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Case Report

Hybrid MRI guided radiotherapy in locally advanced cervical cancer: Case report of an innovative personalized therapeutic approach

L. Boldrini [a], G. Chiloiro [a], A. Pesce [a,*], A. Romano [a], S. Teodoli [b], L. Placidi [b], M. Campitelli [a], M.A. Gambacorta [a], V. Valentini [a]

[a] Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, U.O.C. di Radioterapia Oncologica, Roma, Italy
[b] Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, U.O.C. di Fisica Sanitaria, Roma, Italy

1. Introduction

Cervical cancer represents one of the most common female cancer and is characterized by an annual mortality of nearly 250.000 women worldwide [1].

The gold standard treatment for locally advanced cervical cancer is represented by definitive chemoradiotherapy (CRT) followed by brachytherapy (BRT).

In order to improve survival outcomes, some studies analyzed the impact of neoadjuvant CRT or chemotherapy (CT) followed by surgery in order to eliminate potential chemo- and/or radioresistant residual disease foci [2].

Unfortunately, treatment related early and late toxicities are still common and may hamper treatment outcomes and patient's quality of life.

Despite the development of modern dynamic-volumetric irradiation techniques and the use of advanced Image Guided Radiotherapy (IGRT) solutions, such as Cone Beam Computed Tomography (CBCT), one of the most significant limits of these treatments is represented by the need of large clinical target volume (CTV) to planning target volume (PTV) margins. A PTV margin of at least 10 mm (with 10–15 mm in anterior-posterior direction) may be considered for the centropelvic CTV and 7–10 mm for the nodal CTV [3].

Magnetic resonance imaging (MRI) represents the modality of choice for diagnosis, staging and response assessment in cervical cancer. In consideration of the excellent resolution and soft tissue contrast, its use is recommended in treatment planning.

Cervical cancer lesions are generally clearly visible in T2-weighted MRI sequences, as high signal intensity masses, and the coregistration with planning CT scan is strongly recommended both in external beam radiotherapy and brachytherapy settings [4].

Furthermore, cervical cancer has a marked radiosensitivity and rapid tumor regression during chemoradiation treatment is often observed, requiring adequate replanning strategies [5].

Besides the accurate definition of the therapy volumes, organ motion is a crucial issue in cervical cancer radiotherapy, as it is strongly influenced the different filling of the hollow pelvic organs (i.e. bladder and rectum) and by uterine movement itself.

A recent review has analyzed various IGRT strategies, describing the different available imaging modalities (Megavoltage CT, 4D CT, MRI, gold seeds implants, kilovoltage portal images): the authors conclude that an offline only IGRT strategy may not be sufficient to ensure a safe delivery of the treatment, considering the particularity and complexity of the movements of this anatomical site [6]. In this context, the introduction of Magnetic Resonance guided Radiotherapy (MRgRT) represents a paradigm shifting innovation, allowing a more precise and reliable volume identification and a safer image guided delivery [7].

1.1. Case presentation

1.1.1. History

A 42-years old woman, affected by cervical cancer underwent a pelvic ultrasound scan in July 2018, following severe metrorrhagia. A bulky lesion of the cervix (8 cm) was observed.

Patient then underwent a gynecological examination in anesthesia, confirming the presence of cervical lesion, involving the anterior vaginal fornix and left parametrium.

The biopsy later disclosed a moderately differentiated (G2) keratinizing squamous cells carcinoma and patient was addressed to staging exams.

Patient's records reported no family history of cancer and she suffered for hypertension and maculopathy.

1.1.2. Staging radiological findings and treatment choice

The staging MRI acquired in August 2018 confirmed the presence of cervical cancer with largest diameter of 7.8 cm and parametrial infiltration.

* Corresponding author at: U.O.C. di Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Roma, Italy.

E-mail addresses: luca.boldrini@policlinicogemelli.it (L. Boldrini), giuditta.chiloiro@policlinicogemelli.it (G. Chiloiro), adele.pesce1987@gmail.com (A. Pesce), stefania.teodoli@policlinicogemelli.it (S. Teodoli), lorenzo.placidi@policlinicogemelli.it (L. Placidi), maura.campitelli@policlinicogemelli.it (M. Campitelli), maura.campitelli@policlinicogemelli.it (M.A. Gambacorta), vincenzo.valentini@policlinicogemelli.it (V. Valentini).

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The 18-F FDG PET-CT scan confirmed the presence of bulky primary lesion and showed an increased uptake in one internal iliac node.

The case was discussed in the institutional multidisciplinary board for gynecological cancers and the disease was staged as FIGO III C1 (as for FIGO 2018 classification) and the indication to platinum based neoadjuvant CRT was agreed, according to our institutional guidelines.

1.2. Neoadjuvant concomitant chemoradiotherapy

1.2.1. Simulation

The patient was addressed to a 0.35 T Tri-^{60}Co hybrid MRgRT unit (MRIdian, ViewRay Inc., Mountain View, USA).

Simulation MR images were acquired on MRIdian using a TRUe Fast Imaging (TRUFI) with steady-state precession sequence, with image resolution of $1.5 \times 1.5 \times 1.5\ mm^3$ and acquisition time of 175 s.

A non-contrast enhanced standard simulation CT was then acquired and co-registered with the simulation MR for electronic density transfer.

The patient was immobilized using the FluxBoard device (Fluxboard™, MacroMedics, The Netherlands), in the most appropriate and comfortable configuration.

Accurate bowel and bladder preparation were requested for simulation and prior to each treatment fraction.

1.2.2. Therapy volumes choice and dose prescription

Clinical Target Volume 1 (CTV1) included the Gross Tumor Volume (GTV) as shown by staging MRI and 18-F FDG PET-CT, while Clinical Target Volume 2 (CTV2) included the entire uterus, the parametria, the entire vagina and nodal drainage (i.e. presacral, having the S2-S3 interspace as lower limit, internal, external iliac nodes and obturator nodes).

All the organs at risk (i.e. rectum, bladder, femoral heads and peritoneal bag) were contoured according to our institutional guidelines.

Planning Target Volume (PTV) 1 and PTV2 were obtained by adding a 5 mm isotropic margin to the corresponding CTV1 and CTV2.

A total dose of 50.6 Gy at 2.3 Gy per fraction was prescribed to PTV 1, while 39.6 Gy at 1.8 Gy per fraction were prescribed to PTV2.

Planning quality and acceptability were evaluated using institutional OARs constraints and target coverage objectives.

1.2.3. Treatment delivery

Treatment was delivered using a simultaneous integrated boost (SIB) protocol, with a step and shoot IMRT delivery technique.

Daily 25 s TRUFI MR images were used for daily alignment and intra-fraction motion was managed applying a gating approach based on the real time acquisition of a sagittal cine MRI during the whole fraction time (temporal resolution: 4 frames/s) (Fig. 1).

The CTV1 was defined as gating target structure, which was triggered and immediately turned off the beam every time CTV1 movements exceeded a 5 mm isotropic boundary (MRIdian gating parameters setting: Region of interest 5%; boundary: 5 mm, isotropic; delay time: 0 s).

Concomitant CT with cisplatin (40 mg/mq q7) was administered during the whole radiotherapy.

The daily alignment 25 s MRI acquired at the delivered dose of 13.8 Gy (fraction 6), showed a significant reduction of the primary lesion (CTV1) with consequent shift of a bowel loop between rectum and uterus with evidence of parietal oedema in absence of symptoms or clinical manifestation (Fig. 2a).

A first offline replanning was therefore performed in order to preserve the bowel loop trapped between the target and the anterior rectal wall from unnecessary irradiation, preventing the onset

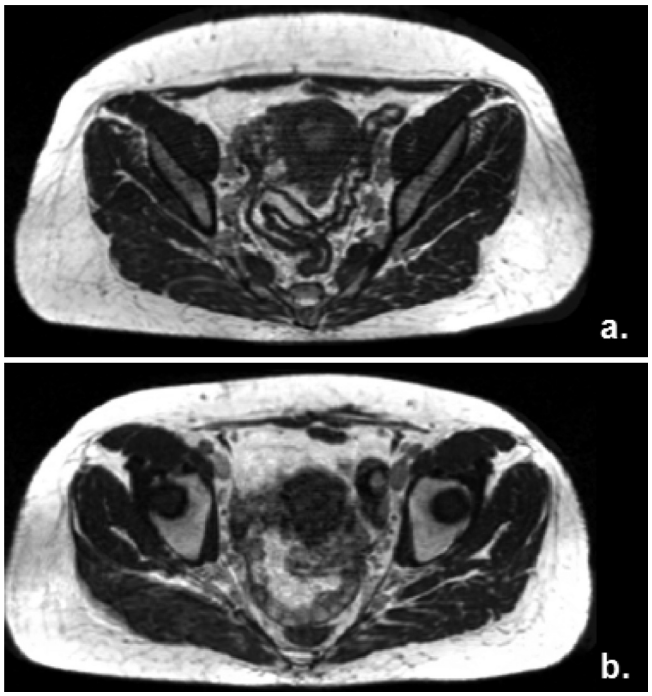

Fig. 2. Oedema of the intestinal loop at is presentation (a) and after resolution (b). The position of the loop appears different in relation to pelvic bony anatomy, as it is correlated to tumor response.

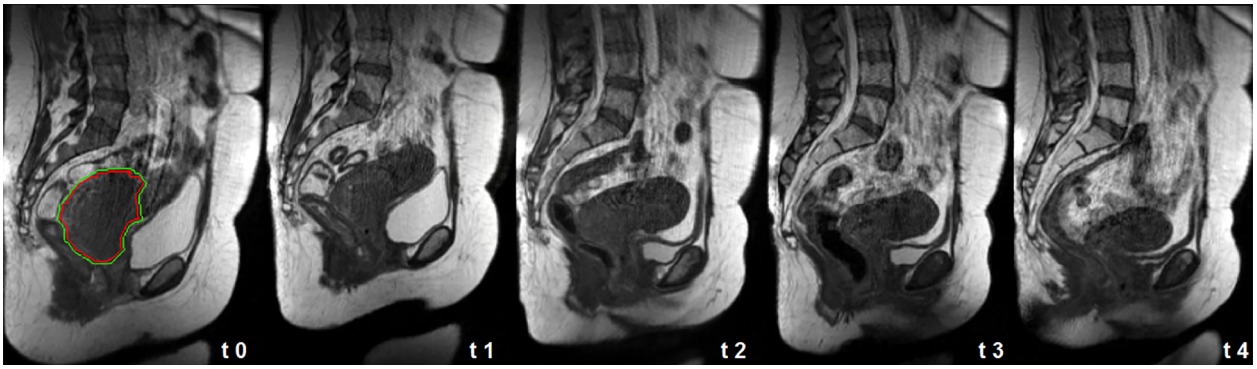

Fig. 1. Tumor shrinkage of the primary lesion (Gross Tumor Volume contoured in red, PTV in green) during whole treatment. Note the intentional different bladder filling from image t2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

of early gastrointestinal toxicity and leading to the complete resolution of the oedema in 4 days (fraction 10) (Fig. 2b).

Due to the significant reduction of the disease during the treatment, a new replanning was requested when a total dose of 36.8 Gy was reached (fraction 16): the patient was requested to change her preparation protocol, emptying the bladder in order to make larger room for the bowel loop, displaced by the new disease anatomy (t2 in Fig. 2).

The patient completed the treatment with no interruptions with optimal compliance and only G1 urinary toxicity (according to CTCAE v 4.0) was reported.

1.2.4. Response assessment and restaging

Restaging MRI acquired (December 2018), after 5 weeks since the end of neoadjuvant CRT showed a significant response to the treatment with a residual asymmetry of the right side of cervix.

The response was confirmed also by the 18-F FDG PET-CT with persistent suspicious uptake in the known left internal iliac node.

1.2.5. Surgery and pathological response

The patient underwent a radical hysterectomy with bilateral annessectomy and nodal dissection in January 2019, according to our internal protocol [2]. No surgical complications were observed and the pathological examination showed microscopic response with residual microscopical disease foci of the cervix (pR1), with negative resection margins towards residual vagina and parametria.

No nodal disease was observer in the examined pelvic nodes.

2. Conclusions

As far as the Authors know, this is the first report of the use of MRgRT in cervical cancer and represents a good example of the advantages introduced by this new technology, aiming to a fully personalized therapeutic approach.

The use of high soft tissue contrast MRI alignment images will allow to monitor toxicity onset and assess tumor response, opening new perspectives for radiotherapy decision making and replanning rationale definition, thanks to the a previously not possible visualization of tissue changes occurring during the treatment itself and innovative quantitative image analysis approaches [8].

The better visualization of therapy volumes obtained with MRI and the aforementioned delivery solutions may successfully limit the unnecessary irradiation of the organs at risk and the subsequent toxicity as previously reported in other sites [9–11].

On the other hand, the real time information provided by the cine-MRI acquired during the treatment represents an innovative solution for the possible displacement of the target related to the bladder or rectal filling and unexpected movements, allowing innovative gating solutions [12–15].

Furthermore, the recent technological developments in the MRgRT technology, such as the introduction of MRI Linacs and the possibility to acquire functional imaging (i.e. Diffusion Weighted Imaging – DWI) and cine-MRI images up to 8 frames/s, represent a new perspective of this innovative therapeutic approach and lead the way to new target definition modalities (i.e. dose painting escalation, biological targeting), toxicity monitoring methods and radiobiological modeling studies.

Conflict of interest

Luca Boldrini received speaker honoraria and travel reimbursement from ViewRay Inc.

Vincenzo Valentini and the has a research agreement with ViewRay Inc.

The other authors do not have any potential COI to disclose.

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