Received:
6 June 2013

Revised:
15 September 2013

Accepted:
16 September 2013

doi: 10.1259/bjr.20130334

Cite this article as:

Milgrom SA, Alberto Vargas H, Sala E, Frankel Kelvin J, Hricak H, Goodman KA. Acute effects of pelvic irradiation on the adult uterus revealed by dynamic contrast-enhanced MRI. *Br J Radiol* 2013;86:20130334.

FULL PAPER

Acute effects of pelvic irradiation on the adult uterus revealed by dynamic contrast-enhanced MRI

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Objective: Pelvic radiation therapy (RT) can influence fertility in female rectal cancer survivors. Data regarding its effects on the adult uterus are scant. This study aims to evaluate the uterus before and after RT, using dynamic contrast-enhanced MRI.

Methods: Eligible patients ($n=10$) received RT for rectal cancer, had an intact uterus and underwent dynamic contrast-enhanced MRI before and after RT. Seven patients were pre-menopausal.

Results: Patients received pelvic RT (median, 50.2 Gy) with concurrent 5-fluorouracil. Five patients were treated with intensity modulated RT (IMRT) and five with a three-field technique. The median D95 of the uterus was 30 Gy; D05 was 48 Gy; and V95 was 97%. The median cervical D95 was 45 Gy; D05, 50 Gy; and V95, 100%. Cervical dose was higher with IMRT than with three-field plans ($p \leq 0.038$).

On T_2 MRI, the junctional zone was visible in nine patients before and in one after RT ($p=0.001$). Median cervical length (2.3 vs 3.0 cm) and endometrial thickness (2.6 vs 5.9 mm) were reduced after RT ($p \leq 0.008$). In pre-menopausal patients, the volume transfer constant, K_{trans} , (0.069 vs 0.195, $p=0.006$) and the extracellular extravascular volume fraction, V_e , (0.217 vs 0.520, $p=0.053$) decreased.

Conclusion: Pelvic RT significantly affected uterine anatomy and perfusion. Cervical dose was higher with IMRT than three-field plans, but no attempt was made to constrain the dose.

Advances in knowledge: Pelvic RT significantly affects the adult uterus. These findings are crucial to understand the potential consequences of RT on fertility, and they lay the groundwork for further prospective studies.

As the cure rate in locally advanced rectal cancer continues to improve, understanding the long-term sequelae of therapy is gaining importance. Research has shown that young cancer survivors are concerned about treatment-related effects on fertility, pregnancy and neonatal outcomes [1,2]. Previously, pelvic irradiation, standard in the management of locally advanced rectal cancer, invariably caused sterility in females as a result of acute ovarian failure. Currently, however, the risk of ovarian dysfunction may be greatly reduced by transposing the ovaries to the paracolic gutters before radiation therapy (RT) [3]. Additionally, an increasing number of females undergo embryo or oocyte cryopreservation before receiving RT [4]. These advances prompt the question: if a young female has undergone pelvic RT, can she carry a pregnancy to term?

Answering this question requires an understanding of the effects of the pelvic RT on the uterus. Ultrasounds of

paediatric cancer survivors suggest that pelvic RT alters uterine volume, distensibility and vasculature, with patients who are younger at the time of RT being the most vulnerable to these effects [5–7]. Additionally, population-based studies of paediatric cancer survivors have demonstrated an association between abdominal and/or pelvic RT and adverse pregnancy and neonatal outcomes, including placental abnormalities, pre-term delivery, low birth weight infants and perinatal mortality [8–11]. However, only sparse data exist regarding the effects of pelvic RT on the adult uterus, which may be more radioresistant.

The aim of this study was to use dynamic contrast-enhanced (DCE) MRI to assess the acute effects of RT on the uterus in females treated for locally advanced rectal cancer. A second aim was to compare dosimetric parameters of conventional three-field RT and intensity modulated RT (IMRT) treatment plans.

METHODS AND MATERIALS

Study design

After obtaining a waiver of authorisation from the institutional review board, females who received pelvic RT for rectal cancer at a single institution between January 2008 and December 2012 were identified retrospectively. Eligibility criteria included the presence of an intact uterus and evaluation by DCE MRI, using the same acquisition protocol, before and during the 12 weeks after the completion of pelvic RT. 10 patients were eligible for analysis.

Treatment information

Pelvic RT with concurrent 5-fluorouracil was recommended. RT was provided using either a conventional three-field technique or IMRT, according to the institutional practice. The three-field treatments used posteroanterior and opposed lateral fields to treat the whole pelvis to 45 Gy, followed by a 5.4 Gy boost to the rectal tumour, to give a total dose of 50.4 Gy at 1.8 Gy per fraction. With IMRT, the pelvis was treated to 45 Gy at 1.8 Gy per fraction, and the rectal tumour was treated to 50 Gy at 2 Gy per fraction using an integrated boost (Figure 1). Contouring was performed according to the Radiation Therapy Oncology Group consensus guidelines [12]. The uterus and cervix were contoured by a single person to ensure consistency. Treatment plans for both IMRT and conventional three-field RT were generated using an in-house treatment-planning system (Memorial Sloan-Kettering Radiation Treatment Planning System; New York, NY). Dosimetric data were extracted, and the dose to the uterus and the cervix with IMRT *vs* the three-field treatment plans was compared using the mean and the maximum dose to the organ, the volume of the organ receiving at least 95% of the prescription dose (V95) and 5% of the prescription dose (V05) and the dose to 95% of the organ (D95) and 5% of the organ (D05). The prescription dose was defined as the dose to the pelvis (45 Gy).

MRI evaluation

Patients underwent pelvic MRI examination, including DCE MRI, before and during the 12 weeks after RT. All images were

obtained on 1.5- or 3-T MRI systems (Signa HDx; GE Healthcare Technologies, Waukesha, WI) using a multichannel phased-array pelvic coil. Axial, sagittal and coronal two-dimensional fast-recovery fast spin echo T_2 weighted images were obtained with the following parameters: repetition time/echo time, 4000–6000 ms/102–120 ms; echo-train length, 24; flip angle, 90°; bandwidth, 32 MHz; field of view, 18–36 cm; section thickness, 3-mm and 1-mm intersection gap; matrix, 192–224×320. DCE MRIs were acquired after intravenous injection of 0.1 mmol kg⁻¹ body weight gadolinium-diethylene triamine pentaacetic acid (Magnevist®; Berlex Laboratories, Montville, NJ) at a rate of 2 ml s⁻¹ with an automatic injector (MEDRAD, Warrendale, PA), using a transverse three-dimensional T_1 weighted spoiled gradient-echo sequence (repetition time/echo time, 3.3–4.1 ms/1.2–1.4 ms; section thickness, 4–6 mm; field of view, 24 cm; matrix, 256×128–256×160). Temporal resolution was 5–8 s.

All studies were evaluated in consensus by two fellowship-trained genitourinary radiologists. The following parameters were recorded at each MRI examination: uterine volume [(anteroposterior×transverse×craniocaudal dimensions)/2], cervical length, myometrial thickness and endometrial thickness. A region of interest of approximately 10 mm² was marked over a homogeneous-appearing area of the myometrium, cervical stroma and gluteus maximus muscle on T_2 weighted images, and the corresponding signal intensity (SI) in each region of interest was recorded. The SI of the myometrium and cervical stroma normalised to muscle was calculated according to the following formulae:

$$\left[\frac{(SI_{\text{myometrium}} - SI_{\text{muscle}})}{SI_{\text{muscle}}} \right] \times 100$$

and

$$\left[\frac{(SI_{\text{cervix}} - SI_{\text{muscle}})}{SI_{\text{muscle}}} \right] \times 100.$$

Figure 1. Intensity modulated radiation therapy (IMRT) and three-field radiation therapy (RT) treatment plans. Axial slices from treatment plans of two patients, one treated with IMRT (a) and another with conventional three-field RT (b). Dotted lines represent the central axis of each beam. Triangles represent wedges. The cervix is shown as the central oval shape in each image. The isodose lines represent the dose measured in Gray.

Figure 2. Representative pre- and post-radiation therapy (RT) MR images. Sagittal, T_2 weighted MR images from a single patient, obtained before RT (a) and after RT (b). The cervical length is 4.1cm (a) and 3.2cm (b). These images also show decreased endometrial thickness and loss of junctional anatomy after RT.

Regions of interest in similar locations were also placed on the raw DCE images, and, subsequently, kinetic analysis of the DCE MRI data was performed with commercially available software (CINetool™; GE Healthcare, Milwaukee, WI) using a population-based arterial input function and a two-compartment pharmacokinetic model as proposed by Tofts et al [13]. The following quantitative and semiquantitative parameters were calculated: volume transfer constant (K_{trans}), extracellular extravascular volume fraction (V_e), redistribution rate constant between extravascular/extracellular space and blood plasma (K_{ep}), contrast-enhancement ratio (ratio of the average signal after the arrival of contrast to the average signal in the pre-contrast images), initial area under the gadolinium curve after 180 s (AUC_{180}), and slope of contrast enhancement (measured per second).

Statistical analysis

Dosimetric parameters of 3-field RT and IMRT plans were compared using the independent samples *t*-test. DCE MRI findings before and after RT were compared using the paired samples *t*-test for continuous variables and Fisher's exact test for categorical variables. Statistical analysis was performed using IBM SPSS® software (IBM Corporation, Armonk, NY). $p \leq 0.05$ was considered significant.

RESULTS

Patient, disease and treatment characteristics

The median age at the time of pelvic RT was 43.5 years (range, 26–68 years). Of the 10 patients, 7 patients were pre-menopausal; of these, 3 underwent ovarian transposition before RT and maintained ovarian function after treatment. Patients were gravida 0–4 and para 0–4 (median gravida 2 and para 1).

The rectal cancers were staged T3–4, N0–2. All 10 females received pelvic RT with concurrent 5-fluorouracil. Five patients were treated with IMRT and an integrated boost to a total dose of 45 Gy to the pelvis and 50 Gy to the rectal tumour. The remaining five patients were treated with a three-field technique to a total dose of 45 Gy to the pelvis and 50.4 Gy to the rectal tumour.

Radiation dose to the uterus and cervix

Dosimetric information is summarised in Table 1. For the total cohort, the median dose to the pelvis was 45 Gy and to the rectal

tumour was 50.2 Gy (range, 50–50.4 Gy). The median D95 of the uterus was 30 Gy (range, 3–45 Gy), D05 was 48 Gy (range, 44–52 Gy), mean dose was 44 Gy (range, 21–49 Gy) and maximum dose was 52 Gy (range, 49–54 Gy). The median uterus V95 was 97% of the prescription dose (range, 11–100%) and V05 was 100% (range, 98–100%). The median cervix D95 was 45 Gy (range, 42–47 Gy), D05 was 50 Gy (range, 45–52 Gy), mean dose was 47 Gy (range, 44–50 Gy) and maximum dose was 52 Gy (range, 48–53 Gy). The median cervix V95 was 100% of the prescription dose (range, 99–100%).

Dosimetric comparison of three-field radiation therapy and intensity modulated radiation therapy
Dosimetric parameters of three-field RT and IMRT plans are compared in Table 2. There was no statistically significant difference in uterine dose. On the other hand, the cervix received significantly higher doses with IMRT. The median cervix D95 was 45 Gy (range, 42–45 Gy) for three-field vs 46 Gy (range, 45–47 Gy) for IMRT ($p=0.038$); D05 was 46 Gy (range, 45–48 Gy) for three-

Table 1. Dosimetric information for the complete cohort

Parameter	Median (range)
Dose prescribed to rectum/pelvis (Gy)	50.2 (50.0–50.4)/45.0 (45.0)
Uterus D95 (Gy)	30 (3–45)
Uterus D05 (Gy)	48 (44–52)
Uterus mean dose (Gy)	44 (21–49)
Uterus maximum dose (Gy)	52 (49–54)
Uterus V95 (%)	97 (11–100)
Uterus V05 (%)	100 (98–100)
Cervix D95 (Gy)	45 (42–47)
Cervix D05 (Gy)	50 (45–52)
Cervix mean dose (Gy)	47 (44–50)
Cervix maximum dose (Gy)	52 (48–53)
Cervix V95 (%)	100 (99–100)
Cervix V05 (%)	100 (100)

Table 2. Dosimetric information of three-field radiation therapy (RT) vs intensity modulated RT (IMRT)

Parameter	Three-field (<i>n</i> =5), median (range)	IMRT (<i>n</i> =5), median (range)	<i>p</i> -value
Dose prescribed to rectum/pelvis (Gy)	50.4/45.0	50.0/45.0	
Uterus D95 (Gy)	29 (3–45)	31 (4–45)	0.748
Uterus D05 (Gy)	47 (45–49)	51 (44–52)	0.163
Uterus mean dose (Gy)	44 (21–46)	43 (33–49)	0.400
Uterus maximum dose (Gy)	51 (50–54)	52 (49–53)	0.749
Uterus V95 (%)	100 (42–100)	61 (11–100)	0.218
Uterus V05 (%)	100 (98–100)	100 (99–100)	0.593
Cervix D95 (Gy)	45 (42–45)	46 (45–47)	0.038
Cervix D05 (Gy)	46 (45–48)	52 (51–52)	<0.001
Cervix mean dose (Gy)	45 (44–46)	50 (48–50)	<0.001
Cervix maximum dose (Gy)	52 (48–53)	53 (52–53)	0.094
Cervix V95 (%)	100 (100)	100 (99–100)	0.193
Cervix V05 (%)	100 (100)	100 (100)	–

Bold *p*-values are statistically significant ($p < 0.05$).

field vs 52 Gy (range, 51–52 Gy) for IMRT ($p < 0.001$); and mean dose was 45 Gy (range, 44–46 Gy) for 3-field vs 50 Gy (range, 48–50 Gy) for IMRT ($p < 0.001$). The median cervix V95 was 100% for both three-field RT and IMRT.

MRI findings

Patients underwent DCE MRI before and at a median of 5 weeks (range, 4–7 weeks) after the completion of RT. The MRI findings are summarised in Table 3 and representative images are shown in Figure 2. The junctional zone was visible on T_2 weighted MRI in 9 of 10 patients before RT but only 1 of 10 after RT ($p = 0.001$). On T_2 weighted MRI, cervical length was significantly decreased after RT (2.3 vs 3.0 cm, $p = 0.008$). Endometrial thickness was also significantly reduced (2.6 vs 5.9 mm, $p = 0.002$). Other measurements, such as uterine volume, myometrial thickness, myometrial and cervical SI and kinetic DCE MRI parameters (K_{trans} , K_{ep} and V_e) were not significantly different between pre- and post-RT DCE MRI examinations.

A separate analysis was performed that included only the pre-menopausal patients ($n = 7$). As shown in Table 3, this subset experienced the same significant changes in cervical length, endometrial thickness and junctional zone thickness as the total cohort. Additionally, in the pre-menopausal patients, there was a significant reduction in K_{trans} (0.069 vs 0.195, $p = 0.006$) after RT and a reduction in V_e that approached statistical significance (0.217 vs 0.520, $p = 0.053$).

DISCUSSION

A major consideration for young female rectal cancer survivors is the effect of treatment on fertility, pregnancy and neonatal outcomes. In this study of the acute uterine effects of pelvic RT by DCE MRI, post-RT changes in cervical length, junctional zone anatomy and endometrial thickness were identified. Although the pathophysiology underlying these radiographic findings is not certain, it may be hypothesised that cervical shortening and

junctional zone changes reflect atrophy or early fibrosis [14]. The reduction in endometrial thickness must be interpreted with caution, because it changes significantly with normal hormonal variation, and MRI evaluations were not performed at a specific phase of the menstrual cycle; however, bearing this limitation in mind, the finding may also be a sign of atrophy.

To date, the only study on this topic was published in 1989 by Arrivé et al [14]. The authors compared the MRI studies of 23 patients who had undergone pelvic RT with 30 age-matched controls, and they correlated MR characteristics with post-hysterectomy histological findings. Patients received external beam RT, primarily for gynaecological malignancies, to a mean dose of 47 Gy (range, 40–65 Gy) and were evaluated using MRI at a mean of 4.1 months (range, 1–9 months) after the completion of therapy. The authors found that in pre-menopausal females ($n = 11$; mean age, 40.1 years), RT induced a loss of uterine zonal anatomy, decrease in myometrial SI, decrease in uterine size and decrease in endometrial thickness and SI. In post-menopausal females ($n = 12$; mean age, 62.3 years), RT did not significantly alter the uterine appearance on MRI. Histological correlation with post-hysterectomy specimens was performed for seven of the irradiated patients (four pre-menopausal and three post-menopausal). In the pre-menopausal irradiated patients, the myometrium was mildly atrophic and fibrotic, and the endometrium was atrophic and contained circumferentially thickened blood vessels with decreased lumen diameter. In the post-menopausal patients, the myometrium and endometrium were atrophic in both irradiated and non-irradiated uteri; however, compared with the non-irradiated uteri, the vessels of the irradiated uteri had marked circumferential thickening of the intima and decreased lumen diameter. The authors concluded that the post-RT changes that are apparent on MRI reflect atrophy and fibrosis, possibly resulting from decreased perfusion, and are similar to the changes usually seen in the non-irradiated post-menopausal uterus.

Table 3. Uterine findings by dynamic contrast-enhanced (DCE) MRI before and after radiation therapy (RT)

Parameters	Pre-RT median (range)	Post-RT median (range)	<i>p</i> -value
Total cohort (<i>n</i>=10)			
Uterus volume (mm ³)	59 980 (34 891–260 378)	50 110 (34 586–304 110)	0.2840
Endometrial thickness (mm)	5.9 (1.7–10.6)	2.6 (1.5–4.7)	0.0020
Myometrial thickness (mm)	16.8 (11.4–20.5)	16.2 (13.6–19.4)	0.9380
Junctional zone apparent on <i>T</i> ₂	9/10	1/10	0.0010
Cervical length (mm)	30.0 (24.4–40.5)	22.9 (15.5–32.3)	0.0080
Myometrial signal intensity normalised to muscle	63.4 (0.584–226)	56.9 (5.500–228)	0.3680
Cervical signal intensity normalised to muscle	−7.72 (−61.90 to 20.10)	−36.00 (−63.50 to 6.30)	0.1010
<i>K</i> _{trans}	0.186 (0.000–0.439)	0.073 (0.035–0.249)	0.2540
<i>K</i> _{ep}	0.349 (0.000–1.012)	0.447 (0.184–0.887)	0.5490
<i>V</i> _e	0.441 (0.057–1.000)	0.214 (0.092–0.383)	0.1000
Pre-menopausal patients (<i>n</i>=7)			
Uterus volume (mm ³)	61 443 (36 647–159 424)	51 220 (34 586–98 592)	0.0820
Endometrial thickness (mm)	6.0 (3.5–10.6)	2.4 (1.5–4.7)	0.0030
Myometrial thickness (mm)	16.9 (11.4–20.5)	16.3 (14.5–19.4)	0.9490
Junctional zone apparent on <i>T</i> ₂	7/7	0/7	0.0006
Cervical length (mm)	30.6 (24.4–40.5)	22.7 (15.5–32.3)	0.0230
Myometrial signal intensity normalised to muscle	64.3 (12.7–226)	78.2 (16.0–228)	0.7250
Cervical signal intensity normalised to muscle	12.8 (−34.4 to 20.1)	−24.5 (−43.8 to 6.26)	0.1710
<i>K</i> _{trans}	0.195 (0.063–0.439)	0.069 (0.035–0.243)	0.0060
<i>K</i> _{ep}	0.526 (0.279–1.012)	0.459 (0.184–0.887)	0.7820
<i>V</i> _e	0.520 (0.179–0.836)	0.217 (0.094–0.303)	0.0530

*K*_{trans}, volume transfer constant; *K*_{ep}, redistribution rate constant between extravascular/extracellular space and blood plasma; RT, radiation therapy; *V*_e, extracellular extravascular volume fraction.

Findings are shown for the total cohort (*n*=10) and for the subset of pre-menopausal patients (*n*=7).

Bold *p*-values are statistically significant (*p*<0.05).

The present study corroborates the findings published by Arrivé et al and provides additional information. One strength of our study, compared with that of Arrivé et al, is that each post-RT MRI was compared with a pre-RT evaluation of the same patient. Similar to the study by Arrivé et al, we identified decreased endometrial thickness and loss of zonal anatomy after RT. Additionally, Arrivé et al identified a reduction in uterine volume, which did not appear until 3 months after RT. We did not find a change in uterine volume; however, the patients in our cohort were evaluated using MRI at a median of 5 weeks (range, 4–7 weeks) after RT, which is earlier than this finding was observed by their group. Arrivé et al did not address changes in cervical length, whereas we identified significant cervical shortening. On the other hand, Arrivé et al identified decreased endometrial and myometrial SI, which was not apparent in our study population. One possible explanation for this discrepancy is the shorter time that elapsed between the completion of RT and MRI evaluation in our study.

The distinct appearance on MRI reported by Arrivé et al in pre- vs post-menopausal females after RT prompted us to perform

a separate analysis of the pre-menopausal patients in our cohort (*n*=7). This group experienced the same statistically significant changes in cervical length, endometrial thickness and junctional zone appearance as the total cohort. In addition, when the analysis was limited to pre-menopausal patients, we observed a reduction in *K*_{trans} (*p*=0.006) and *V*_e (*p*=0.053). These results suggest reduced perfusion of the pre-menopausal myometrium after RT.

Our findings provide new information regarding the mechanism of RT-induced uterine changes. In the study by Arrivé et al, the pre-menopausal females experienced premature ovarian failure as a result of pelvic RT. Thus, as the authors had discussed, it was not possible to distinguish between the two mechanisms of uterine injury: the direct effect of radiation on uterine tissue and the indirect effect of radiation-induced ovarian dysfunction resulting in decreased endocrine stimulation of the uterus. In the present study, three pre-menopausal patients underwent ovarian transposition and maintained ovarian function after RT and three patients were post-menopausal before RT. In these six patients, representing the majority of the cohort, radiation-

induced ovarian failure would not account for the changes in uterine anatomy. Furthermore, radiographic changes were present within weeks after RT, before ovarian failure and its effects on the uterus would be apparent. Thus, our results suggest that at least some degree of uterine change is a direct effect of RT on the uterus.

Interestingly, we found that the cervix receives a significantly higher dose when treatment is provided with IMRT than with a conventional three-field technique. It must be noted that no attempt was made to constrain uterine or cervical dose. This finding is likely the result of the anterior oblique beams used to deliver IMRT, which displace the high-dose region anteriorly towards the cervix, as shown in [Figure 1](#). Importantly, the number of patients per group was small, and the study was retrospective in design; therefore, this result is hypothesis-generating only. Prospective evaluation is warranted to compare the dosimetry of three-field vs IMRT techniques and to determine the feasibility of reducing uterine and cervical dose using appropriate constraints. We hypothesise that the uterine and cervical doses would be lower with IMRT than with a three-field technique, if an attempt were made to constrain the dose.

This study is subject to the limitations of any retrospective analysis. However, every effort was made to select a homogeneous patient population that was evaluated using uniform techniques. To this end, only patients who received RT and were evaluated by MRI using the same acquisition protocol at a single institution were included. To minimise the confounding influence of normal ageing on the uterus, this study was limited to the acute effects of RT. Ultimately, a prospective study is warranted to further characterise both acute and late uterine changes after pelvic RT.

CONCLUSIONS

Treatment-related effects on fertility are a concern for many young cancer survivors. The results of this study suggest that pelvic irradiation results in significant changes to the uterus and cervix. The clinician must understand the potential consequences of therapy on fertility, pregnancy and neonatal outcomes to accurately counsel patients. Furthermore, in this era of improved normal tissue sparing with IMRT and of advanced assisted reproductive technology options, additional studies may reveal ways to mitigate some effects of RT on fertility, creating the possibility for rectal cancer survivors to successfully carry a pregnancy after treatment.

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