GEC-ESTRO Recommendations

# Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (IV): Basic principles and parameters for MR imaging within the frame of image based adaptive cervix cancer brachytherapy

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## ARTICLE INFO

## ABSTRACT

The GYN GEC-ESTRO working group issued three parts of recommendations and highlighted the pivotal role of MRI for the successful implementation of 3D image-based cervical cancer brachytherapy (BT). The main advantage of MRI as an imaging modality is its superior soft tissue depiction quality. To exploit the full potential of MRI for the better ability of the radiation oncologist to make the appropriate choice for the BT application technique and to accurately define the target volumes and the organs at risk, certain MR imaging criteria have to be fulfilled. Technical requirements, patient preparation, as well as image acquisition protocols have to be tailored to the needs of 3D image-based BT. The present recommendation is focused on the general principles of MR imaging for 3D image-based BT.

Methods and parameters have been developed and progressively validated from clinical experience from different institutions (IGR, Universities of Vienna, Leuven, Aarhus and Ljubljana) and successfully applied during expert meetings, contouring workshops, as well as within clinical and interobserver studies.

It is useful to perform pelvic MRI scanning prior to radiotherapy ("Pre-RT-MRI examination") and at the time of BT ("BT MRI examination") with one MR imager. Both low and high-field imagers, as well as both open and close magnet configurations conform to the requirements of 3D image-based cervical cancer BT. Multiplanar (transversal, sagittal, coronal and oblique image orientation) T2-weighted images obtained with pelvic surface coils are considered as the golden standard for visualisation of the tumour and the critical organs. The use of complementary MRI sequences (e.g. contrast-enhanced T1-weighted or 3D isotropic MRI sequences) is optional. Patient preparation has to be adapted to the needs of BT intervention and MR imaging. It is recommended to visualise and interpret the MR images on dedicated DICOM-viewer workstations, which should also assist the contouring procedure. Choice of imaging parameters and BT equipment is made after taking into account aspects of interaction between imaging and applicator reconstruction, as well as those between imaging, geometry and dose calculation.

In a prospective clinical context, to implement 3D image-based cervical cancer brachytherapy and to take advantage of its full potential, it is essential to successfully meet the MR imaging criteria described in the present recommendations of the GYN GEC-ESTRO working group.

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Radiotherapy (RT) and in particular brachytherapy (BT) have been major treatment modalities for cervical cancer for over 100 years with BT treatment planning mainly based on radiographs and point dosimetry. In the late 90's MR image guidance was introduced into BT treatment planning. The Gynaecological (GYN) GEC-ESTRO working group then issued recommendations for MRI based adaptive target concepts, 3D based adaptive dose volume parameters for target and organs at risk including aspects of 3D image-based MRI anatomy, radiation physics and radiobiology, and recently also for applicator reconstruction [1–3].

According to the dramatic changes in regard to tumour, target and normal tissue topography during external beam radiochemotherapy repetitive imaging studies are necessary to assess the individual situation at a given time point during treatment [4–11].

In the GYN GEC-ESTRO recommendations the suggestion has been to perform MR imaging prior to treatment ("Pre-RT MRI examination") and at the time of BT ("BT MRI examination") with

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the applicator in place. The "*Pre-RT MRI examination*" as addressed here is related to the needs of the following RT and should be performed as much as possible along the lines of the following repetitive imaging studies, in particular at the time of BT.

The basic imaging concepts of diagnostic radiology therefore can be applied for the "*Pre-RT MRI examination*" with some adaptations for comparability to the subsequent "*BT MRI examination*" which has to be performed according to the needs of BT treatment planning. The basic principles are elaborated within the following recommendations. Taking into account these principles appropriate institutional MR imaging protocols have to be set up in close cooperation between radiation oncologists and diagnostic radiologists.

In order to achieve this aim of combining diagnostic and therapeutic radiology needs within the GYN GEC-ESTRO working group and network at least one diagnostic radiologist (PP) with subspecialisation in gynaecologic imaging has participated continuously in the expert meetings, the various workshops and in the ESTRO 3D Gyn Teaching Course. This close cooperation has been the backbone of these imaging recommendations which deal with all the different issues of interest in the context of MRI based adaptive cervix cancer BT. Dedicated imaging protocols were developed, implemented and evaluated by various members of the working group and the network in their respective clinical context and in small scale studies including interobserver studies using various MRI scanners (0.2–1.5 Tesla (T)) from different vendors. The feasibility of these protocols could be shown [12–24]. The image studies as being proposed within the following recommendations enable under the suggested conditions straightforward image reading and an appropriate definition of target and organs at risk (OAR) and adaptive treatment planning according to the terms and concepts as elaborated in the three preceding recommendations. In addition there is agreement among the clinical and imaging experts that the adaptive treatment planning process has to be based also on repetitive clinical gynaecological examination with documentation on repetitive 3D clinical drawings ("clinical imaging"). [1,3].

The following recommendations from the GYN GEC-ESTRO working group/network, on imaging for 3D image-based adaptive treatment planning in cervical cancer BT, are based on the expert experience from clinical practice in a limited number of centres and on evidence from a limited number of clinical imaging studies [12–15,18–22,24].

## Demands on MR imaging for cervical cancer BT

For the individual patient the choice of appropriate BT application technique, as well as precision of target and organ contouring depend, even if only to a certain degree (see also clinical examination in [1,3]), on parameters obtained from MRI. To meet these demands for 3D image-based cervical cancer BT, MRI must provide:

– sufficient information about tumour extent, tumour growth pattern and topography of patho-anatomical structures in three dimensions (3D) at the time of diagnosis ("*Pre-RT MRI examination*"),
– sufficient information about tumour/target extent, tumour/target growth pattern and topography of patho-anatomical structures in three dimensions (3D) at the time of BT with the applicators in place ("*BT MRI examination*"),
– comprehensive information about quantitative and qualitative tumour regression during the entire course of RT in four dimensions (4D-including changes in time) ("*Pre-RT MRI examination*"/"*BT MRI examination*" comparison).

Reproducible observation of this imaging information throughout RT treatment course can only be guaranteed if dedicated imaging protocols are applied for both "*Pre-RT MRI examination*" and "*BT*

*MRI examination*". Repetitive imaging with reproducible image quality and reproducible image contrast is only provided if these protocols meet certain criteria regarding technical requirements for the MRI unit, patient preparation, image acquisition and compatibility of BT equipment with MRI, taking also into consideration the important aspects of the interaction between imaging and applicator reconstruction, as well as those of the interaction between imaging, geometry and dose calculation.

## Technical requirements

### Magnet field strength

Both low (0.1–0.5 T) and high 1.0–1.5 T field imagers conform to the requirements of "*Pre-RT MRI examination*" and "*BT MRI examination*" [25,26]. Clinical experience with higher magnet field strength (3 T or higher) in diagnostic radiology is growing, but reports with its use for 3D image-based cervical cancer BT are limited, mainly because of issues of image distortion, artefacts and potential heating effects from BT applicators during MRI scanning [27]. Data about the clinical use of lowest magnet field strength MRI scanners (0.02 T) for cervical cancer patients are also limited [28,29]. However, for the radiation oncologist, to avoid differences in contrast and image quality between "*Pre-RT MRI examination*" and "*BT MRI examination*" it is useful to obtain both scans with the same imager.

### Magnet configuration

Both open and closed magnet configurations can be used for "*Pre-RT MRI examination*" and "*BT MRI examination*". Open MRI scanners offer improved patient accessibility, but to date, "*real-time*" image-guidance during the BT intervention is possible neither with open nor closed scanners. However, direct visualisation of the applicator during insertion in "*real-time*" may be enabled by future developments in the field.

### Coils

Coils are used to increase the signal-to-noise ratio (SNR) of the scanned region [30–34]. A surface pelvic coil wrapped around the pelvis is considered as standard for diagnostic pelvic MR imaging (staging and follow-up) and is also recommended for "*Pre-RT MRI examination*" and "*BT MRI examination*". MR imaging with intracavitary, (i.e. intrarectal or intravaginal) coils improve visualisation of small intracervical tumours, but are not routinely used. The use of such intracavitary coils for cervical cancer BT is neither described nor is it recommended. Changes in organ shape and topography after MR image acquisition and coil removal would be associated with major dosimetric uncertainties during treatment planning. In addition, MRI scans performed with intrarectal coils would not cover the entire region of interest [30,32,34].

### Patient preparation – contrast application

To conform to the requirements of BT intervention and MR imaging, bowel preparation (e.g. per oral application of Polyethylenglycol 3350 with electrolytes) started 2 days prior to the intervention, can be performed.

To reduce bowel motion, intravenous or intramuscular antispasmodic drug administration should be considered (e.g. N-Butylscopolan or Glucagon chlorhydrate) (Fig. 1a and b). MR image quality can be further improved by reducing the anterior abdominal wall motion amplitude with a large elastic band and by reducing the signal from the air/subcutaneous fat interface with an
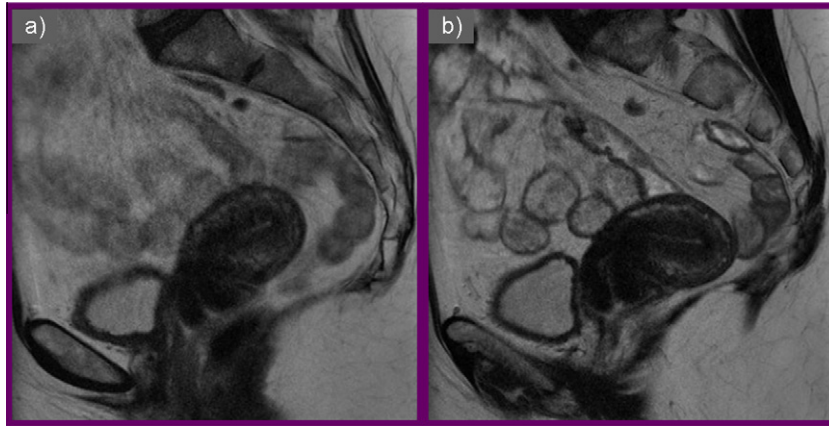
**Fig. 1.** Effect of antispasmodic drug administration on MR image quality: small bowel peristalsis causes movement artefacts in MRI (a). A spasmolytic agent (e.g. N-Butylscopolan or Glucagon chlorhydrate) is therefore commonly administered intravenously to inhibit bowel motion shortly before performing pelvic MRI (b). In (a) the sagittal T2w MR image is blurred due to small bowel motion and due to uterine contraction. In (b) the sagittal T2w MR image of the same patient appears with significant improvement of image quality since it is obtained after injection of Glucagon chlorhydrate.

anterior pre-saturation band. The signal from the air/subcutaneous fat interface alters image quality in the phase-encoding direction.

Clinical examination is considered to be the golden standard for evaluation of vaginal invasion, due to direct examination of the organ, in particular in combination with vaginal impression [35,36]. Intracavitary contrast-enhanced imaging with intravaginal application of intermediate-to-high signal intensity contrast-media for "*Pre-RT MRI examination*" unfolds the vaginal fornices thus reveal-

ing signs of invasion and exophytic tumour growth [37,38] (Fig. 2). Van Hoe et al. used a mixture of barium, water, and maltodextrin/calcium lactate for this purpose [38]. Ultrasound gel is a widely available alternative. With the patient in supine position on the MRI table, 30–50 cc of the gel are injected with a sterile syringe into the vagina until reflux is obtained [15,38].

Urine is displayed with high-signal intensity on T2-weighted images and with sufficient contrast to the low-intensity muscular
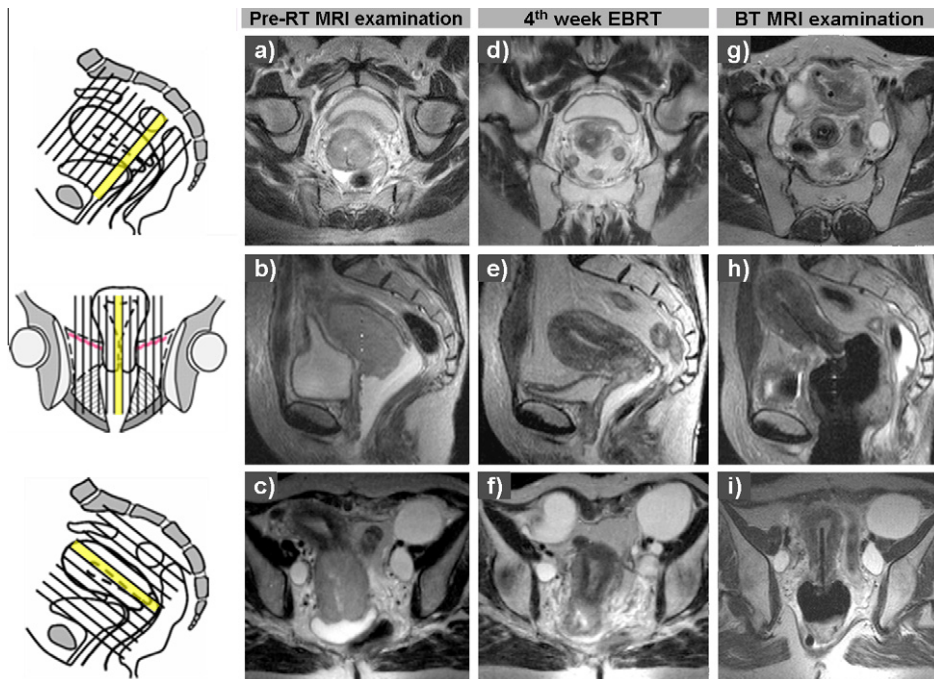


**Fig. 2.** MR image plane orientation and coverage of T2w pelvic scanning for assessment of dynamic tumour response during radiochemotherapy of a cervix cancer patient with bulky IIB disease: (a–c) demonstrate the "*Pre-RT MRI examination*" with para-axial, sagittal and para-coronal slice orientation, respectively. The MR image plane orientation remained the same for "*4th week EBRT MRI examination*" (d–f) and for "*BT MRI examination*" (g–i). "*4th week EBRT MRI examination*", was performed to illustrate tumour response during EBRT in this particular patient. Such repetitive MRI is not necessarily required for the performance of MR image guided cervix cancer brachytherapy, however clinical repetitive examination is mandatory with documentation on 3D clinical drawing. Para-axial, sagittal and para-coronal slice orientation is selected on sagittal, coronal and sagittal scout views, respectively. Para-axial slices are orientated perpendicular to the long axis of the cervical canal. Sagittal and para-coronal slices are orientated parallel to the long axis of the cervical canal. The coverage which should be obtained is described in detail in the text. The "*Pre-RT MRI examination*" demonstrates the bulky IIB tumour which is mainly located in the anterior part of the cervix and invades both parametria (right > left). During EBRT the tumour is shrinking significantly, the remnants are remaining mainly located in the anterior part of the cervix and both parametria are still invaded. On "*BT MRI examination*" which is obtained after applicator insertion additional shrinkage of the tumour is observed and residual gross tumour, as well as grey zones are restricted to the right anterior parts of the cervix and the inner part of the right parametria.

bladder. Therefore, retrograde intravesical contrast application is not required.

It is recommended to apply dedicated bladder filling protocols in order to achieve reproducible bladder filling during image acquisition and BT delivery.

A foley catheter is inserted and the catheter-balloon is filled with 7 cm$^3$ of fluid which is either diluted gadolinium contrast agent (e.g. dilution 1:1) for 0.2 T MR imaging or it is normal saline solution for 1.5 T MR imaging. When using HDR, a specific bladder filling can be used by opening the catheter to empty the bladder and then instilling, prior to MRI scanning, a certain volume (e.g. 50 ml) of saline solution. The urinary catheter is then left open throughout the entire treatment planning procedure and the 50 ml saline solution is then again instilled prior to the BT delivery process. When using PDR, the catheter has to be left open during treatment, and therefore the bladder should be emptied prior to MR scanning.

The "*BT MRI examination*" has to be performed with the BT applicator in place. On T2-weighted sequences, commercially available MRI-compatible applicators and MRI-compatible interstitial titanium or plastic needles are depicted with low-signal intensity and with sufficient contrast to the adjacent patho-anatomical structures, which are displayed with intermediate to high signal intensity [39,40].

For the fixation of the applicator and to displace the rectum and the bladder from the intravaginal parts of the applicator, it is recommended to use vaginal packing with a cotton gauze. The packing can be impregnated with diluted gadolinium contrast agent (e.g. dilution 1:10 in 0.2 T) or can be left dry (e.g. in 1.5 T). In this way, the packing will be depicted with low signal on T2-weighted sequences (Fig. 2). The latter guarantees improved discrimination quality for the depiction of the lower parts of the cervix/tumour which are displayed with high to intermediate signal on T2-weighted sequences [15]. A similar effect is observed for the border between the vagina and packing if there is no signal in the vagina (Fig. 2).

The use of rectal in vivo diode dosimeters (e.g. PTW AM6 diode, diameter 10 mm, PTW Freiburg, Germany) is optional. Such diodes are inserted through a plastic probe into the rectum to approximately 15 cm from the anus. The diode dosimeters contain metal and have to be removed during MR image acquisition. The plastic probe, which is remaining in the patient, is also depicted with low signal-intensity on T2-weighted MR images.

*Image acquisition*

Imaging parameters: technique (e.g. spin echo (SE), fast spin echo (FSE), turbo spin echo (TSE)), repetition times (TR), echo times (TE), field of view (FOV) and matrix of data collection are summarised in Tables 1 and 2.

*Sequences*

OAR (bladder, vagina, rectum and sigmoid colon) and the relevant patho-anatomical structures (uterine cervix and corpus, vagina, parametria, tumour, "*grey zones*") are appropriately visualised on T2-weighted MR images, without contrast media injection [15,41–43]. Therefore, T2-weighted sequences are considered to be the basic sequences, which should always be performed. SE and FSE T2-weighted sequences are of equal value, although the latter reduce image acquisition time.

Acquisition of T1-weighted spin-echo images is not mandatory, but can be performed in addition for pelvic nodal status evaluation. Contrast-enhanced T1-weighted images may help to define pathological conditions such as fistulas, tumour necrosis and pelvic abscesses.

The most commonly used post contrast-enhanced T1-weighted sequences are 2D *SE or 3D Gradient-echo (GRE) sequences*, which can be obtained with or without fat-saturation. The choice of whether using fat-saturation or not, depends on scanner type and individual preferences.

Contrast-enhanced images overestimate tumour extension due to enhancement of peri-tumoural oedema [35,44]. Therefore, dynamic-acquisition and post contrast-enhanced T1-weighted MRI sequences do not replace T2-weighted sequences, especially with regard to estimation of parametrial tumour extension.

**Table 1**

Image acquisition protocols for pre-RT MRI scan and BT MRI scan. This table summarises the important information regarding sequence, plane orientation, coverage/borders for each of the different MRI sequences.

| Protocol | Number | Mandatory (M)/ optional (O) | Sequence | Plane orientation | Coverage/borders |
|---|---|---|---|---|---|
| Pre-RT MRI scan | 1 | M | T2 FSE | Para-axial (according to cervix uteri) | Above uterine corpus – inferior border of symphysis pubis/entire vagina if distal vaginal involvement |
| | 2 | M | T2 FSE | Sagittal | Pelvic side wall (obturator muscle) |
| | 3 | M | T2 FSE | Para-coronal (according to cervix uteri) | Uterine corpus – cervix – vagina – tumour |
| | 4 | M | T2 FSE | Axial | Discus L4–L5 – inferior border of symphysis pubis/entire vagina and inguinal regions if distal vaginal involvement |
| | 5 | O | T1 FSE or 3D GRE without contrast[a] | Axial | Discus L4–L5 – inferior border of symphysis pubis/entire vagina and inguinal regions if distal vaginal involvement |
| | 6 | O | T1 FSE with contrast[a] | Sagittal | Pelvic side wall (obturator muscle) |
| | 7 | O | T1 FSE or 3D GRE with contrast[a] | Axial (isotropic 3D GRE) | Uterine corpus – cervix – vagina – tumour |
| BT MRI scan | 8 | M | T2 FSE | Para-axial (according to cervix uteri) | Above uterine corpus – 3 cm below lower surface of vaginal applicator/ entire vagina if distal vaginal involvement |
| | 9 | M | T2 FSE | Para-sagittal (according to cervix uteri) | Pelvic side wall (obturator muscle) |
| | 10 | M | T2 FSE | Para-coronal (according to cervix uteri) | Uterine corpus – cervix – vagina – tumour |
| | 11 | O | T2 FSE | Axial | Above uterine corpus – 3 cm below lower surface of vaginal applicator/ entire vagina if distal vaginal involvement |
| | 12 | O | 3D T2 FSE isotropic | Coronal or axial with reconstructions | Large coverage inherent in this sequence |
| | 13 | O | T1 FSE, FLASH, T1 GRE 3D | As appropriate | At least entire applicator |

[a] When contrast series are applied (6 and/or 7): use same T1 sequence for pre-contrast and lymph node evaluation.

**Table 2**

Image acquisition protocols for pre-RT MRI scan and BT MRI scan. This table summarises the important information regarding sequence parameters for each of the different MRI sequences. The numbering of sequences is the same as in Table 1.

| Protocol | Number | | Fatsat | TR (ms)[a] | TE (ms)[b] | ETL[c] | FOV (cm²)[d] | M(f)[e] | M(p)[e] | Nex[f] | SW[g] | NPW[h] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pre-RT MRI scan | 1 | | No | 2000–5000 | 90–120 | 4–20 | 35 × 20 | 512 | 256 | 2 | 3–4 | Yes |
| | 2 | | No | 2000–5000 | 90–120 | 4–20 | 35 × 40 | 512 | 256 | 2 | 5 | Yes |
| | 3 | | No | 2000–5000 | 90–120 | 4–20 | 35 × 20 | 512 | 256 | 2 | 3–4 | Yes |
| | 4 | | No | 2000–5000 | 90–120 | 4–20 | 35 × 40 | 512 | 256 | 2 | 5 | Yes |
| | 5 | TSE | Optional | 500–700 | 10–20 | NA | 35 × 20 | 512 | 256 | 2 | 5–7 | Yes |
| | | 3D GRE[i] | Optional | 5–10 | 2–5 | i | 37 × 30 | i | i | i | 1–4 | i |
| | 6 | TSE | Optional | 500–700 | 10–20 | NA | 35 × 20 | 256 | 256 | 2 | 3–5 | Yes |
| | 7 | TSE | Optional | 500–700 | 10–20 | NA | 35 × 20 | 256 | 256 | 2 | 3–5 | Yes |
| | | 3D GRE[i] | Optional | 5–10 | 2–5 | i | 37 × 30 | i | i | i | 1–4 | i |
| BT MRI scan | 8 | | No | 2000–5000 | 90–120 | 4–20 | 35 × 20 | 512 | 256 | 2 | 3–5 | Yes |
| | 9 | | No | 2000–5000 | 90–120 | 4–20 | 35 × 40 | 512 | 256 | 2 | 3–5 | Yes |
| | 10 | | No | 2000–5000 | 90–120 | 4–20 | 35 × 20 | 512 | 256 | 2 | 3–5 | Yes |
| | 11 | | No | 2000–5000 | 90–120 | 4–20 | 35 × 40 | 512 | 256 | 2 | 3–5 | Yes |
| | 12 | | No | See Refs. [22,48–56] for sequence parameters | | | | | | | | |
| | 13 | | No | | | | | | | | | |

[a] TR = time of repetition.
[b] E = time of echo.
[c] ETL = echo train length or turbo factor.
[d] FOV = minimum field of view.
[e] M = matrix: (f) = frequency, (p) = phase.
[f] Nex = number of excitations.
[g] SW = slice width.
[h] NPW = no phase wrap.
[i] Exact parameters depending on vendor, gradient performance, and parallel imaging abilities, GRE = gradient echo.

*Imaging plane orientation and coverage*

Minimum requirement for "*Pre-RT MRI examination*" are T2-weighted sequences in para-axial (orthogonal to the uterine axis), para-sagittal and para-coronal (parallel to the uterine axis) orientation (Fig. 2). T1-weighted sequences in axial orientation, as well as dynamic contrast-enhanced T1-weighted sequences in para-axial and para-sagittal orientation after bolus injection of contrast can be performed in addition.

"*BT MRI examination*" images are acquired after applicator placement (Fig. 2). Minimum requirements for "*BT MRI examination*" are T2-weighted sequences in para-axial, para-sagittal and para-coronal orientation, which are orientated orthogonal and parallel to the applicator axis [15,21,45] (Fig. 2). Axial images, orientated orthogonal to the MRI table, have to be acquired in addition, if this is required by the treatment planning system [21,23].

Para-axial images (Fig. 2) are obtained from the level above the uterine fundus to inferior border of the symphysis pubis below any vaginal tumour extension. In case of invasion of the distal vagina, axial "*Pre-RT MRI examination*" images should also cover the vulva and the groins and the "*BT MRI examination*" should include the vagina. The superior border of axial "*Pre-RT MRI examination*" images is set at the level of the intervertebral disc L4–L5. Sagittal images are obtained between internal obturator muscles (Fig. 2). Para-coronal (Fig. 2) and para-axial images (Fig. 2) include the tumour, entire cervix, corpus uteri, parametria and vagina. Image coverage between "*Pre-RT MRI examination*" and "*BT MRI examination*" should not differ. Sagittal imaging facilitates detection of organ invasion (bladder, rectum, vagina, small bowel and sigmoid colon) [46]. Para-coronal MR images (Fig. 2) facilitate evaluation of parametrial invasion [47] and may exclude partial volume artefacts at the level of the vaginal fornices.

*Sequence parameters*

Scanning parameters differ principally between MR scanners and have to be adapted to the specific device in collaboration with the diagnostic radiologist. Tables 1 and 2 summarise characteristic scanning parameters. TR, TE and echo train length (ETL) determine the weighting of the sequence (e.g. T2- or T1-weighted sequences). ETL determines the repetition of the received echo in fast spin-echo sequences. The FOV should be adapted to the individual patient in order to encompass the entire pelvis and to avoid fold-over artefacts. FOV usually ranges from 35 to 45 cm, but for para-coronal sequences it should range between 20 and 35 cm to enable improved tumour delineation accuracy into the direction of the parametria. In order to keep the acquisition time short for routine examinations, the matrix in the phase-encoding direction should not exceed 256 and should be placed in anterior–posterior direction on axial MRI sequences. In 3 T scanning, the phase direction can be placed also in cranio-caudal or left–right direction. The matrix size in the frequency-encoding direction can range from 256 to 512. On sagittal and axial T2-weighted MR images, slice thickness can vary, but should not exceed 5 mm. Interslice gap (ISG) between two slices can be used to avoid slice interference, but may be omitted for the para-transverse or transverse "*BT MRI examination*" in order to improve accuracy of applicator reconstruction. On para-axial T2-weighted images, 3 mm slice thickness increases diagnostic accuracy for the detection of parametrial invasion [47]. Sufficient SNR can be mostly achieved with two or more excitations, which also allows the use of fold over suppression (no phase wrap).

**3D isotropic fast spin-echo imaging with high sampling efficiency**

Conventional 3D T2w TSE MRI is characterised by long scanning times, which is reflected in high sensitivity for motion and susceptibility artefacts. Standard technique of MRI therefore currently consists of 2D T2w TSE image acquisition in three main orthogonal planes. Recently, 3D T2w TSE MRI sequence with high sampling efficiency (SPACE) has been introduced for diagnostic imaging of the pelvis and other anatomical regions [48–56]. Parallel imaging, high turbofactor and magnetisation restore pulses are applied in this sequence, along with non slice-selective pulse trains consisting of variable flip angle radiofrequency pulses along the echo train, as opposed to the constant flip angle refocusing of the

conventional TSE imaging [53]. The 3D sequence is characterised by a large field of view, enabling coverage of the entire pelvis within one single acquisition, and a sufficient signal-to-noise and contrast-to noise ratios. Due to a small isotropic voxel size (e.g. $1 \times 1 \times 1$ mm), free reformatting of thin slices in any plane is possible during image interpretation while partial volume artefacts are avoided. The ability to reconstruct high-resolution images in any relevant plane allows tracing of key patho-anatomical features and the BT applicator without the need for additional scanning. Fusion between 3D isotropic sequences and 2D T2W para-axial is promising for 3D image-based cervical cancer BT planning, for the purpose of both contouring [22] and for accurate reconstruction of the BT applicators [2]. Further studies are needed, however, to elucidate the role of 3D MRI in "*Pre-RT MRI examination*" and "*BT MRI examination*" by benchmarking it against the gold-standard 2D approach as the higher and isotropic resolution comes at the price of different contrast behaviours of the 3D sequence.

*MRI compatibility of BT equipment*

Applicators have to be MRI-compatible in order to avoid image distortion, heating and mechanical tissue injuries. Non-metallic (e.g. plastic) and titanium applicators are commercially available, and the individually produced resin mould applicator is also MRI compatible. Non-metallic applicators do not interfere with the magnetic field, and they appear as black voids in the images. Titanium applicators are usually validated by the vendors up to field strengths of 1.5 T with regard to heating effects and magnetic displacement. Validation of titanium applicators for 3 T scanners is typically pending, but initial studies indicate that they can be safely used with regard to heating and torque [27]. Although titanium applicators are MRI-compatible, they do induce susceptibility artefacts on both 1.5 T and 3 T – particularly in regions of considerable material thickness which is typically at the end of the tandem, needle, ovoid, and ring channels. In particular with 3 T MRI, titanium applicators may compromise the image quality due to susceptibility artefacts. The titanium artefacts depend on image sequence and may extend beyond 5–10 mm on 3 T T2-weighted sequences whereas they may be less than 3–5 mm on 3 T T1-weighted MRI [27]. The position and extent of titanium artefacts should be assessed by performing both MR and CT imaging of the applicator in a phantom.

Rectal in vivo diode dosimeters contain metal and have to be removed during MR imaging. A sheath can be inserted in order to facilitate insertion of the dosimeter after imaging.

*Geometry considerations and dose calculation*

The spatial accuracy of MR images is crucial for precise dose planning in RT [17,57,58]. The impact of spatial distortions will directly translate into dose calculation uncertainties according to the BT dose gradient of around 5–10% per mm. Therefore, it has to be kept in mind that control of the geometric accuracy of the MR imaging system is mandatory to make this concept meaningful. However, as opposed to external beam RT, BT dose calculation does not rely on the external body contour, and it is fortunately only necessary to address the spatial accuracy in the region of the applicator and relevant anatomy (target and OAR). For a dose precision of e.g. 5% at point A (2 cm from the intrauterine channel and typical dose gradient of 6% per mm) the geometrical accuracy of the MR acquisition needs to be within 1 mm. Such accuracy can be obtained with typical MRI sequences in the region of the BT applicator [59]. Of special concern is the geometrical accuracy in the immediate vicinity of the tandem, applicator and needles, where susceptibility artefacts introduce local geometrical distortions. Susceptibility distortions are field dependent, but it has so far been proven that these distortions are acceptable for magnetic field strengths up to 1.5 T [60] and 3 T [27].

Geometric distortions are sequence dependent and this has to be taken into account when choosing MRI-sequences. Fortunately the geometric stability of standard T2-weighted spin-echo and turbo spin-echo sequences is fairly robust to susceptibility artefacts, while fast imaging techniques like gradient echo techniques and echo planar imaging (EPI) techniques as used for diffusion weighted imaging (DWI) are much more prone to induce geometrical instability.

To assure constant quality of MR imaging during time of BT and to assess the impact of magnetic-field sensitive devices or implants and their repercussions on geometry in "*BT MRI examination*", calibration tests done before and during "*BT MRI examination*" should be performed with phantoms that allow estimation of the geometric/spatial accuracy, and a regular schedule should be established in accordance with local guidelines.

Advanced BT dose calculation takes into account tissue inhomogeneities by basing the calculation on CT and electron density information. However, with high energy sources like 192-Ir, 137-Cs, 60-Co, the energy dependence on tissue inhomogeneities is modest, and furthermore, in cervical cancer, the radiation is delivered far from the surface of the patient. Therefore the dose calculation accuracy is not compromised when using MR images for dose planning based on water dose calculation.

*Imaging and applicator reconstruction*

The choice of image sequences should take into account applicator reconstruction. GEC-ESTRO recommendations for applicator reconstruction have been published and these describe in detail the complete reconstruction procedure [2]. In the following paragraph, issues related to MRI and applicator reconstruction will be described.

The traditional X-ray marker string with small metal markers is not MRI-compatible and it is more difficult to define the source channel on MRI than with CT or X-ray. Special MRI markers like catheters containing water, CuSo4 solution or glycerine are alternatives [12,60,61], or other markers can be used to guide the reconstruction [62]. Slice thickness is an important parameter which has direct impact on the precision of reconstruction, and it is recommended to perform reconstruction in image series obtained with a slice thickness less than or equal to 5 mm. T2-weighted 3D sequences offer an excellent visualisation of the applicator and markers inserted into the source channels. 3D imaging also makes it possible to perform reconstruction in the same image sequence as contouring [22]. Alternative strategies may involve reconstruction in other image sequence (e.g. CT or additional MRI sequences) which are fused to the T2-weighted images which contain the contours [14]. This approach is particularly useful in cases with needles which may be difficult to define accurately on T2-weighted images. However, it has to be taken into account that fusion uncertainties will add on top of reconstruction uncertainties. Miss-registrations can involve considerable reconstruction errors with significant impact on dose [63,64].

**Discussion**

The present manuscript is published to supplement in particular the Recommendations from the Gynaecological (GYN) GEC-ESTRO Working Group (I), which emphasised on concepts and terms on MRI assessment of gross target volume (GTV) and clinical target volume (CTV) for cervical cancer BT [1]. In the subsequent paragraphs the GYN GEC-ESTRO recommendations for MR imaging for 3D image-based cervical cancer BT are discussed based on the

relevant issues derived from the existing multi-institutional clinical experience and as supported by data from the literature.

MR imaging, when performed with adequate imaging protocols, meets the demands for 3D image-based BT for cervical cancer [5,13,18–21,65–68]. It provides essential information about tumour extent, topography and regression, as well as topography of patho-anatomical structures [4–11,15]. A systematic analysis of MRI findings before EBRT and at the time of BT with the applicator in place, provided information helpful to reduce uncertainties regarding the definition of GTV, CTVs and patho-anatomical structures [15]. The parametrial space, as the region of potential tumour spread, was defined on axial T2-weighted MR images based on visible radiological criteria [15]. An additional evaluation with systematic analysis of tumour spread and regression on MRI enabled the recognition of different types of parametrial spread and regression and provided a thorough description of extent, quality and topography of tumour remnants [69]. Based on these two systematic evaluations, it appears feasible to accurately define the target within the frame of modern adaptive BT on T2-weighted axial MR images using the adaptive target approach, which was described in the first part of the GYN GEC-ESTRO recommendations [1,15,69]. The information provided with MRI is also valuable for the development of novel combined intracavitary and interstitial BT applicators [39,40].

Image quality and image characteristics depend on multiple parameters which principally vary between MRI scanners. On T2-weighted MR images, tumour signal intensity decreases with increasing field strength (Fig. 3a and b). It is therefore not only suggested to perform "*Pre-RT MRI examination*" and "*BT MRI examination*" with MRI scanners with similar field strength, but to perform these scans preferably using the same MRI scanner. Uniformity in image contrast and quality enables direct comparison between these MRI scans, with assessment of tumour extension and growth pattern at the time of diagnosis and at the time of BT, as well as assessment of quantitative and qualitative tumour regression [4,5,7,10,11,21,66,69] (Fig. 2).

Imaging based on 1.5 T magnets is currently considered as the standard for diagnostic body imaging. Imaging with open low field MRI scanners has improved over the years, but closed MRI scanners with higher magnetic field strength continue to provide superior images. Scanners with 3 T are increasingly utilised in the radiology community. With higher field strength the signal-to-noise ratio decreases and the voxel volume can be reduced [70]. However, image distortion, motion artefacts as well as susceptibility artefacts increase with increasing field strength [57], and further improvements are needed to gain the full benefit of the improved signal-to-noise ratio at 3 T. Higher magnetic fields, like 7 T and 8 T have been installed only in a few research centres as they present some technical challenges, e.g. the safety limits can be exceeded due to higher gradient amplitudes and radiofrequency power deposition [70,71].

In summary, it is not clear whether imaging with increasing field strength and improvement of image quality can be translated into increased precision for target delineation for cervical cancer BT.

The present recommendations for MR imaging for 3D image-based cervical cancer BT are therefore mainly based on the existing experience with 0.2 T and 1.5 T machines.

MRI scanners with closed magnet configuration and 1.5 T field strength are used in the majority of institutions [13,18,20,59,65–67,72]. Both 60 cm and 70 cm openings are suitable to offer sufficient space for patients who are not obese. Whether images obtained with 3 T MRI scanners are appropriate for the definition of tumour and BT targets, has to be validated in the future.

Low field 0.2–0.5 T open MRI scanners offer improved patient accessibility and represent the only acceptable option for the claustrophobic, overweight or obese patient [25,26]. The use of these scanners for "*Pre-RT MRI examination*" and "*BT MRI examination*" has been described in the literature [15,19,24,67,73,74]. However, low field magnet strength is associated with longer scanning times [73]. BT experience with more recent open-configuration high field (1–1.5 T) MR scanners has not been reported so far.

In case of complex BT implants (combined intracervical/interstitial implants), low field open MRI scanners enable a "*step by step*" interventional procedure, which can be performed in the MRI suite [39]. To date, "*real-time*" image-guided placement of MRI-compatible material (intrauterine and intravaginal applicator, needles, etc.), under the direct guidance of MRI, has not been implemented, neither by open nor by closed magnet configurations. This may be due to the lack of "*real-time*" MR imaging algorithms but may also be associated with hardware related patient access problems. Nevertheless, in the future development of dedicated MR imaging algorithms combined with high-field open bore magnet technology may provide solutions for such direct guidance procedures.

Patient preparation and contrast application for MR image acquisition has to be adapted to the needs of 3D image-based BT [5,13,15,18–21,65–68].
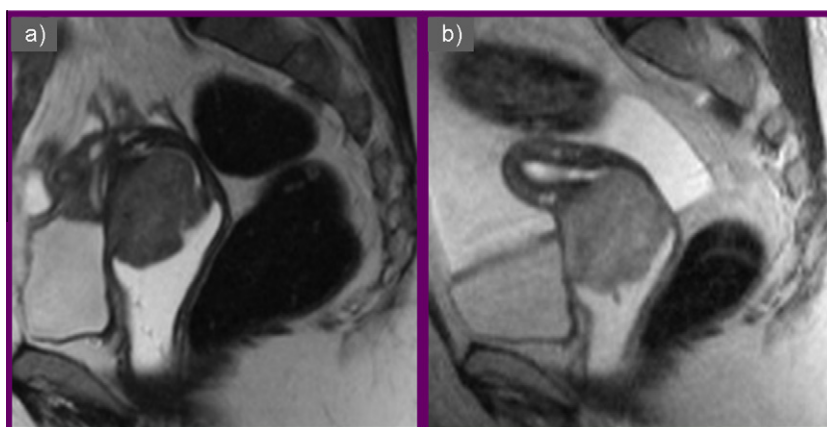


**Fig. 3.** Differences resulting due to different magnet field strength: comparison between T2w sagittal MR images obtained with a high-field MR scanner (1.5 T (a)) and a low-field MR scanner (0.2 T (b)). Prior to imaging intravaginal contrast (ultrasound gel) was injected in order to distend the vaginal walls and to improve visualisation of vaginal tumour extension. The impact of magnet field strength on signal intensity of tumour and intravaginal contrast is significant. The high field MR images depict the tumour with intermediate-to-high signal intensity and the low-field images of the same patient with high signal intensity.

Vaginal involvement is well amenable to clinical evaluation in most patients. Nevertheless, assessment of initial tumour growth pattern and extension seems to be also accurate with MRI, after application of vaginal contrast, since distension of the vaginal walls improves visualisation of the vaginal walls and lower parts of the cervix [15,37,38] (Fig. 2). It can be hypothesised, that the contrast induced vaginal wall distension makes "*Pre-RT MRI examination*" more comparable to the subsequent "*BT MRI examination*" with applicator and packing induced vaginal wall distension [5] (Fig. 2).

Intravenous or intramuscular drug administration in combination with bowel preparation and an anterior pre-saturation band improves image quality for both "*Pre-RT MRI examination*" and "*BT MRI examination*" due to reduction of bowel motion artefacts (Fig. 1a and b).

Reproducible bladder filling for the duration of "*BT MRI examination*" acquisition and the duration of the entire treatment and the planning procedure can be achieved with dedicated protocols [19,20]. It may be an open urinary catheter or a limited amount of fluid (e.g. 50 cm$^2$) filled into the emptied bladder. The aim is to minimise dosimetric and inter-/intra-fraction uncertainties [14,75].

Use of commercially available MRI-compatible applicators, vaginal packing (e.g. impregnated with contrast agents or dry) and foley catheters (filled with some contrast media) have been reported as a feasible way of providing appropriate visibility of relevant structures during BT [15] (Fig. 2). Intravaginal gauze packing impregnated with diluted Gadolinium and dry gauzes fix the applicator and displays low-signal intensity, in contrast to the high signal intensity of tumour for 0.2 T machines [5] and 1.5 T machines, respectively. Resin-made hollow vaginal mould applicators display homogeneous peripheral low-signal intensity and represent another option [67,76]. In future, various different solutions will likely be developed for appropriate visibility of the application related "instrumentarium" within various clinical and application settings.

Axial, sagittal and coronal oriented T2-weighted images are among others, the basic sequences for the evaluation of cervical cancer in diagnostic radiology, and should serve as the basis for "*Pre-RT MRI examination*" and "*BT MRI examination*" performed for the purpose of 3D image-based BT of cervical cancer. Only limited data about the impact of MR image orientation on contouring for 3D image-based BT of cervical cancer are available at present. In an investigation estimating the agreement between High Risk (HR)-CTV outlines delineated by two observers on transverse and para-transverse MR images, interobserver and interplanar conformity indices were high, while interobserver variation and interplanar topographic variation of dose volume histogram (DVH) parameters were not significant [21]. However, contouring seemed to be significantly easier in the para-transversal planes. Current recommendations therefore suggest to use (para)-images orientated parallel and orthogonal to the applicator (sources) axis to obtain a "*BT orientated view*" (BOV) [21,23].

It has been demonstrated, that para-axial and para-coronal T2-weighted MR images help to reduce potential misinterpretation due to partial volume effects. If used for diagnostic purposes, they improve the depiction of tumour in the parametria, vaginal fornices, and the lower parts of the cervix [47]. On "*BT MRI examination*", these sequences support assessment of GTV, grey zones and CTVs and facilitate target contouring [15,21]. Para-axial and para-coronal T2-weighted MR images should not only be performed at time of BT, when applicator-oriented, but also at "*Pre-RT MRI examination*". If MRI for staging also serves as "*Pre-RT MRI examination*", these two additional image sequences should be obtained.

If 3D sequences can be improved to provide better contrast properties for discrimination of cervix and grey zones, a single acquisition of a 3D T2w high resolution volume data set may serve as an alternative to the 2D multi-planar T2w imaging). There is currently some debate whether the 3D isotropic MRI improves the diagnostic potential of MRI in pelvic imaging [51–54]. Nevertheless, the contrast generating mechanism during the long spin-echo readout trains, currently represents the major limitation of 3D MRI. Currently, fusion of the 3D isotropic sequence and the para-axial T2 weighted sequence represents a good solution to combine the 3D free formatting with good T2 contrast, in order to support contouring at the time of BT. The imaging time can be shortened and an additional DICOM viewer may not be necessary during delineation, reducing the infrastructural requirements of the brachytherapy department [22]. Furthermore, imaging with small slice thickness or the use of 3D high-resolution isotropic MRI allows for a more accurate and convenient applicator reconstruction (see also "*Imaging and applicator reconstruction*") and has been recommended by the GYN GEC-ESTRO working group [2].

T1-weighted images are complementary to T2-weighted MR images, and are mostly used for staging purposes for lymph node evaluation, or, if contrast-enhanced, for tumour evaluation, particularly if the tumour is not well seen on T2-weighted images.

"*Pre-RT MRI examination*" and "*BT MRI examination*" should be accessible in a standardised DICOM format in order to enable image reading on a diagnostic imaging workstation, which should be placed next to the treatment planning system. Requirements for the imaging workstation are: multiplanar imaging capability simultaneous visualisation of multiple planes, reference lines, scroll capacity and localisation tools, which enable direct comparison of "*Pre-RT MRI examination*" and "*BT MRI examination*".

It is well known that there are significant intra- and inter-tumour variations which are relevant for the response to radiation. Investigation of clinical parameters together with functional imaging may provide additional biological tools in the future for assessment of tumour characteristics. Intra-tumour hypoxia in cervical cancer has proven to predict poor local control and survival [77,78]. Radio resistance of hypoxic cells may play a crucial role and there is currently a wide interest in integrating biological information in RT treatment planning with the aim of targeting radiation resistant regions by creating a heterogeneous dose pattern – the concept has been designated "dose painting" [79,80]. New possibilities in functional MRI may have potential to supply more information on tumour topography and intra-tumour heterogeneity. Diffusion of water molecules can be measured with DWI MRI. Tissue with high density of cells – like tumour tissue – limits the diffusion of water molecules, and visualisation of diffusion may have potential to supply additional information about the extent of the tumour target on MR images [81,82]. Intra-tumour perfusion and vascularisation can be visualised by dynamic contrast enhanced (DCE) MRI. The intensity distribution in DCE MRI has shown to correlate with local recurrences, which has generated the hypothesis that signal intensity in DCE MRI correlates with hypoxia [83,84].

Geometric stability is not a real concern for diagnostic MR imaging of the pelvis, but stable geometry is crucial for RT planning. New achievements in MRI technology like novel pulse sequences (e.g. DWI) and the introduction of high field magnets (e.g. 3 T) might produce geometric instabilities which can be unacceptable for RT planning [27].

Finally, BT applicator material, increasing magnet field strength and certain pulse sequences are all factors which might introduce image artefacts inside and in the vicinity of the tumour. The amount of these artefacts varies. However, for most potential combinations of scanners, sequences and BT equipment it is feasible to develop dedicated imaging protocols in order to obtain geometric stabilities which are acceptable for BT dose planning.

## Acknowledgements

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