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Review

MRI in medical practice and its future use in radiation oncology. Resume of XXV GOCO Congress (Montpellier) 2017

Xavier Druet[a], *Estrella Acosta Sanchez*[b], *Ken Soleakhena*[c], *Anne Laprie*[c], *Jordi Sáez*[d], *Stéphanie Nougaret*[a], *Olivier Riou*[a], *Elodie Rigal*[a], *Laura Kibranian*[a], *Miguel Palacios*[e], *Ismael Membrive*[f,*]

[a] *ICM, Montpellier, France*
[b] *Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*
[c] *IUCT Oncopole, Toulouse, France*
[d] *Hospital Clínic, Barcelona, Spain*
[e] *VUMC Amsterdam, Netherlands*
[f] *Hospital del Mar, Parc Salut Mar, Barcelona, Spain*

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ABSTRACT

This publication is a resume of the GOCO Congress (Montpellier 2017). A part of this congress was about the use of MRI in clinical practice, focused on the oncology field. The role of this tool was described in diagnosis, staging of tumors, evaluation of treatment response and the future use in prognostic and investigation (radiomics). After that, in the context of the present and future uses of MRI in radiation oncology, MRI guided radiotherapy was explained, as a method that allows an increased precision in image guided treatments. This publication is a resume of the GOCO Congress (Montpellier 2017). A part of this congress was about the use of MRI in clinical practice, focused on the oncology field. The role of this tool was described in diagnosis, staging of tumors, evaluation of treatment response and the future use in prognostic and investigation (radiomics).

1. Introduction

This publication is a resume of the GOCO Congress (Montpellier 2017). A part of this congress was about the use of MRI in clinical practice, focused on the oncology field. The role of this tool was described in diagnosis, staging of tumors, evaluation of treatment response and the future use in prognostic and investigation (radiomics).

After that, in the context of the present and future uses of MRI in radiation oncology, MRI guided radiotherapy was explained, as a method that allows an increased precision in image guided treatments.

The next sessions were about the use of MRI in radiation oncology. It can be used in the planning part of the radiotherapy process, employing the MRI to perform the simulation, focused in this case on the use of the MRI in SBRT of liver

* *Corresponding author.*
E-mail address: imembrive@parcdesalutmar.cat (I. Membrive).
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tumors. In centers where MRI is not available to the planning of the radiation treatment it also can be used. The last session was about the use of the fusion to employ the MRI in combination with CT planning.

2. MRI in medical practice

MRI plays an important role in the patient disease history, from the initial evaluation of the extent of the disease to the appropriate treatment selection and follow-up.[1]

2.1. *Diagnosis*

MRI improved diagnosis of malignant tumors in the liver, ovary, and pancreas. Diffusion MRI allowed better visualization of liver tumors, tumors are hypercellular and as such show hypersignal on diffusion sequences. MRI allowed diagnosis, cartography and better visualization of carcinomatosis.[2–4]

2.2. *Staging*

MRI allowed a better visualization of pelvic tumors.

For rectal tumors, treatment sequence consists of several MRIs. Depending on the indications, the first MRI is done at the beginning, the second one during chemotherapy or chemoradiotherapy. At the end of this sequence, another MRI is done before surgery to evaluate the response and to decide on the type of surgery. Depending on the treatment response, surgery could allow sphincter preservation, or intensification could be proposed.[5–7]

Traditionally, the rectum has been divided into thirds, the surgical management is affected by the location of the tumor (low rectal tumor 0–5 cm, mid rectal >5–10 cm, upper rectal >10 cm). MRI in rectal cancer establishes the TNM staging but is also useful for the choice of a surgical procedure.

In cervical cancer, MRI established the local extension. In non-invasive cervical cancer, treatment depends on the size of the tumor (<4 cm, >4 cm) and this is an important aspect to decide on the type of treatment: surgery or chemoradiotherapy.

For advanced disease with parametrial invasion, sidewall invasion, bladder or rectal invasion, treatment is a combination of chemotherapy and radiotherapy.[8,1,9–11]

One of the decisive evaluations is the stratification between IIB stage or not, which differentiates invasiveness of the tumors, and that can only be visualized on MRI.[12,13]

2.3. *Response evaluation*

MRI in response evaluation can be difficult since the spectrum of response is wide, from complete response with anatomical restitution ad integrum, to fibrosis and desmoplatic response.

MRI diffusion-weight sequences allowed analysis of cellular proliferation and were useful tools for detection of tumor residue.[14–17]

Hypoxic tumors have a higher risk of developing metastases and are more resistant to radiation and chemotherapy. Dynamic contrast enhanced imaging assesses tumor perfusion and provides indirect estimate of hypoxia with the assumption being that hypoxic tumors are worse perfused.

There are mainly two methods to analyze contrast-enhanced MR images. One is semi-quantitative and the other is quantitative analysis. The semi-quantitative analysis measures a change in SI that represents the wash-in speed of the contrast material. This method is straightforward, but it is not based on physiology. The quantitative analysis is more complex and is based on pharmacokinetic modeling.

Several studies evaluated the relationship between tumor perfusion at baseline and subsequent response to CRT. They seem to indicate that tumors that are highly perfused at baseline or that undergo conversion from low to highly perfused tumors early during treatment have more favorable response and prognosis.[18–22]

Hypoxia in cancer is known as an important factor for predicting clinical outcome, since it can promote tumor progression and resistance to therapy. Noninvasive assessment of hypoxia using imaging techniques can be achieved with positron emission tomography (PET) or single photon emission tomography (SPECT). Dynamic contrast enhanced MRI (DCE-MRI) has shown to provide indirect estimates of hypoxia but without a clear relationship to tumor hypoxia. BOLD MRI, which is widely used to evaluate brain function, is a promising technique for tumor imaging, since it allows noninvasive measurement of hypoxia. Therefore, a change of T2* values on BOLD may represent changes in tissue pO2. BOLD-MRI does not require administration of exogenous radioactive contrast material and images at high temporal and with high spatial resolution can be obtained and repeated as needed. While BOLD-MRI appears sensitive to oxygen levels adjacent to perfused vessels (that is, perfusion-related or acute hypoxia), BOLD-MRI sensitivity to more distant diffusion or chronic hypoxia is still unknown. Padhani et al. suggested that future studies will need to evaluate both heterotopic tumor models and chemically induced tumors to more accurately reflect the human situation. Deoxyhemoglobin is paramagnetic (iron atom) and creates signal loss onT2*WI. The concentration of deoxyhemoglobin within the vessel increases with rising oxygen consumption, leading to a decreasing T2* relaxation time of surrounding tissue. The rate of spin dephasing ($R2^* = 1/T2^*$) is an index of oxygenation of tissue.[23–26]

2.4. *Perspective and radiomics*

MRI is the integration of data imaging and tumoral characteristics in order to correlate the amount of information.

First studies showed a correlation between tumoral heterogeneity and survival.[27] Patients with carcinomatosis homogeneity have better survival versus patients with heterogeneity (69 months versus 10 months).[28]

3. MRI and radiotherapy

3.1. *History*

First publication of MRI use in treatment planning comes from the 80 s. Through the wish to improve radiotherapy planning, and thus delineation of gross tumor volume (GTV), radiation

oncologists are likely to use a lot of imaging modalities. MRI can be useful in delineating the extent of tumor thanks to the difference in spin relaxation time between normal tissues and tumor.[29] The extent of access to these modalities, such as positron emitted tomography (PET-scan) and MRI, allowed a more sophisticated treatment planning, since they provided more information about anatomical patterns and density of tissues. The consequence is more complex beam planning and an increase of tumor conformity. The ultimate goal is to improve the results of radiation therapy.[30]

3.2. *State of art in MRI-guided radiotherapy*

The world's first MR-guided radiation therapy program was implemented at the Washington University. A daily high precision image was acquired for each patient with a 0.35 tesla MR, allowing localization based on soft tissue imaging and modification to the treatment plan when required. RT treatment can be delivered with 3D conformity, intensity modulation (IMRT), or even cine gating (4D).[31,32]

Its implementation permits to deliver radiotherapy with care of position and proximity of organs at risk next to the planning target volume (PTV). It also allowed the visualization of interfraction variability of shape and size of PTV. The direct consequence of these considerations is the online process of radiation delivery since physicists or dosimetrists may become online planners to adapt the treatment to the patient depending on the radiation oncologist directive.[33]

One of the more challenging elements to take into account is the inability to shift the patient position during the treatment delivery. One of the options is to create a virtual couch shift, in which the multi-leaf collimator defined aperture shifts rather than the couch moving the patient. The MRI-accelerator will adapt to the patient.[34]

3.3. *Simulation with MRI-guided radiotherapy*

Simulation in radiation oncology must fulfill some characteristics that are not the same as diagnosis modalities. MRI simulation modalities depend on physical characteristics and medical delineation (Table 1).[35]

As a consequence of MRI acquisition, radiation oncology centers may acquire a new technology not to interfere with the quality of simulation. Carbon fiber flatbed has not been reported to interfere with MRI (image quality or heating).[36] On the other hand, MRI coils must be as close as possible to the patient to reduce wrapping, and all immobilization devices may be rethought.

MRI scanner device should be optimized and standardized to be used in radiation planning. Contrast-to-noise ratio, image intensity uniformity and post-processing corrections to reduce or correct non-linearity induced geometric distortions are necessary.[37] In order to reduce distortion, the magnetic field has to be homogenous, thanks to the shimming process. Distortion is an important factor that can lead to geometric miss as far as 0–3.9 mm and only accurate imaging protocol could prevent that type of mistake.[38,39]

Lack of knowledge in MRI technology in the Radiation Oncology community is a major brake to MRI use in daily practice. Chemical shift can lead to a difference in acquisition, due to the difference between protons in fat and in water. Protons in fat experience a weaker magnetic field than protons in water. Tissues in fat will so experience a shift with respect to the other tissues. Some guidelines have been published to improve the quality assurance of MRI simulation by Liney and Moerland:[40]

(1) The field strength should be no less than 1.5 T and no more than 3.0 T.
(2) The magnet should be a closed-tunnel configuration, preferably with a wide bore.
(3) A flat bed or tabletop insert should be used.
(4) Appropriate RF coils (multichannel) should be used that cater to immobilization devices and surface coil intensity correction should always be employed.
(5) Geometric distortion should be verified in all 3 directions, and this will inform the useable FOV (in plane) and slice coverage (through plane).
(6) Spin-echo-based sequences (i.e. fast or turbo spin-echo) should be used rather than gradient-echo for the gold-standard anatomical image.
(7) Slice thickness should match the planning CT acquisition where possible.
(8) Multiple (i.e. concatenated) acquisitions should be examined for gross movement between adjacent slices and avoided if motion cannot be mitigated.
(9) The scanner's software for correction of the gradient errors should always be turned on.
(10) Pixel bandwidth should be set to a minimum of twice the water-fat shift (i.e. 220 Hz at 1.5 T and 440 Hz at 3 T).
(11) QA of the optimum patient setup and imaging protocol should be carried out before clinical scans.

3.4. *Consideration about a new workflow*

Delineation process will change with the use of MRI-guided radiotherapy. New atlas-based delineation has to be created, taking into account rigid and deformable process of the image. Besides, automatic delineation must be controlled and manually corrected.

Since the target volume will undergo morphing, physicians and radiophysicists will have to adapt to the new workflow and, therefore, fast planning techniques may emerge.[41]

Radiotherapy dose planning depends of CT-scans and density of electron. To overcome this difficulty, atlas-based

Table 1 – Difference between MRI diagnostic and MRI simulation.[35]

Typical diagnostic MRI	Needs for simulation
Reduced field of view	Full imaging
Thick slices, interslice spacing, non-axial	Thin, contiguous, axial slices
Artifacts	Limit artifacts
Large field of view distortion	Distortions quantified and mitigated
Auxiliary systems	Mimic RT geometry
Bandwith	High bandwith
Curved couch	Flat tabletop
No lasers	Lasers

electron density mapping, synthetic CT-models, or voxel by voxel reconstruction are published in order to provide tools for MRI-alone treatment planning.[42–44]

Quality plans and also delivery plans and numbers of monitors unity has to be calculated directly with patients on table.

3.5. *Potential indication of MRI-guided radiotherapy*

MRIdian is one of the technologies actually available. Its advantages are a better coverage of the target, a better sparing of normal tissues compared to gammaknife, tomotherapy, thanks to a low penumbra. MRI allows a better definition, makes cine-IRM possible, and allows fast re-planning in daily practice. One of the most important possibilities is image guided radiotherapy, which allows stereotaxic radiotherapy or hypofractionation. Adaptive radiotherapy allows adaptation to the modification of the planning target volume or organs at risk (OARs). MRI definition allows the visualization of target tissue non visible by CT-scan.

3.5.1. *Pancreas*

Pancreatic tumors are mobile, OARs are varying with time, and this glandular tumor is better visualized with MRI.

Besides, classic fractionated RT results are nowadays disappointing with low survival.

Lagerwaard et al. show that stereotaxic MR-guided radiotherapy is feasible with limiting recountouring from physicians, allowing reductions in lower intermediate and high doses. Finally, MRI-guided radiotherapy improved PTV coverage and better spare the duodenum and stomach.[45]

Preliminary data show an improvement in patient treated with biological equivalent dose (BED) > 70 Gy versus <70 Gy, based on a probability algorithm.[46] There is now interest in increasing the dose in pancreas cancer and the phase II study SMART, proposing BED of 100 Gy, is ongoing.

3.5.2. *Liver tumors*

Thanks to cine-MRI, very mobile target treatment is allowed. Liver tumors are subject to change in location and volume, and only MRI allowed a good definition of this tissue.

Treatment with SBRT is actually feasible but very complex and MRI-guided RT will take place in a strategy of treatment simplification.

3.5.3. *Abdominal tumors*

The same considerations about change in location and volume are taken into account. MRI allowed a very good definition of tumors located in the abdomen.

4. MRI-4D: control of movement in RT

4.1. *Liver stereotactic radiotherapy procedure (SBRT)*

Soléakhéna Ken and the University Cancer Institute of Toulouse described the technique they use in their hospital to obtain adequate movement control with MRI in patients receiving treatment with SBRT in liver tumors. After the patient choice, the radiologist must implant gold markers guided by ultrasound or scanner, creating a triangle in the tumor. Then, they acquire the 4D CT through the RMP system to plan the SBRT. The MRI images are acquired in the treatment position using immobilization systems.[47–50] For the acquisition of MRI images in the treatment unit, they use a compatible ORFIT plane for MRI images where the constraints are adapted to the 4D CT. For MRI acquisitions, flexible and fast spiraling sequences are used that are not very sensitive to movement. Then, they perform the registry according to the reference markers previously placed on the tumor and the lesion is described for SBRT planning (Fig. 1). There is a *DIXON VIBE* (volumetric interpolated breath-hold examination) that lasts 15 s during which the patient is asked to maintain apnea at the end of expiration.[49,51–53] There is also a T2 BLADE sequence (*PROPELLER* **P**eriodically **R**otated **O**verlapping Parall**EL** **L**ines with **E**nhanced **R**econstruction) and a sequence with contrast, these sequences are subordinated to the patient's breathing. The monitoring of the markers during the application of the treatment allows a good local control with low toxicity rates as a final result.[48,54–57]

4.2. *Limitations of the current procedure*

This protocol generally works well but has some limitations: in the TC-4D there are 6 phases of the respiratory cycle (0%, 16%, 33%, 50%, 66% and 83%) but the lesions are not always visible, even with the admission of contrast. For this protocol, MRI is only shown in the expiratory phase. The most stable phases are 33% and 66%, this causes limitation to a single

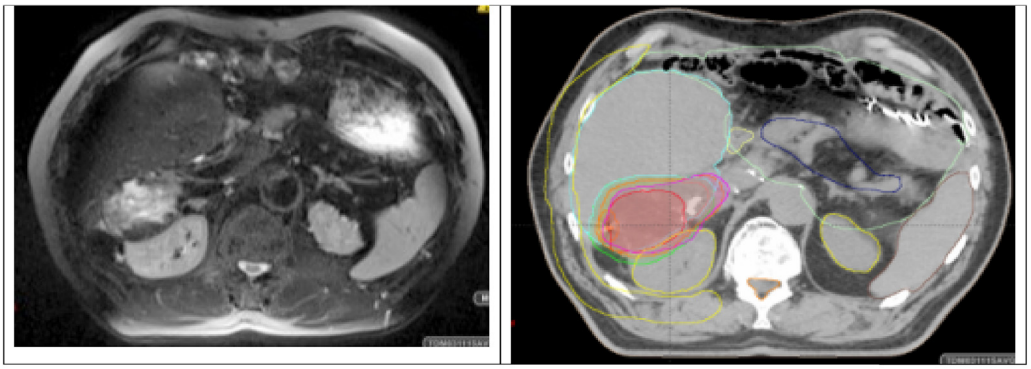

Fig. 1 – MRI with registration based on fiducial markers.

phase, which prevents visualizing all the dynamic behavior of the organ.

From these data, the idea of improving this procedure with an MRI-4D sequence arose. At the University of Basel they conducted an investigation using the same magnetic resonance machine (1.5T Siemens Magneto Aera) and a modified sequence of CAIPIRINHA. The image acquisition was performed in an interlaced manner with an axial image and followed by a sagittal navigator with a temporal resolution of 0.44 ms. The axial image crossed the entire organ while the sagittal navigator remained in a fixed position. The resolution of the image is 1 mm^2 and its thickness is equivalent to that of RT. We carried out a validation study of this MRI-4D sequence in a mobile ghost compatible with IRM in healthy volunteers. The MRI-4D is repeated 10 times to cover the entire respiratory cycle and the images in the spectrum are acquired with the same respiratory movements. For MRI-4D acquisitions, the volunteer was asked to breathe regularly for a period of 6 s. Twenty repetitions were performed to ensure coverage of the entire respiratory cycle.

The detection of respiratory phases is carried out automatically thanks to a matlab code. Then, between two inspirations, we define all the times "delta_t" that correspond to all imaginary breathing cycles. For the results in the phantom, the variations in the volume of the sphere and the displacement of the center of mass were measured. In the 4D-MRI images the volume of the sphere was overestimated (between 7 and 29%): at a fixed amplitude (20 mm) the longer the period, the more the volume increases. In the 4D scan, we observe the same overestimation results of the volume. For a fixed breathing period (6 s), the volume of the sphere increases in amplitude. This effect is less pronounced in the 4D scan. After all these contour measurements in the 4D images, we checked the static magnetic resonance and realized that the volume of the sphere is in fact overestimated as a function of the magnetic resonance (20%, external contour).

The displacement with two modes of action was up to 20% for a wave amplitude of 20 mm. The amplitude of the displacement is best estimated in the MRI for the smallest period of 4 s. The CT obtained a worse estimation for this period. For the respiratory period of 6 s, the displacement amplitude is underestimated in the MRI by 20% for all amplitudes. In CT images, the worst estimation was obtained for the highest amplitude (30 mm). For the results in the 4D-MRI images of the volunteers, the reproduction of the automatic detection was tested in 5 positions of ROI placed differently but always at the level of the diaphragm. They found the same results in 94.5% of the cases.

The work showed encouraging results since the MRI-4D images with spherical mobile lens (fantoma) were similar to the 4D CT. The images taken in the healthy volunteers had a good contrast and a good signal-to-noise ratio. The automatic detection of respiratory cycles and the automatic classification of images according to phases was possible thanks to the exploitation of browsers as an internal substitute. In this way, it was possible to reconstruct the data in the 4D CT and visualize all the respiratory phases. All respiratory phases can be detected. The next step should be to make acquisitions in patients with fiducial markers to visualize the dynamics of these during the realization of the SBRT.

5. MRI scan fusion (location off head and neck)

5.1. *Introduction*

Magnetic resonance imaging (MRI) is a very useful tool in the diagnosis and characterization of several tumors.[58–62] In certain anatomic locations and in certain types of tumors, MRI is superior to CT.[63] MRI is also more useful in radiotherapy to delineate critical anatomical structures. At present, international clinical guidelines recommend the use of MRI for planning but, unfortunately, few radiotherapy services currently have the availability of an MRI machine. The great advances made in technology make fusion of MRI and CT images reliable.[64,65]

In 2011, Dolezel et al.[66] carried out a study (previous planning based on MRI using fusion of CT and MRI data in patients with cervical cancer treated with Brachytherapy (BQT) 3D: viability and precision study). In this study, the planning of MRI assisted radiation allows an improved tumor contour with respect to TC. The purpose of this study was to analyze the feasibility and accuracy of information from computed tomography (CT) and MRI for treatment planning based on MRI in an institution that does not have an MRI scanner in its radiotherapy department. First part of the treatment consists in external RT with concomitant CDDP until reaching a dose of 45 Gy (1.8 Gy per fraction). Later, they initiated their MRI and CT fusion protocol for treatment with BQT in gynecological tumors.

The MRI was performed before the 1st and 4th fraction of BQT. They used phase T2 of the MRI. The next day, they place the applicators again, maintaining the same length of intrauterine catheter and respecting the angulation in the ovoids. For the rest of the planning, for contouring the risk organs they use the TC. The CT-MRI fusion is performed and the applicator is used as a reference for the image registration, the images are combined automatically and then adjusted with a manually. After the MRI, the applicator is removed and dosimetry is performed using the MRI images. A dose of 5 Gy is applied in 6 fractions 2 weeks after the end of the external RT. In 3 of the 42 fusions, it was considered that the degree of imprecision between the applicator in the MRI and the CT was too high to be considered correct (>2 mm). This work was the first evidence of the systematic integration of the MRI-based pre-planning with the fusion of consecutive CT/MRI data in clinical practice. Their results suggest that this technique is feasible and safe although with an acceptable inaccuracy of soft tissue registration. The inaccuracy of fusion must be taken into account during the planning process.

In another study, in 2016, Tait et al.,[67] propose that the incorporation of MRI in image-based brachytherapy (IBBT) is limited by logistics, reimbursement and workflow demands. The objective was to determine if the deformable image record (DIR) using a preimplantation MRI is feasible to construct

a high-risk target volume during IBBT. In the study, they evaluated the use of deformable fusion by preimplantation MRI with the CT planning for BQT to contour the high-risk volume (GTV) and perform a planning based on the IRM-guided CT. MRI was performed on 20 patients up to 7 days before BQT. The volume of high risk and risk organs were defined in the CT. The applicator is placed and a simulation CT is performed. Subsequently, the T2 images of the MRI were combined with the planning CT using the bone patterns and delineated an area of interest centered on the applicator.

After the fusion, the delineation of the high risk volume is done in the MRI image and in the planning CT.

The conclusion was that the DIR is feasible to define an HR-CTV for ITBB guided by MRI. The HR-CTV MRI predicted a smaller treatment volume in comparison with the HR-CTV BT. The DIR is limited by the anatomy of the patient and is most beneficial in patients with severe disease.

Finally, Trifiletti et al.[68] proposed that intracavitary BQT based on MRI images offered several advantages over BQT based on CT, but many centers cannot offer it at BQT time due to logistical and/or financial considerations. They implemented an MRI integration method in a CT-guided intracavitary BQT workflow and a high dose rate in clinics that do not have MRI available immediately.

To perform this technique a "Smit sleeve" is inserted into the cervix before the implantation of the BQT applicator. Subsequently, the planning CT is performed and after the dosimetry, the first BQT session is performed. The pelvic MRI is performed between the 1st and 2nd fraction of BQT. The sequence T2 is used to perform the fusion. In this MRI, the GTV of the residual cervical tumor is delineated. The MRI is fused rigidly using the smit sleeve inserted as reference, so that the GTV can be delimited in the merged image. For dosimetry, a traditional A-point plan adapted to the CT image is used to completely cover the high-risk volume. After the end of the treatment, the applicator is removed keeping the "smit sleeve" in place.

The conclusions were that in some cases, delineation of tumors by MRI is better than that performed by CT. The use of MRI in treatment planning is already recommended in the clinical guidelines. The fusion (rigid or deformable) of MRI and CT is currently feasible to characterize certain tumors better. The workflow and the way to obtain the MRI should be adapted according to the conditions and needs of each center. They must have availability of software capable of making deformable or rigid quality registration. These techniques can make the planning more precise thus improving the quality of the treatments.[69,70]

Conflict of interest

None declared.

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