1.5T 7 MV FFF	19 Pelvis (mainly prostate cancer)	Median (range) 62 (43-80)	-	Treatment time % replanning
Bruynzeel 2019 The Netherlands	Phase-2 study	Up to 3 months FU	0.35 T 6 MV FFF	101 prostate	Median (range) 72 (55-88)	100%	Toxicity HRQoL
Chen 2017 USA	Case series	Up to 2 years FU	0.35 T ^{60}Cobalt	13 head and neck	Mean (range) 62 (50-78)	75%	OS PFS Toxicity Response
Chen 2018 USA	Case series	Median (range) 18 months (3-23)	0.35 T ^{60}Cobalt	18 head and neck	Mean (range) 58 (15-76)	83%	OS PFS HRQoL Toxicity Response
Chiloiro 2019 Italy	Case series (retrospective, step&shot)	FU until surgery 6-8 weeks	0.35 T ^{60}Cobalt	22 rectal	Median (range) 64 (41-86)	68%	Toxicity Response
El-Bared 2018 USA	Case series with cross-sectional information for target coverage and OAR constraint violations	Median (range) 10 months (2-18)	0.35 T ^{60}Cobalt	10 pancreas	-	-	Target coverage Toxicity OAR constraints violation Response
Finazzi 2019a The Netherlands	Case series with cross-sectional information for OAR constraint violations	Median (range) 14.9 months (4.0-25.8)	0.35 T ^{60}Cobalt 0.35 T 6 MV FFF	23* lung * some patients are probably presented in both studies.	Median (range) 68 (37-85)	78%	Toxicity Target coverage Treatment time % replanning OAR constraints violations OS PFS

Project: MR-Linac
Appendix 2 – Characteristics of included studies

Author Year Country	Study Design	Duration of follow-up	Study Group MRgRT system	Patients (n) Type of cancer	Age Years (range)	Men (%)	Outcome variables
Finazzi 2019b The Netherlands	Case series with cross-sectional information for target coverage and OAR constraint violations	No FU	0.35 T ^{60}Cobalt 0.35 T 6 MV FFF	25* lung	Median (range) 73 (34-86)	-	Target coverage % replanning Treatment time OAR constraints violation
Ficher-Valuck 2017 USA	Case series	No FU	0.35 T ^{60}Cobalt	67 abdomen, breast, pelvis thorax	-	-	% replanning
Henke 2018b USA	Case series with cross-sectional information for target coverage and OAR constraint violations	FU during treatment	0.35 T ^{60}Cobalt	12 thorax	Median (range) 73.5 (28-80)	-	Target coverage OAR constraints violation % replanning
Henke 2018d USA	Phase-1 with cross-sectional information for target coverage and OAR constraint violations	Median (range) 15 months (4-22)	0.35 T ^{60}Cobalt	20 abdomen oligometastases	Median (range) 64 (48-79)	-	Target coverage Treatment time Toxicity PFS OS %replanning OAR constraints violation HRQoL
Kim 2018 Republic of Korea	Case series with comparative retrospective case:control	Median (range) 20.5 weeks (16-31)	0.35 T ^{60}Cobalt vs Linac	8 Lung vs 8 lung	Median ($\pm$SD) 73 $\pm$ 7 91 $\pm$ 9	 50% 75%	OAR constraints violation
Kim 2019 Republic of Korea	Case series with cross-sectional information for target coverage and OAR constraint violations	FU during treatment	0.35 T ^{60}Cobalt	19 prostate	Mean (range) 77 (65-86)	100%	Target coverage OAR constraints violation
Llorente 2019 USA	Case series	Median (range) 12.3 months (0-32)	0.35 T ^{60}Cobalt	9 spinal metastases	-	-	Treatment time OAR constraints violation PFS
Palacios 2018	Case series	FU during treatment	0.35 T ^{60}Cobalt	17 adrenal metastases	-	-	Treatment time Target coverage

Project: MR-Linac
Appendix 2 – Characteristics of included studies

Author Year Country	Study Design	Duration of follow-up	Study Group MRgRT system	Patients (n) Type of cancer	Age Years (range)	Men (%)	Outcome variables
The Netherlands	with cross-sectional information for target coverage and OAR constraint violations						OAR constraints violation
Rosenberg 2019 USA	Case series	Median 21.2 months	0.35 T ^{60}Cobalt	26 Liver	Median (range) 70 (30-90)	65%	Toxicity OS PFS
Rudra 2019 The Netherlands	Case series (retrospective, multicentre)	Median (range) 17 (-)	0.35 T ^{60}Cobalt	44 pancreas	Median (range) 66 (47-85)	59%	Toxicity OS PFS % replanning
Tetar 2018 The Netherlands	Case series	FU during treatment	0.35 T ^{60}Cobalt	150 Prostate, pancreas, lung, adrenal,liver, kidney, other	Median (range) 69 (35-92)	76%	Treatment time Patient treatment experience
Tetar 2019 The Netherlands	Case series (40 pts) Phase-2 (100 pts)	FU during treament	0.35 T ^{60}Cobalt 0.35 T 6 MV FFF	140 Prostate (100 presented in Bruynzeel 2019)	-	100%	Treatment time Patient treatment experience % replanning
Van Sörnsen de Koste 2018 The Netherlands	Case series	FU during treatment	0.35 T ^{60}Cobalt	15 Lung, pancreas, adrenal	-	-	Treatment time % replanning
Winkel 2019 The Netherlands	Case series	-	1.5T 7 MV FFF	10 Pelvic metastases	-	-	Target coverage

FU = follow-up, T = Tesla, OAR = Organ at risk, pts = patients, MV = MegaVolt, FFF= free Flattening Filter, MRgRT= magnetic resonance guided radiotherapy

Project: MR Linac - Excluded articles
Appendix 3

Author, year	Reason for exclusion
Acharya, 2016	Case series with 5 patients and only limited information on further 15 patients.
Al Ward, 2018	Wrong I – only plan, no treatment
Datta, 2018	Wrong study design – theoretical overview
Fast, 2018	Wrong I – only plan, no treatment
Feldman, 2019	Wrong O
Gao, 2017	Wrong type of publication – method development
Giaj-Levra 2019	Wrong I - no MR-Linac
Guerreiro, 2018	Wrong I- not MR linac
Han, 2018	Wrong type of publication – method development
Henke et al, 2018a	Wrong publication type – overview of MR-Linac implementation
Henke et al, 2016b Simulated online…	Wrong I – only plan, no treatment
Henke et al, 2016a Online adaptive	Wrong publication type - abstract
Henke et al, 2018c	Case series with 5 patients
Henke et al, 2016c, Adaptive MR-guided	Wrong publication type - abstract
Kashani, 2018	Wrong publication type - review
Kim, 2017	Wrong intervention – gating system
Kishan 2015	Wrong intervention - no MR linac exposure
Jeon, 2017	Wrong outcome
Lagerwaard, 2018	Only one patient
Lagendijk, 2016	No patient population
Lips, 2012	Wrong publication type - abstract
Menard, 2014	Wrong publication type - editorial
Menten, 2016	No treatment
Mittauer 2019	Wrong publication type
Noel, 2015	Wrong outcome – physician rated visibility
Olberg, 2018	Method development
Olsen, 2015	Wrong study design
Park, 2018	Wrong outcome
Prins, 2019	Wrong outcome – recording of organ motion
Raghavan, 2016	Wrong outcome
Thomas, 2018	Wrong outcome
Tyran, 2018	Wrong I – only plan, no treatment
Vestergaard, 2016	Wrong I – no MR-Linac
Wee, 2018	Wrong I – MR linac not used
Werensteijn-Honingh 2019	Case series not > 5 patients
Winkel, 2018	Wrong I – only plan, no treatment
Wojcieszynski, 2017	Only planning – no outcomes
Wooten, 2015	Wrong I – only plan, no treatment
Yang, 2016	Wrong O

Project: MR-linac
Appendix 4.1
Outcome variable: Overall survival (OS)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= Type of cancer	Withdrawals - dropouts	Results Overall survival (follow up time)		Comments	Directness *	Study limitations *	Precision *
				Intervention MR guided treatment Adapted RT	Control MR guided treatment Non-adapted RT				
Chen 2017 USA	Case series	13 head and neck	1 (1 pat withdraw before treatment started)		61% (1 yr) 53% (2 yr)		NA	NA	NA
Chen 2018 USA	Case series	18 head and neck	1 (1 pat did not complete treatment)		96% (1 yr est)	Estimated OS as follow-up was less than 1 yr.	NA	NA	NA
Finazzi 2019a The Netherlands	Case series	23 lung	-	96% (1 yr) (95% CI, 87.7-100.0)		Kaplan-Meier estimate OS based on median follow up of 15 months (range 4 – 26)	NA	NA	NA
Henke 2018d USA	Case series	20 abdomen	-	75% (1 yr)	-		NA	NA	NA
Rosenberg 2019 USA	Case series	26 liver	-		69% (1 yr) 60% (2 yr)		NA	NA	NA
Rudra 2019 The Netherlands	Case series	44 pancreas	-	High dose group (n=24): 49% (2 years) Standard dose group (n=20): 30% (2 years) Total (n=44): 40%		Pts treated with RT and chemotherapy. High dose group: biologically effective dose$_{10}$ > 70 Gy Standard dose group: biologically effective dose $_{10} \leq$ 70 Gy	NA	NA	NA

RT = radiotherapy, FU = follow-up, Pat= patient, yr= year, mo=months, est=estimated, OS =overall survival, pts = patients, NA= Not assessed.

Project: MR Linac
Appendix 4.2
Outcome variable: HRQL and Patient reported treatment experience

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Patients (n) Type of cancer	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR- guided treatment adapted RT	Control MR- guided treatment non-adapted RT				
HrQOL									
Bruynzeel, 2019 The Netherlands	Case series	101 prostate	Additional 3 withdrew due to severe claustrophobia during simulation	**IPSS (median)** Baseline = 7.3 End of RT = 13.0 6 w = 8.5 3 mo = 6.0 **EORTC** Global QoL Baseline = 82.8 End of RT = 76.6 6 weeks = 79.0 3 months = 79.5	-	International Prostate Symptoms Score (IPSS) European Organization for research and treatment of cancer (EORTC) Quality of Life Questionnaire (QLQ C-30)	NA	NA	NA
Chen 2018 USA	Case series	18 head and neck	1 (did not complete treatment)	6 months:15 patients eligible Swallow: as well as ever: 9/15 (60%) Saliva: normal/less than normal but enough: 8/15 (53%) HRQL: very good/outstanding: 9/15 (60%) Global QoL: Very good/ outstanding: 8/15 (53%) 1 year: 10 patients eligible Swallow: as well as ever: 7/10 (70%) Saliva: normal/less than normal but enough 6/10 (60%) HRQL: very good/outstanding: 7/10 (70%) Global QoL: Very good/ outstanding: 6/10 (60%)	- - 	University of Washington Quality of life (UW-QOL) questionnaire	NA	NA	NA

Project: MR Linac
Appendix 4.2
Outcome variable: HRQL and Patient reported treatment experience

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Patients (n) Type of cancer	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR- guided treatment adapted RT	Control MR- guided treatment non-adapted RT				
Henke 2018d USA	Case series	20 liver& abdomen met	-	QoL at 0, 6, 26 weeks after treatment start Median global QoL scores were not significantly different Scores for diarrhoea, constipation, nausea, emesis, appetite, pain or activity tolerance were unchanged	-	European Organization for research and treatment of cancer (EORTC) Quality of Life Questionnaire (QLQ C-30)	NA	NA	NA
Patient reported treatment experience									
Tetar 2018 The Netherlands	Case series	150 all sites	-	**Reported MR related complaints** Some complaints: Noisy 60 % Feeling cold 29 % Paresthesia 28 % Considerable complaints: Noisy 17 % Feeling cold 10 % Paresthesia 6 %	-	PRO-Q (in-house developed patient reported outcome questionnaire),	NA	NA	NA
Tetar 2019 The Netherlands	Prospective phase 2 (100 patients) Case series (40 patients)	140 Prostate cancer	89 (64%) patients answered	**Reported MR related complaints** Some (little) complaints: Noisy 35 % Feeling cold 18 % Paresthesia 18 % Considerable (moderate/very much) complaints: Noisy 13 % Feeling cold 8 % Paresthesia 2 %	-	PRO-Q (in-house developed patient reported outcome questionnaire),	NA	NA	NA

QoL= quality of life, HRQL= health related quality of life, RT = radiotherapy

Project: MR Linac
Appendix 4.3
Outcome variable: Acute and late toxicity

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Patients (n) Type of Cancer	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations	Precision *
				Acute toxicity (< 6 months after treatment) Number of pat	Late toxicity (> 6 months after treatment) Number of pat				
Bruynzeel 2019 The Netherlands	Case series	101 prostate	Additional 3 withdrew prior to RT	GI: Grade > 2 = 3 (end of RT) GI: Grade > 2 = 1 (after 3 mo) GU: Grade >2 = 20 (end of RT) GU: Grade > 2 = 4 (after 3 mo)	-	CTCAE 4.0 classification	NA	NA	NA
Chen 2017 USA	Case series	13 Head and neck	1 (unknown reason)	Grade 3-5 (skin) = 5 Grade 3-5 (swallow) = 4 Grade 3-5 (mucosit) = 4 Grade 3-5 (keratitis) = 1	Fibrosis of neck (number of pat not defined) Aspiration pneumonitis= 1	NCCTC 4.0	NA	NA	NA
Chen 2018 USA	Case series	18 Head and neck	1 (did not complete treatment)	Grade 3-5 (skin) = 6 Grade 3-5 (swallow) = 6 Grade 3-5 (mucosit) = 5 Grade 3-5 (anorexia) = 4 Grade 3-5 (larynxedema) = 1	Xerostomia = 11 (61%) Esophagus stricture = 1	NCCTC 4.0	NA	NA	NA
Chiloiro 2019 Italy	Case series	22 rectal	-	Grade 2 (Proctitis) = 7 Grade 2 (diarrhea) = 2 Grade 3 (abdominal pain) = 1 Grade 3 (diarrhea) = 5	-	CTCAE 4.0 classification	NA	NA	NA
El Bared 2018 USA	Case series	10 pancreas		Grade 3-5 = 0	Grade 3-5 = 0	NCCTC 5.0	NA	NA	NA
Finazzi 2019a The Netherlands	Case series	23 lung		Grade 3 = 1 Grade 2 (chest wall pain) = 3 Grade 2 (pleural effusion = 1 Grade 2 (radiation pneumonitis) =1 Grade 2 (fatigue) = 1		CTCAE 5.0 classification Not reported if toxicities are acute or late	NA	NA	NA
Henke 2018d USA	Case series	20 abdomen		Grade 3-5 (GI) = 0 Grade 2 (GI) = 1 Grade 4 (anemia, trombocytopenia) = 2*	Grade 3-5 = 0	CTCAE 4.0 classification *Not correlated to radiotherapy	NA	NA	NA
Rosenberg 2019 USA	Case series	26 liver		Grade 4-5 (GI) = 0 Hilar stricture = 1 Portal hypertension = 1	Grade 3 (GI) = 2	NCCTC 4.0	NA	NA	NA
Rudra 2019 The Netherlands	Case series	44 pancreas	-	Grade ≥ 3 = 3 (7%)	-	CTCAE 4.0 classification	NA	NA	NA

RTOG = Radiation Therapy Oncology Group, NCCT = National Cancer Institute Common Toxicity Criteria version 4.0, CTCAE = Common Terminology Criteria for Adverse Events, GI=Gastro Intestinal, GU=Genito Urethral, NA: Not assessed.

Project: MR-linac
Appendix 4.4
Outcome variable: Progression free survival (PFS)

*	+ No or minor problems
	? Some problems
	- Major problems

Author year country	Study design	Number of patients n= Type of cancer	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR guided treatment adapted RT	Control MR guided treatment non-adapted RT				
Chen 2017 USA	Case series	13 head and neck	1 patient withdrew before treatment	-	65% (1year) 59% (2 years)	Unclear definition of PFS in this study, as reported PFS >OS	NA	NA	NA
Chen 2018 USA	Case series	18 head and neck	1 patient did not complete treatment	-	95% (1 year estimated)	Estimated PFS as follow-up was less than 1 year.	NA	NA	NA
Finazzi 2019a The Netherlands	Case series	23 lung	-	89% (1 year) (95% CI: 77-100)		Kaplan-Meier estimate PFS	NA	NA	NA
Henke 2018d USA	Case series	20 abdomen	-	45% (1 yr) in 11 patients with oligo-metastatic disease at baseline	-		NA	NA	NA
Rosenberg 2019 USA	Case series	26 liver	-		35%	Not clear if PFS is at 1 year	NA	NA	NA
Llorente 2019 USA	Case series	9 spinal metastases	1 patient lost to FU shortly after RT	100% no infield recurrence, however 6 patients died and one was lost to FU; 2/9 (22%)	-	FU 12.3 months (range: 0-32)	NA	NA	NA
Rudra 2019 The Netherlands	Case series	44 pancreas	-	High dose group (N=24): 77% (2 years) Standard dose group (N=20): 57% (2 years) Total (N=44):67%		Patients treated with RT and chemotherapy. High dose group: biologically effective dose$_{10}$ > 70 Gy Standard dose group: biologically effective dose $_{10} \leq$ 70 Gy Unclear definition of PFS in this study, as reported PFS >OS	NA	NA	NA

NA=Not assessed, FU=follow-up, RT=radiotherapy, PFS=progression free survival

Project: MR Linac
Appendix 4.5
Outcome variable: Treatment time

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Patients (n)	Results		Directness *	Study limitations *	Precision *
			Intervention MR- guided treatment (adapted RT)	Control MR- guided treatment (non-adapted RT)			
Bertelsen 2019 Denmark	Case series	19	Median (range) 42 min (29-91)	Median (range) 26 (21-78)	NA	NA	NA
Finazzi 2019a The Netherlands	Case series	23	Median (5^{th}-95^{th} percentile) MR Linac = 48 min (32-80) Cobalt-60 = 62 min (46-105)	-	NA	NA	NA
Finazzi 2019 b The Netherlands	Case series	25	Median (2 SD) Cobalt-60= 59 min (43-86) MR-Linac = 50 min (38-70)		NA	NA	NA
Henke 2018d USA	Case series	20	Median on table time/fx min (range): 79 min/fx (36-160) MR-imaging set up: 3.5 min/fx (1-14) Time for physician arrival: 4 min/fx (0-15) Patient localization/shift application: 2 min/fx (0-14) Re-segmentation: 9 min/fx (2-24) Re-planning: 10 min/fx (2-24) QA:4 min/fx (1-14) Beam-on-time: 33.5 min (16-107)	If adaptation was not required re-segmentation, re-planning, QA were zero/not applicable. MR-imaging set up: 3.5 min/fx (1-14) Time for physician arrival: 4 min/fx (0-15) Patient localization/shift application: 2 min/fx (0-14) Beam-on-time: 33.5 min (16-107)	NA	NA	NA
Llorente 2019 USA	Case series	9	Beam-on- time median (range) 26.5 min (18.9-61)	-	NA	NA	NA
Palacios 2018 The Netheralnds	Case series	17	Recontour and re-optimize Average (SD) 16 .5 +6.2 min		NA	NA	NA
Tetar 2018 The Netherlands	Case series	150	Mean duration (range) of a single fx: Free-breathing SBRT: 45 min (33-55) Breath-hold (SMART): 60 min (50-75)	-	NA	NA	NA
Tetar 2019 The Netherlands	Case series (40 pts) Phase-2-study (100 pts)	140	Mean duration (range) of a single fx: 45 min (40-70)	-	NA	NA	NA
van Sörnsen de Koste, 2018 The Netherlands	Case series	15	On-line adaptation/re-optimization approx 15 min Gated delivery approx. 1/3 of total in-room treatment duration 45-60 min,	-	NA	NA	NA

ART=adaptive radio therapy, QA=quality assurance, fx=fractions, MR=magnetic resonance, SBRT=stereotactic radiotherapy, SMART= stereotactic MR-guided adaptive radiation therapy, MR= magnetic resonance, approx=approximately, RT = radiothearpy

Project: MR Linac
Appendix 4.6
Outcome variable: Organ at risk constraints violations

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= Type of cancer	Fractionation schedule N = number of fractions	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR- guided treatment (adapted RT)	**Control MR- guided treatment** (non-adapted RT)				
El-Bared 2018 USA	Cross sectional retrospective	10 pancreas	6,6 Gyx5 (1 pt) 7 Gyx5 (3 pt) 8 Gyx5 (6 pt) N=50	29/50 (58%) fx meet all OAR objectives	23/50 (46%) fx meet all OAR objectives	Adaptive plans were calculated on original treatment plans, thus 50 fx, but 100 treatment plans	+	?	-
Finazzi 2019a The Netherlands	Cross sectional retrospective	23 Lung	18Gyx3 (3 pt) 11Gyx5 (18 pt) 7.5Gyx8 (4pt) N=131/128*	15/112 (13%) fx with OAR violations	18/112 (16%) fx with OAR violations	*128 fx i text, 131 fx i table 1. 112 fx were analyzed	+	?/+	?
Finazzi 2019 b The Netherlands	Cross sectional retrospective	25 lung	7.5 Gy x 8 (20 pt) 11 Gy x 5 (5pt) N=182	Total number of OAR violations 93 Comparison initial vs adapted plan: ($p<0.05$)	Total number of OAR violations 127	Max OAR doses in predicted and reoptimized plans were comparable	+	?/+	?
Henke 2018b USA	Cross sectional retrospective	12 Central thorax	6,25 Gyx10 (3 pt) 5 Gyx12 (9 pt)	For fx 6: No OAR violations For fx 10: 11 OAR violations 8/12 patients	For fx 6: 8 OAR violations 5/12 patients For fx 10: 10 OAR violations 6/12 patients	Retrospective adaptive plans based on MRI from fx 6. These plan were then evaluated without further adaptation for fx10	+	?	-
Henke 2018d USA	Cross sectional prospective	20 Mets in abdomen (10) and liver (10)	10 Gyx5 (17 pt) 15 Gyx4 (3 pt) N= 50 N=47	No OAR violations in adapted plans	Abdomen: 44/50 fx required adaptation due to OAR violations Liver: 17/47 fx required adaptation due to OAR violations	97 fx in total (3 pts had 4 fx)	+	?	-
Kim 2019 Republic of Korea	Cross sectional retrospective	19 prostate	2.5 Gy x 28 (19pt)	19 patients with 5 adapted plans each. No OAR violations in 95 adapted plans	19 patients with 5 adapted plans each. No OAR violations in 95 on-adapted plans		?	-	-

Project: MR Linac
Appendix 4.6
Outcome variable: Organ at risk constraints violations

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n= Type of cancer	Fractionation schedule N = number of fractions	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR- guided treatment (adapted RT)	**Control MR- guided treatment** (non-adapted RT)				
Llorente 2019 USA	Case series-retrospective	9 Spinal mets	16 Gy x1 (7pt) 10 Gy x 3 (1 pt) 8 Gy x 3 (1pt)	No OAR violations in adapted plans			NA	NA	NA
Palacios 2018 The Netherlands	Cross sectional prospective	17 Adrenal mets	10 Gyx5 (14 pt) 8 Gyx3 (2 pt) 7,5 Gyx1 (1 pt)	% of fx with OAR violations Stomach 4% Bowel 0% Duodenum 0%	% of fx with OAR violations Stomach 27% Bowel 13% Duodenum 3%	84 fx in total	+	-	-

fx: fraction, SBRT: stereotactic radiotherapy, SD: standard deviation, Gy: Gray, OAR: organs at risk, RT=radiotherapy, mets= metastases, NA: Not assessed

Author year country	Study design	Number of patients n= Type of cancer	Fractionation schedule	Results*		Comments	Directness *	Study limitations *	Precision *
				Intervention	**Control**				
Kim 2018 Republic of Korea	Case series comparative (retrospective)	8 lung 8 lung	15 Gyx4 (14 pt) 13 Gyx4 (2 pt)	**MR-^{60}CO guided treatment (non-adapted)** Mean dose (SD) ipsilateral lung 7.17 (±1.55) Mean dose (SD) contralateral lung 1.35 (±0.6) V20Gy (SD) 218.36 (±153.31)	**Linac VMAT treatment (non-adapted)** Mean dose (SD) ipsilateral lung 4.66 (±2.42) p = 0.012 Mean dose (SD) contralateral lung 0.67 (±0.35) p = 0.036 V20Gy (SD) 92.09 (±40.43) p = 0.017		-	?	?

fx: fraction, SD: standard deviation, Gy: Gray,

*This table presents a different comparison in which two **non-adapted** treatment methods are compared. The intervention using cobalt technique was the first generation of MR-guided technique and is no longer considered for new investments. The control group treatment using Linac is without integrated MR technique.

Project: MR Linac
Appendix 4.7
Outcome variable: Target coverage (PTV coverage, GTV coverage)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Patients (n) Type of cancer	Fractionation schedule N=number of fractions	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR guided treatment (adapted RT)	Control MR guided treatment (non-adapted RT)				
Acharya 2016b USA	Cross sectional	36 breast	3.85 Gy BID 10 fx/pat N=360	PTV coverage (delivered dose) Mean diff % (SD) 0.6 (± 0.1) Median diff % (SD) 0.1 (± 0.1)	-	Treatment goal: 95% of PTV covered by 95% of prescribed dose Differences are between delivered and planned dose	?	?	?
El Bared 2018 USA	Cross sectional retrospective	10 pancreas	6.6 Gyx5 (1 pt) 7 Gyx5 (3 pt) 8 Gyx5 (6 pt) N=50	PTV coverage (proportion of fx achieving treatment goal) 100% (50 fx)	PTV coverage (proportion of fx achieving treatment goal) 16% (8 fx)	Treatment goal: 100% of PTV is covered by 90% of prescribed dose.	+	?	-
Finazzi 2019a The Netherlands	Case series	23 Lung	18 Gyx3 (3 pt) 11 Gyx5 (18 pt) 7.5 Gyx8 (4 pt) N=131*	Improved PTV coverage in 58% of fx	-	* Inconsistent information in publication whether 131 or 128 fxs were included in the analysis	+	+/?	?
Finazzi 2019b The Netherlands	Cross sectional retrospective	25 Lung	7,5 Gy x 8 (20pt) 11 Gy x 5 (5pt) N=185	Improved PTV coverage in 61% of fx.	-	Comparison between initial and adapted plan Adaptation increased the rate of acceptable plans from 71% to 94%.	+	+/?	?
Henke 2018b USA	Cross sectional retrospective	12 Central thorax	6.25 Gyx10 (3 pt) 5 Gyx12 (9 pt) N=138	PTV coverage (Median) fx 1 not adapted for fx 6: 87.3% for fx 10: 87.0% (fx 10)	PTV coverage (Median) Fx 1: 83.7% For fx 6: 81.9% For fx 10: 82.8%	Treatment goal: 95% of PTV covered by 95% of prescribed dose Adapted plans were constructed retrospectively based on MRI for fx 6 and evaluated based on fx 6 and fx 10.	+	?	-
Henke 2018d USA	Cross sectional prospective	20 Mets in abdomen (10) and liver (10)	10 Gyx5 (17 pt) 15 Gyx4 (3 pt) N=97	PTV coverage cumulative adaptive Mean % (SD) 79.4 ± 24.1 Median % (range) 88.6 (20.7 - 100) GTV coverage cumulative adaptive Mean % (SD) 89.6 (17.2) Median % (range) 99.3 (33.1 - 100)	PTV coverage non-adaptive Mean % (SD) 76.2 ± 26.2 Median % (range) 81.6 (0.4 - 100) GTV coverage non-adaptive Mean % (SD) 85.6 (24.4) Median % (range) 94.7 (0 - 100)	Treatment goal: 95% of PTV covered by 95% of prescribed dose Treatment goal: 95% of GTV covered by 100% of prescribed dose	+	+	-

Project: MR Linac
Appendix 4.7
Outcome variable: Target coverage (PTV coverage, GTV coverage)

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Patients (n) Type of cancer	Fractionation schedule N=number of fractions	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR guided treatment (adapted RT)	Control MR guided treatment (non-adapted RT)				
Kim 2019 Republic of Korea	Cross sectional retrospective	19 prostate	2.5 Gy x 28 (19pt) N=532	PTV coverage 100%	PTV coverage 98.5%	Treatment goal: 95% of PTV receiving 95% of prescribed dose	?	-	-
Palacios 2018 The Netherlands	Cross sectional prospective	17 adrenal mets	10 Gyx5 (14 pt) 8 Gyx3 (2 pt) 7.5 Gyx8 (1 pt) N=84	PTV coverage (proportion of fx achieving treatment goal) 51%	PTV coverage (proportion of fx achieving treatment goal) 20%	Treatment goal: 95% of PTV receiving 95% of prescribed dose	+	?	-
Winkel 2019 The Netherlands	Case series	10 Pelvis mets	7 Gy x 5 N=50	PTV coverage V35Gy Median (range) 99.9 % (90.7-100)	-		NA	NA	NA

BID = twice daily, fx=fraction, mets= metastases, SMART=stereotactic MR-guided online adaptive ration therapy, NA: Not assessed.

Project: MR Linac

* + No or minor problems
? Some problems
- Major problems

Appendix 4.8
Outcome variable: Partial/complete response

Author year country	Study design	Number of patients n=	Withdrawals - dropouts	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR guided treatment (adapted RT)	Control MR guided treatment (non-adapted RT)				
Chen 2017 USA	Case series	13 head and neck	1	-	Complete response 50% (6 pat) Partial response 33% (4 pat)	Time point at which response is validated was not stated	NA	NA	NA
Chen 2018 USA	Case series	18 head and neck	1	-	At 3 months Complete response 83% (15 pat) Partial response 11 % (2 pat)	18 pts included in study, however data from 17 pts reported.	NA	NA	NA
Chiloiro 2019 Italy	Case series	22 rectal	-	Complete response 27.3% (6 pts)			NA	NA	NA
El Bared 2018 USA	Case series	10 pancreas		complete response 12.5% (1 pat/8) moderate response 37.5% (3 pat/8)			NA	NA	NA

mo = months, pat = patient, pts = patients, NA= not assessed.

Project: MR Linac
Appendix 4.9
Outcome variable: % of cases/fractions that were re-planned/ received online adapted radiotherapy

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Fraction schedule N=total number of fractions	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR guided treatment (adapted RT)	Control MR guided treatment (non-adapted RT)				
Bertelsen 2019 Denmark	Case series	19	3 Gy x 20 (6 pt) 5 Gy x 3 (3 pt) 10 Gy x 3 (4 pt) 6 Gy x 5 (2 pt) 9 Gy x 3 (1 pt) 15 Gy x 3 (1pt) 7.5 Gy x 8 (1 pt) 5 Gy x 6 (1pt) 6.1 Gy x 7 (1 pt) N=176	49 adapted fx/176 fx = 28%	NA	One patient had two separate treatments	NA	NA	NA
Finazzi 2019a The Netherlands	Case series	23	18Gyx3 (3 pt) 11Gyx5 (18 pt) 7.5Gyx8 (4pt) N=131	116 reoptimized fx / 128 fx = 91%	NA	For each fx, clinician selected either predicted plan (recalculated on anatomy of the day and adaptation of contours) or reoptimized plan (optimization of beam fluences, considering adapted GTV and OARs)	NA	NA	NA
Finazzi 2019b The Netheralnds	Case series	25	7.5 Gy x 8 (20 pt) 11 Gy x 5 (5pt) N=185	168 adapted fx/185 fx = 92%	NA -	As above	NA	NA	NA
Fischer-Valuck 2017 USA	Case series	67	Not reported	244 adapted fx/371fx = 66%	NA		NA	NA	NA
Henke 2018b USA	Case series retrospective	12	6,25 Gy x 10 (3 pt) 5 Gy x 12 (9 pt) N=138	78 adapted fx/138 fx =57%	NA	No daily adaptation. Fx 6 was adapted in all pat, and they received this adapted plan the remaining fx	NA	NA	NA
Henke 2018d USA	Phase-1	20	10 Gyx5 (17 pt) 15 Gyx4 (3 pt) N=97	81 adapted fx/97 fx = 83.5%	NA	All patients required adapted planning > 1 fraction.	NA	NA	NA

Project: MR Linac
Appendix 4.9
Outcome variable: % of cases/fractions that were re-planned/ received online adapted radiotherapy

* + No or minor problems
? Some problems
- Major problems

Author year country	Study design	Number of patients n=	Fraction schedule N=total number of fractions	Results		Comments	Directness *	Study limitations *	Precision *
				Intervention MR guided treatment (adapted RT)	Control MR guided treatment (non-adapted RT)				
Palacios 2018 The Netherlands	Case series prospective	17	10 Gy x 5 (14 pt) 8 Gy x3 (2 pt) 7,5 Gy x 8 (1 pt) N=84	53 adapted fx/84 fx = 63%	NA		NA	NA	NA
Rudra 2019 The Netherlands	Case series	44	44-50Gy in 25-28fx 30-35Gy in 5fx 40-52Gy in 5fx 50-67.5 in 10-15fx	High-dose group = 83% Standard-dose group = 15%	NA	High dose group: biologically effective dose$_{10}$ > 70 Gy Standard dose group: biologically effective dose $_{10}$ ≤ 70 Gy	NA	NA	NA
Tetar 2019 The Netherlands	Case series and phase-2 study	140	7.25 Gy x 5 (130 pts) 7 Gy x 5 (10 pts) N=700	677 adapted fx/700 fx = 97%	NA		NA	NA	NA
Van Sörnsen de Koste 2018 The Netherlands	Case series Prospective	15	11 Gy x 5 (1 pt) 10 Gy x 5 (3 pts) 8 Gy x 5 (6 pts) 7,5 Gy x 8 (4 pts) 7 Gy x 5 (1 pt) N=87	100% underwent online adaptation/plan/ reoptimization	NA		NA	NA	NA

Fx = fractions, SBRT= Stereotactic Radiotherapy, mets=metastases, pts=patients, pt=patient

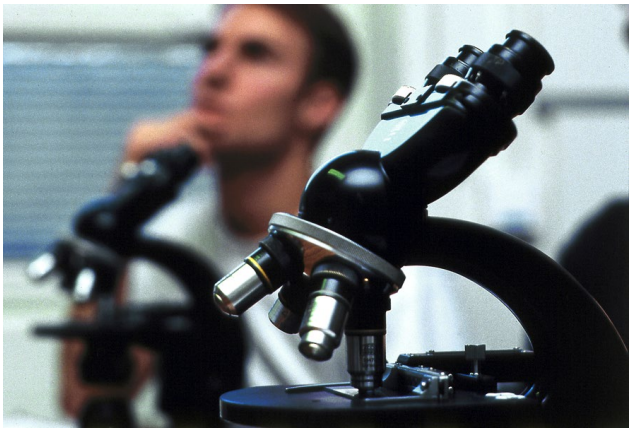
Innehållsdeklaration

Denna HTA-rapport är baserad på följande moment:

- [x] Metodbeskrivning
- [x] PICO
- [x] Uttömmande litteratursökning
- [x] Flödesschema
- [x] Urval relevans
- [x] Kvalitetsgranskning
- [x] Tabelldata
- [x] Sammanvägning av resultat
- [x] Metaanalys
- [x] Evidensgradering enligt GRADE
- [x] Sammanfattning
- [x] Ekonomi
- [x] Organisation
- [x] Etik
- [x] Pågående studier
- [x] Exkluderade artiklar
- [x] Expertgrupp deltar
- [ ] Extern granskning
- [x] Kunskapsluckor identifierade
- [x] Jävsdeklaration inhämtad från projektdeltagarna

Region Västra Götaland, HTA-centrum

Health Technology Assessment
Regional activity-based HTA



HTA

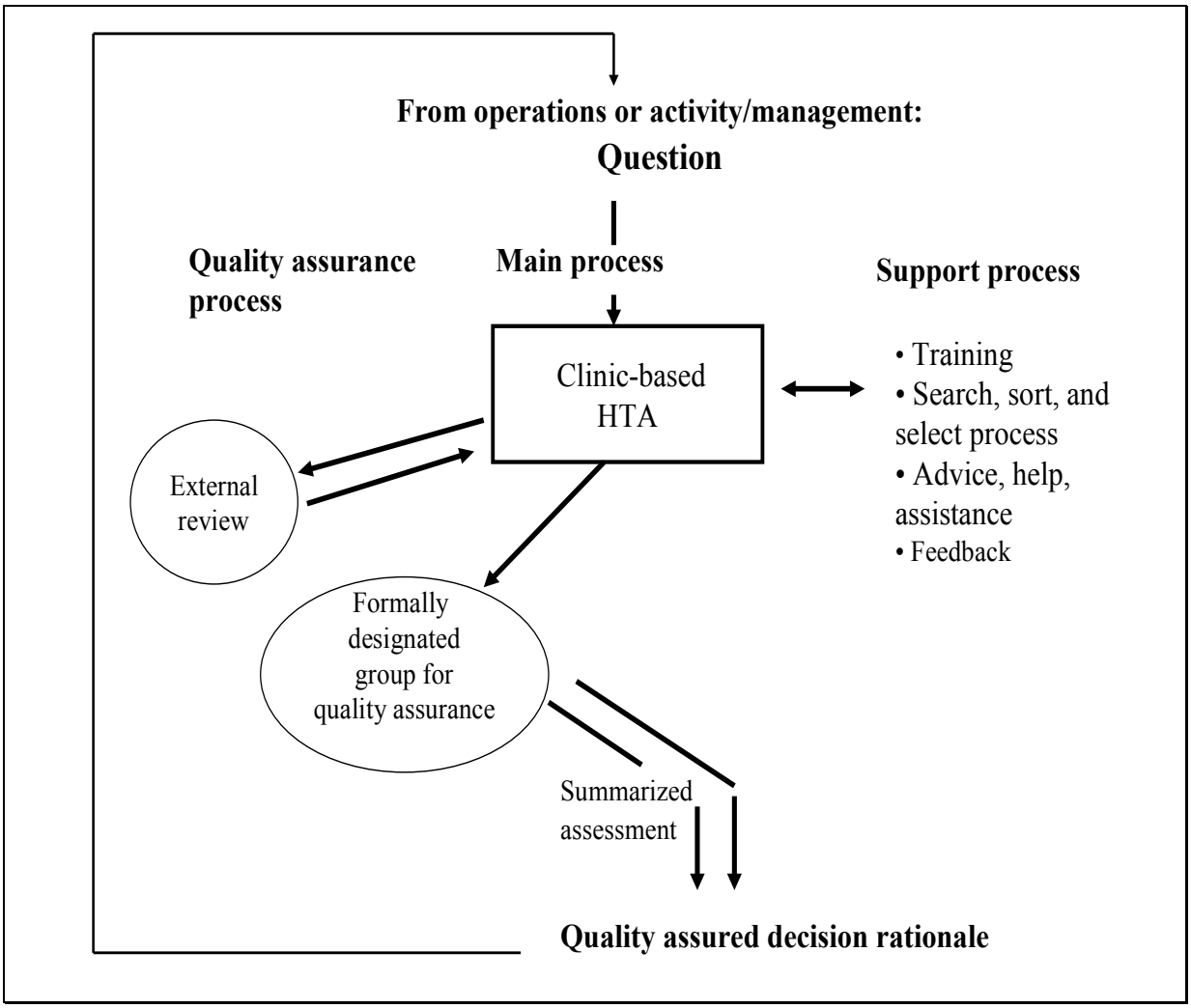
Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the certainty of evidence the Centre of Health Technology Assessment in Region Västra Götaland is currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High certainty of evidence	= (GRADE⊕⊕⊕⊕)
Moderate certainty of evidence	= (GRADE ⊕⊕⊕O)
Low certainty of evidence	= (GRADE ⊕⊕OO)
Very low certainty of evidence	= (GRADE ⊕OOO)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

Christina Bergh
Professor, MD
Head of HTA-centrum


From operations or activity/management:
Question
Quality assurance process
Main process
Support process
Clinic-based HTA
• Training
• Search, sort, and select process
• Advice, help, assistance
• Feedback
External review
Formally designated group for quality assurance
Summarized assessment
Quality assured decision rationale

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