Phase II trial

Impact of post operative intensity modulated radiotherapy on acute gastro-intestinal toxicity for patients with endometrial cancer: Results of the phase II RTCMIENDOMETRE French multicentre trial

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Abstract

Purpose/objective: Whole "conventional" pelvic irradiation (up to 45–50 Gy) following hysterectomy is associated with a high rate of adverse gastro-intestinal (GI) adverse events, of which around 60% correspond to acute grade 2 toxicity. The phase II RTCMIENDOMETRE trial was designed to test the hypothesis that IMRT could reduce the incidence of grade 2 or more acute GI toxicity to less than 30% in patients irradiated post-operatively for an endometrial cancer.

Materials/methods: Patients with post-operative stage Ib G3, Ic or II endometrial carcinomas with no history of chronic inflammatory bowel disease were eligible. Guidelines for volume delineation and dose prescription were detailed in the protocol. The investigators were advised to use a web-based atlas developed for the RTOG 0418 study. The dose of the vaginal and nodal PTV was 45 Gy in 25 fractions. To assess the ability of the participating centres to comply with the protocol guidelines, they were requested to complete a dummy run procedure before inclusion of their 1st patient. GI and genito-urinary (GU) toxicity were graded according to the CTCAE V 3.0 classification and were prospectively recorded every week during irradiation, as well as at time of brachytherapy insertions and during the follow-up visit at week 15 (W15). Special attention was given to note any changes to the grade of adverse events between W5 and W15.

Results: From May 2008 to April 2010, 49 patients from 6 centres were recruited for the trial. One patient could not be treated, one patient died of vascular stroke at W3 without toxicity, and 1 patient refused to be followed-up after treatment. Thus, 46 cases were available for analysis at W15. The distribution by stage was as follows: Ib 16.3%, Ic 64.2%, II 20.4%. Thirty six patients (75%) received an additional vaginal vault boost of 6–10 Gy delivered by HDR brachytherapy in 1 or 2 fractions. Among the 47 patients who completed IMRT, 27% (95% CI 14.5–39.7%) developed at least 1 GI grade 2 adverse event (diarrhoea in 92% of cases), which mainly occurred at W4 and W5. No event corresponding to grade 3 or above was recorded. At W15, the number of patients complaining about GI events was low: 5 patients complained about persistent grade 1 diarrhoea, and 4 patients complained about haemorrhoids. Nineteen percent (95% CI 8.9–32.6%) of patients experienced grade 2 cystitis or urinary frequency which had disappeared by W15.

Conclusion: In accordance with our hypothesis, post-operative IMRT resulted in a low rate (less than 30%) of acute GI grade 2 toxicity, in patients with endometrial carcinomas. At W15, no patient demonstrated a grade 2 adverse event, and the prevalence of remaining grade 1 events was less than 20%.

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complications occur in 3% of cases, mainly in patients who experienced an acute adverse event (grade 2 or higher) [1–4]. Over the past decade there has been interest in the use of intensity-modulated radiation therapy (IMRT) for patients receiving adjuvant post-operative radiation for cervical or endometrial carcinomas. IMRT minimises the dose of radiation to healthy tissue and thereby theoretically reduces the risk of acute and long-term toxicity. Preclinical studies of post-operative IMRT in endometrial cancer demonstrate that the volume of the bowel that receives the prescribed dose may be reduced by 30–50%; therefore, one could expect that the occurrence of GI toxicity is lower for IMRT than for conventional methods [5–8]. Most reports in the literature support this hypothesis, and promising preliminary results from single centre studies have translated into clinical improvements with lower rates of both acute and late toxicity for IMRT than for conventional methods [9–12]. However, there have been few controlled prospective multicentre studies [13].

RTCMIIENDOMETRE is a prospective French phase II multicentre trial which was designed in 2007 to test the hypothesis that among cases of post-operative stage I or II endometrial cancer treated by IMRT, the incidence of acute grade 2 GI toxicity was less than 30%.

Materials and methods

Inclusion and exclusion criteria

Patients who were older than 18 years and had a post-operative stage Ib grade 3, or stage Ic or II grade 1–3 endometrioid carcinoma (1994 FIGO classification) without any history of GI and/or genitourinary (GU) disorders were eligible for inclusion. The patients underwent a total hysterectomy with bilateral oophorectomy by laparotomy or laparoscopy. Bilateral ilio-obturator lymphadenectomy was recommended. Patients with histological subtype 2 carcinomas or with a history of chronic inflammatory bowel disease were excluded. The other exclusion criteria were inadequate surgery, previous pelvic irradiation, another progressive cancer, and a contraindication to injection of contrast agent during a planning CT scan.

Contouring and dose prescription

Patients were positioned supine on a knee wedge and foot rest or with another type of immobilisation device according to the standard protocol at each centre. Two consecutive series of CT-images (3 mm slice thickness) were acquired: one series was carried out without the injection of intravenous contrast agent for dose calculation (reference series), and a second series (using the same DICOM coordinates) was carried out for contouring. The lower limit of the scanned area was set to 2 cm below the lower limit of the lesser trochanter and the upper limit was in the L2–L3 interspace. Patients were treated with a full bladder: they were asked to empty their bladder 30 min before CT and each treatment session, and then to drink 330 cm³—volumes of water within the following 15 min. No measure was taken to control rectum filling because variation of rectal volume is usually small [14]. However, if the rectum was abnormally full or distended, CTs were repeated within 15 min. No measure was taken to control rectum filling because the vaginal volume was given by the vaginal vault and the upper third of the remaining length of the vagina. The clinical target volume (CTV) included the vaginal volume expanding laterally and caudally by 1 cm and cranially by 2 cm, and the internal, external, and common iliac lymph nodes. The planning target volume (PTV) was generated from the CTV by adding 7 mm margins. The outer contours of the bladder, rectum, and sigmoid were drawn. The dummy run procedure demonstrated that the outlining of bowel loops was unreliable and we opted to use the content of the peritoneal cavity, excluding the CTV, as a surrogate of the bowel [16]. The bladder was drawn on each slice, from the base to the dome, the rectum was drawn from the ano-rectal junction to the recto-sigmoid junction, and the sigmoid was drawn from the upper limit of the rectum to the last slide where it was easily seen. The peritoneal cavity was contoured 2 cm above the PTV. Femoral heads were delineated from the top of the hip joint to the lower limit of the lesser trochanter.

The prescribed dose was 45 Gy in fractions of 1.8 Gy, 1 fraction per day, 5 days per week. Dose distribution was considered as optimal if 100% of the CTV received 45 Gy and if PTV dose homogeneity was within 90% and 115% of the prescribed dose (V40.5 Gy ≥ 95% and V52 Gy ≥ 5%). Recommended dose constraints to organs at risk (OAR) are presented in Table 1.

Treatment verification

The alignment of the isocenter had to be checked by 2D orthogonal or by 3D images (CBCT or MVCT) according to the verification and correction procedure of each centre. If an online procedure was used, physicists were advised to take into account the dose delivered by imaging, in the calculation of the dose distribution.

Quality assurance procedure

Participating centres were requested to participate in a dummy run procedure prior to the inclusion of their first patient, to assess their ability to comply with the protocol guidelines. Three out of seven participating centres complied with protocol requirements for CTV delineation without correction. In three centres, the length of the delineated vagina was too long (2/3 instead of 1/3), and in one centre the delineation of the iliac nodes was extended beyond the iliac bifurcation. All four centres were asked to correct these shortcomings. Delineation of the bladder and rectum was highly consistent across centres (mean Kappa index was 0.94 for the bladder and 0.78 for the rectum). All centres delineated the sigmoid with good agreement over most of its volume but its lower and upper anatomical limits varied across centres, thus affecting the Kappa index value (mean Kappa index 0.54). This was acceptable however, because (i) the rectum and the sigmoid are contiguous and are thought to tolerate radiation equally, and (ii), the true upper limit of sigmoid was included in the bowel volume. There was very poor agreement in the delineation of the small intestine whereas the peritoneal cavity was delineated consistently across centres (mean Kappa index 0.91), and was definitely chosen as a surrogate for the bowel in the trial. This dummy run procedure also revealed that all centres had no difficulty in complying with PTV, rectum, and bladder dose constraints (mean V40.5 Gy PTV: 97.8% (range 95–100%); mean V40 Gy rectum 24.7% (range 14–37%); mean 40 Gy bladder: 31% (range 23–40%). Only half of the centres achieved V40 Gy ≤ 40% for the sigmoid (mean 43.5%), and the constraint of V30 Gy ≤ 300 cc to the peritoneal cavity was clearly too

Table 1

<table>
<thead>
<tr>
<th>Dose constraints to organs at risk.</th>
<th>Rectum, sigmoid</th>
<th>Bladder</th>
<th>Femoral heads</th>
<th>Peritoneal cavity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximal dose 45 Gy</td>
<td>Median dose &lt;40 Gy</td>
<td>V40 Gy ≤ 40%</td>
<td>V50 Gy ≤ 10%</td>
<td>V30 Gy ≤ 500 cc or V40 Gy ≤ 300 cc</td>
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stringent; therefore, the more realistic constraints of V30 Gy <500 cc or V40 Gy <300 cc were used in the trial.

On site data monitoring was performed: each centre was visited three times.

Ethics

The protocol was reviewed and approved by the ethics committee and by the French National Agency of Medicine and Health Products Safety (ANSM).

Endpoints

Primary endpoint

The primary endpoint was the incidence of acute GI toxicity classified as grade 2 or higher according to the CTCAE 3.0, observed during irradiation or during the 10 following weeks (i.e. within 90 days of treatment).

Secondary endpoints

The assessment of acute GU toxicity and the evaluation of any other type of toxicity were considered as secondary endpoints.

Evaluation of toxicity

Acute side effects were recorded from week 1 to 5 during the weekly examination, at time of each brachytherapy insertion, and then during the closing visit at week 15. Acute side effects were scored according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE-3.0), and any decline or increase in the severity of the side effects since the end of the irradiation was noted. Symptoms that are not spontaneously reported by patients tend to be under-reported, especially if the symptoms have resolved by the time of examination, and physician directed investigations may introduce bias; therefore, we postulated that the description of symptoms would be more complete if patients were actively involved in recording their symptoms, in addition to undergoing a weekly objective assessment by a physician. We provided a simple notebook that enabled patients to make a daily record of their various symptoms in a number of domains. To construct this patient notebook that enabled patients to make a daily record of their various symptoms, in a number of domains. To construct this patient notebook that enabled patients to make a daily record of their various symptoms, in a number of domains. To construct this patient notebook that enabled patients to make a daily record of their various symptoms, in a number of domains.

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At week 15, 5 of the 46 evaluable patients were still suffering from grade 1 diarrhoea and 4 patients were suffering from grade 1 haemorrhoids.

Genito-Urinary toxicity

Acute urinary toxicity was less frequent than acute GI toxicity. Indeed, considering the whole population and all adverse events, whatever the grade, 39.5% of cases suffered from acute urinary toxicity whereas 85% of cases suffered from acute GI toxicity. Nine patients (19%) (95% CI 8.9–32.6%) experienced a grade 2 urinary side effect: cystitis in 3 patients, and increase of urinary frequency in 6 patients.

Gynaecological examination revealed a grade 1 vaginal erythema in most patients at the end of irradiation, but only 3 patients complained spontaneously in relation to a mild vaginal discharge. Vaginal dryness and vulva pruritus were mentioned by 6 patients.

Other toxicity

The combination of lymphadenectomy and post-operative irradiation led to mild lymphoedema in the legs of 6 patients.

Discussion

IMRT is considered to be a major advance in radiotherapy because this technique limits the dose of radiation to normal tissues.
while potentially delivering a high dose to gross tumour volume (GTV) and/or CTV at many tumour locations. The main motive for the introduction of post-operative pelvic irradiation in clinical practice is that this technique may minimise gastrointestinal toxicity. The PORTEC 2 trial investigated the use of brachytherapy in patients with endometrial cancer of high-intermediate risk [17]. In most cases of patients with stage I intermediate risk, brachytherapy achieved local tumour control rates equivalent to those obtained with pelvic irradiation but with less toxicity [17]. Brachytherapy can be now used as the sole post-operative adjuvant treatment. However, an increasing number of patients with poor prognostic factors are still amenable to the administration of post-operative external beam radiotherapy, whose toxicity could be increased by combining it with chemotherapy. This particular aspect is under investigation in the PORTEC 3 trial.

The RTCMIENDOMETRE phase II multi-institutional trial is the second trial that shows the benefits of irradiation by an intensity modulated technique in patients treated post-operatively for an endometrial carcinoma. Indeed, it is the second trial to show that this technique is associated with a rate of less than 30% of acute GI toxicity (grade 2 or higher) in these patients.

The first phase II trial of post-operative IMRT in gynaecological malignancies (involving cervical and endometrial carcinomas) was launched in 2006 by the Radiation Therapy Oncology Group (RTOG0418 trial). The primary objective of this trial was to determine the feasibility of post-operative IMRT in a multi-institutional setting and to establish whether the promising clinical results observed in single-institution studies could be reproduced. The results of this trial involving acute GI toxicity in patients with endometrial carcinomas have been published [13], and may be considered as the most relevant reference for the discussion of the findings of our RTCMIENDOMETRE trial. The two target populations should be comparable because both trials included around 50 patients with endometrioid carcinomas who received pelvic post-operative IMRT without concurrent administration of chemotherapy. Thirty six patients in the French trial received an additional vaginal boost after IMRT that was delivered by HDR brachytherapy; however, the weekly recording of toxicity was carefully planned to be able to discriminate the influence of each treatment on the side effects. Surgery mainly consisted in total hysterectomy or bilateral salpingo-oophorectomy. A similar percentage of patients from North America (98%) and France (96%) underwent complete lymph node dissection. Thus, the risk of complications related to the extent of surgery should be similar in the two groups. Treatment-related GI bowel adverse events (grade 2 or higher) occurring within 90 days of treatment were carefully assessed using the CTCAE 3.0. Radiation-induced toxicity is usually evaluated by a physician during a weekly examination. However, symptoms of toxicity may be under-evaluated or omitted in the absence of spontaneous complaints by the patient; therefore, we took steps to ensure that all side effects were thoroughly documented in the French trial. Patient self-assessments have been commonly and successfully used to determine pain, quality of life, and in some studies, side effects [18–20]. We thus decided to ask patients to make a daily record of all signs and symptoms during radiation therapy for discussion with their physician at their weekly consultation, to refine the grading of GI adverse events.

Fifty eight patients were recruited by 25 institutions in the RTOG0418 trial and 43 were eligible for analysis. In the RTCMIENDOMETRE trial, we enrolled 49 patients from 6 centres and 47 patients could be evaluated. The incidence of GI acute toxicity (grade 2 or higher) was 28% in the RTOG0418 trial and 27% in the RTCMIENDOMETRE trial. Not surprisingly, the nature and timing of GI toxicity in these two trials were similar: most patients complained of diarrhoea and/or enteritis and/or proctitis, which were mainly diagnosed during the last days of irradiation. However, the conclusions of our study must be considered within the context of its limitations, especially regarding the major issues of CTV definition and organ motion [21]. The accuracy and reproducibility of CTV and OAR delineation are of paramount importance in IMRT, because IMRT produces sharp dose gradients. A variation of just a few millimetres can have a considerable effect on dose distribution and outcome; therefore, emphasis was placed on quality assurance in the RTOG trial, which included a centralised review of each case (contouring and planning). In the RTOG trial, the volume definition of bowel and the dosimetric constraints for bowel, rectum, bladder, and femoral heads required some revision. Nonetheless, fewer than 5 patients had unacceptable dose variation in the PTV; thus implementation of the technique with the use of a detailed protocol and centralised quality assurance was considered feasible across multiple institutions. In the French trial we could only plan a dummy run procedure to assess the ability of the participating centres to comply with the protocol guidelines. This dummy run procedure revealed 4 centres that did not comply with the protocol recommendations regarding the delineation of the CTV and these centres were asked to correct these shortcomings. On the other hand, the delineation of organs at risk was reasonably consistent. The lack of central review for all cases may limit the validity of our results, as we are not able to say that all patients were treated without any major deviations to protocol.

In the mid-2000s, IMRT was not widely used to treat gynaecological cancers and there were very few guidelines for the implementation of this technique in this setting. For this reason, we also recommended the use of the RTOG atlas, which is posted on the RTOG website, to improve the reproducibility of the delineation of nodal CTV [15]. Conversely, we determined vaginal CTV according to our own guidelines used in 3DRT. We did not recommend the construction of an internal target volume (ITV) according to the RTOG trial, because we suspected that this approach would not provide an accurate depiction of the amplitude of the CTV motion in patients that were asked to empty their bladder and then drink before each treatment session. It is clear that this resulted in a small target volume in the anterior–posterior axis that could have limited the exposure of healthy tissue to radiation, with the inherent risk that vaginal vault received too small a dose. However, in our study this risk may have been counterbalanced by the wide use of an additional vaginal vault brachytherapy boost. Seven years later, the significant and regular motion of the target area and of organs at risk with respect to the bone landmarks remains one of the major issues for the successful implementation of IMRT. Routine bladder filling and rectal emptying instructions can be helpful, but do not always result in a reproducible assessment of ITV. Even with the construction of a reliable ITV, interfraction motion (motion between treatment sessions) is a significant problem [22]. Wagner et al. also pointed out that treatment delivery can be further complicated by the fact that the vaginal cuff and surrounding tissues are mobile relative to the pelvis, whereas the pelvic lymph nodes that are also part of the target are relatively fixed [21]. This means that the use of IMRT must be coupled with 3D based image guided radiotherapy protocols (IGRT), either with or without fiducial markers, to account more accurately for interfraction motion.

The review of our dummy run demonstrated that PTV compliance criteria, which were similar to those used in the RTOG trial, were met in all patients. However, we were unable to find any correlation between the observed toxicity and dose parameters, due perhaps to two weak points in our study: (i) the lack of central review of each case, and (ii) because the fact that we only recorded minimal, mean, median, and maximum doses to organs at risk in the patient file. In the RTOG trial, doses received by the bladder exceeded the recommended constraints in 68% of the treatment plans and doses received by the rectum exceeded the recommended constraints in 76% of treatment plans. However, GI acute
toxicity is more closely related to the DVH of the intestine or peritoneal cavity than that of the rectum. A wide range of dose constraints for the bowel are found in the literature, including V15 Gy <100–150 cc, V30 Gy <300–500 cc, and V50 Gy <35–100 cc. Indeed, there is no standard threshold for the volume or percentage of bowel that can be irradiated, because no particular value has been convincingly shown to be associated with higher likelihood of acute toxicity [23–26]. In the framework of our dummy run procedure we proposed V30 Gy ≤300 cc as a dose constraint for the bowel. However, this figure was clearly too stringent and V30 Gy ≤500 cc or V40 Gy ≤300 cc were used in the trial. The mean dose to the bowel was 19 Gy in our population. The investigators of the RTOG trial used V40 Gy ≤30% and observed that dose to the bowel exceeded acceptable variation in 17% of patients. These two studies underline the need for detailed guidelines for the delineation of the bowel in patients treated with pelvic IMRT, in addition to universally accepted dose constraints for this organ, especially for the treatment of a CTV that includes pelvic lymph nodes.

In the RTCIENDOMETRE trial, we only focused on acute toxicity, and thus we cannot conclude anything about late toxicity or treatment efficacy. Results of the RTOG0418 trial regarding these endpoints are pending. The influence of IMRT on survival rates of gynaecological cancers requires further investigation in a phase III trial. The RTOG/GOG have recently opened the phase III randomised Time-C trial, which compares 3DCRT and IMRT in patients post hysterectomy.

Conclusions

According to our hypothesis, the RTCIENDOMETRE trial demonstrates that among cases of post-operative endometrial cancer treated by IMRT, the incidence of acute GI grade 2 toxicity was less than 30%. The incidence of GU grade 2 toxicity was also lower than 20%. Despite the limitations of this trial, these findings are consistent with results of the endometrial arm of the RTOG0418 trial, and suggest that IMRT may be used in centres that are committed to following published guidelines. Detailed definition of OAR, especially the bowel, together with reliable dose/volume constraints and validated IGRT protocols are still needed for further reduction of morbidity and for adequate coverage of target volume. The ongoing phase III randomised time-C trial will contribute to clarify the utility of the post-operative IMRT for the treatment of endometrial carcinoma.

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