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Original research article

Safety of adjuvant intensity-modulated postoperative radiation therapy in endometrial cancer: Clinical data and dosimetric parameters according to the International Commission on Radiation Units (ICRU) 83 report

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ABSTRACT

Aim: To report a single-institution experience using postoperative pelvic Intensity Modulation Radiation Therapy (IMRT) using tomotherapy accelerators (TA) in postoperative endometrial cancer (EC) regarding ICRU 83 recommendations.
Background: IMRT in gynecological malignancies provides excellent dosimetric data, lower rates of adverse events and clinical data similar to historical series.
Material and methods: Seventy-six patients with EC were postoperatively treated with adjuvant IMRT using TA. The IMRT dose was 45 Gy for patients without positive lymph nodes and Type I histology and 50.4 Gy for patients with positive lymph nodes and/or type II histology.
Results: With a median follow-up of 29 months, the 12- and 24-month Overall Survival (OS) and Disease-Free Survival (DFS) were 96%, 93%, 87%, and 74%, respectively. Age of less than 60 years was associated with better OS (HR: 8.9; CI: 1.1–68) and DFS (HR: 3.5; CI: 1.2–10.2). Patients with Type II and Type I Grade III histology had a worse OS (HR: 3.3; CI: 1.1–11). Five women (6.6%) presented in-field local vaginal recurrence, 2 (2.6%) presented non-in-field

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vaginal recurrence, 4 (5.2%) presented pelvic node and distant recurrence and 11 (14.4%) presented only distant metastases. One patient stopped radiation treatment due to Grade III acute diarrhea. No Grade III late toxicity was observed. Planning Target Volume (PTV) coverage showed mean D2, D50, D95, and D98 of 51.64–46.23 Gy, 49.49–44.97 Gy, 48.62–43.96 Gy, and 48.47–43.58 Gy for patients who received 45 and 50.4 Gy, respectively.

Conclusions: IMRT with TA in postoperative EC shows excellent conformity and homogeneity of PTV dose. Without Grade III late toxicity, data from this cohort demonstrated the utility of IMRT.

1. Background

Radiotherapy in the pelvic area is not without acute and chronic adverse effects. Intensity-Modulated Radiation Therapy (IMRT) provides excellent Planning Target Volume (PTV) coverage and conformational planning treatment in the pelvic postoperative area while sparing normal tissues. IMRT in postoperative endometrial cancer patients could provide promising loco-regional data with low rates of urinary and gastrointestinal secondary events.

2. Aim

Endometrial carcinoma is the most frequent gynecological (GYN) cancer in the western world, with an incidence of 15 to 25/100,000 women per year.[1,2] More than 75% of endometrial carcinoma patients are diagnosed at an early stage, resulting in a five-year overall survival rate of 80%.

Randomized trials[3–6] have established that pelvic radiotherapy (RT) as an adjuvant to surgery provides a significant improvement in the local control of tumor growth, primarily in terms of intermediate-risk prognoses. Unfortunately, no effects on survival have been observed. However, the conventional techniques for whole-pelvis RT include four static photon fields and expose most of the contents of the pelvis, including the small bowel, to the prescribed dose of 45 Gy–50 Gy. Several factors predispose patients to acute and late small bowel effects,[7,8] such as prior pelvic surgery, hypertension, diabetes mellitus, pelvic inflammatory disease, extended field radiation, and dose of irradiation. Consequently, the severe morbidity of the small bowel (published rates of 1–25%) significantly reduces the quality of life,[9,10] and these radiation treatments remain a subject of debate.

The development of radiation treatment techniques, such as IMRT, has produced similar control data with lower rates of secondary effects. The data resemble those of gastrointestinal therapies due to the highly conformal technique of IMRT, which improves the therapeutic ratio of postoperative radiation treatments while sparing more of the adjacent normal tissues.[11–13] Similarly, early published results have shown a 30–60% reduction in small bowel doses following GYN IMRT.[14–16] Likewise, these reductions in dose have been suggested to decrease the rates of both acute[11] and chronic gastrointestinal side effects[17,18] in only a small number of patients. Moreover, the results of the ongoing Phase III trials are not expected for another 4–5 years.

Therefore, we sought to report on the clinical data and the feasibility and safety of surgery-adjuvant IMRT in endometrial cancer patients and dosimetric parameters according to the ICRU83 criteria[19] of a prospective observational study performed in the Oscar Lambret Center from 2009 to 2012.

3. Materials and methods

From January 2009 to June 2012, 76 patients with locally advanced endometrial cancer were treated consecutively and prospectively in an observational study registered at the French National Commission for Informatics and Liberty by the Oscar Lambret Center Clinical Research Unit.

Initial tumor staging included a clinical pelvic examination, histological proof of endometrial cancer and pelvic magnetic resonance imaging (MRI). All patients underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomies. Pelvic lymph node dissections were performed in 62 (81.6%) patients based on the preoperative MRI data, the histopathology type and the initial medical condition of the patient. Additional para-aortic dissection surgeries were planned for 29 (38.2%) patients, primarily in cases of malignant infiltration of the pelvic nodes and/or Type II adenocarcinoma diagnosed by histology.

The Clinical Target Volume (CTV) included the upper third of the vagina with an expansion of 1 cm, which was limited to the external contours of the organs at risk (OAR). The CTV also included the pelvic nodes up to the L4–L5 junction and the para-aortic nodes in cases of histologically demonstrated malignant infiltration. The contour of the pelvic nodes was defined according to the RTOG recommendations.[20] The PTV was fixed as a 0.5-cm expansion from the CTV. The rectum was drawn from the ano-rectal junction to the recto-sigmoid junction and from the upper rectum limit to the sigmoid until in the last slide on which it could be observed. The small bowel was contoured as the peritoneal cavity (in all possible places in which it could be positioned).

A dose of 45 Gy was delivered to the PTV in 25 fractions at 5 fractions per week. However, in 17 patients, the PTVs received 50.4 Gy in 28 fractions when IIIc1 or IIIc2 Stage or Type II adenocarcinoma was present and the patient was aged 70 years or less. In one patient, the treatment ceased at 48.6 Gy due to acute severe toxicity. Six patients (7.8%) with IIIc2 stage received 50.4 Gy to the pelvis and para-aortic nodes. The pre-planning theoretical maximum doses to the OAR were as follows: for the small bowel, 50 Gy was the theoretically maximal tolerated dose, and V45 and V40 were required to

be <50 cc and <200 cc, respectively. However, the latter volume was defined to contain all possible organ locations based on the planning CT scan.[19,21] Regarding the bladder, rectum and sigmoid structures, 50 Gy was the theoretically maximal possible dose, and V45 and V40 were required for <20% and <50%, respectively.

The treatments were performed using a tomotherapy system (Accuray Incorporated, Sunnyvale, CA) with daily megavoltage computed tomography (MVCT) as previously described.[22,23] One hour prior to the delivery of each fraction, the patients were instructed to empty their rectums and bladders and to drink 500 ml of water. MVCT was systematically performed. Patients were treated only if they had a half-full bladder and an empty rectum and if the planning and the treatment PTVs correctly overlapped. These MVCTs were reviewed by the radiation oncologist on the first day of treatment and weekly after that and were reviewed daily by the technologist. In the 7 days following the external beam treatment, one high-dose rate brachytherapy session allowed for the delivery of 6.2 Gy at the depth of 0.5 cm to the upper third of the vaginal mucosa.

Toxicity was assessed using the NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) v4.0 scale. Acute toxicity was recorded weekly during the radiation treatment and at 2, 4 and 6 months thereafter. Any toxicity that appeared later than 6 months after the radiation treatment was considered a late side effect. Patients were then followed up three times per year during the first 2 years and twice yearly thereafter.

The overall survival (OS) and disease-free survival (DFS) rates were determined using the Kaplan–Meier Method, and the log rank test was used to determine statistical significance. The Mann–Whitney non-parametric test was used to identify significant differences in the dosimetric parameters between the patient groups. Statistical significance was defined at the level of $p < 0.05$.

4. Results

The characteristics of the patients are reported in Table 1. Type I and Type II adenocarcinomas were present in 65.8% and 34.2% of the patients, respectively. The median age of the patients at diagnosis was 63 years (35–86). Histological exams revealed malignant pelvic and para-aortic nodes in 25.8% and 20.7% of the patients, respectively. Lymphovascular space invasion (LVSI) was observed in 60.5% of the cases.

Radiation treatment was initiated at a median time of 2.8 months following the initial hysterectomy and was delivered by the tomotherapy system. The median treatment duration of the RT was 38 days (33–51). Adjuvant sequential chemotherapy was administered to 28 patients (37%) as part of the treatment (four prescribed cycles of carboplatinum-taxol) after radiation. The decision to administer adjuvant chemotherapy treatment was made by the GYN Tumor Committee according to tumor and patient characteristics: adenocarcinoma Type II, Grade 3, lymph, pelvic and/or aortic involved nodes.

The median follow-up time was 29 months (15–56). The OS rates were 96% at 12 months and 89% at 24 months (Fig. 1). The patient population below 60 years of age exhibited a significantly increased OS (HR: 8.9; CI: 1.1–68) ($p = 0.036$) (Fig. 2). No differences were observed between the patients with Type I and Type II histology ($p = 0.28$) or between the populations with or without lymphovascular space involvement (LVSI) ($p = 0.20$). In the group of patients with Type II and Type I Grade III histology, we observed a lower OS compared to that of the Type I Grade I–II histology patients (HR: 3.3; CI: 1.1–11) ($p = 0.046$).

Table 1 – Characteristics of the patients.

Characteristics ($N = 76$)		n (%)
Histology		
Type I	50	65.8
Grade I	14	18.4
Grade II	24	31.6
Grade III	12	15.8
Type II	26	34.2
TNM		
TIA	8	10.5
TIB	35	46.1
TII	8	10.5
TIIIA	10	13.2
TIIIB	4	5.3
TIIIC1	9	11.8
TIIIC2	2	2.6
Vascular embolism	46	60.5

The DFS rates were 87% at 12 months, 74% at 24 months and 69.6% at 30 months (Fig. 1). The only factor associated with improved DFS in the univariate analysis was age below 60 years (HR: 3.5; CI: 1.2–10.2) ($p = 0.022$) (Fig. 3). Type I versus Type II histology ($p = 0.14$), stage ($p > 0.3$) and LVSI (0.2) did not have significant effects.

Five women (6.6%) developed in-field local vaginal recurrence, and four of these cases were associated with distant disease (the recurrence treatments were systemic chemotherapy for the patients with distant disease and exclusive interstitial brachytherapy for the patient who had only local vaginal recurrence). Two (2.6%) patients developed out-of-field vaginal recurrence and were treated with interstitial brachytherapy. Four patients (5.2%) developed pelvic node recurrence, and all of these cases were associated with distant metastases. The sites of recurrence were the lung (three patients) and peritoneum (one patient) (the recurrence treatment was systemic chemotherapy). Eleven (14.4%) patients presented with only distant metastatic recurrence (the sites of recurrence were the brain, lung, liver, bone and peritoneum), which was treated with systemic chemotherapy in all but two patients, who received the best supportive care.

The delivered PTV doses are presented in Fig. 4. D2, D50, D95 and D98 indicate the minimal doses delivered to the top 2%, 50%, 90%, and 98% of the PTV, respectively, and underline the relative homogeneity of the delivered treatments. Table 2 presents the doses that were delivered to the different OARs. The median maximal dose of 2 cc of any of the different OARs was limited to 45 Gy. The doses to the small bowel were low, and the median values of the volumes that received at least 40 Gy and 45 Gy were 77 cc and 7 cc, respectively.

The acute and late toxicities are presented in Fig. 5. We observed one case of Grade 3 diarrhea that required an interruption of treatment at 48.6 Gy. No severe side effects were

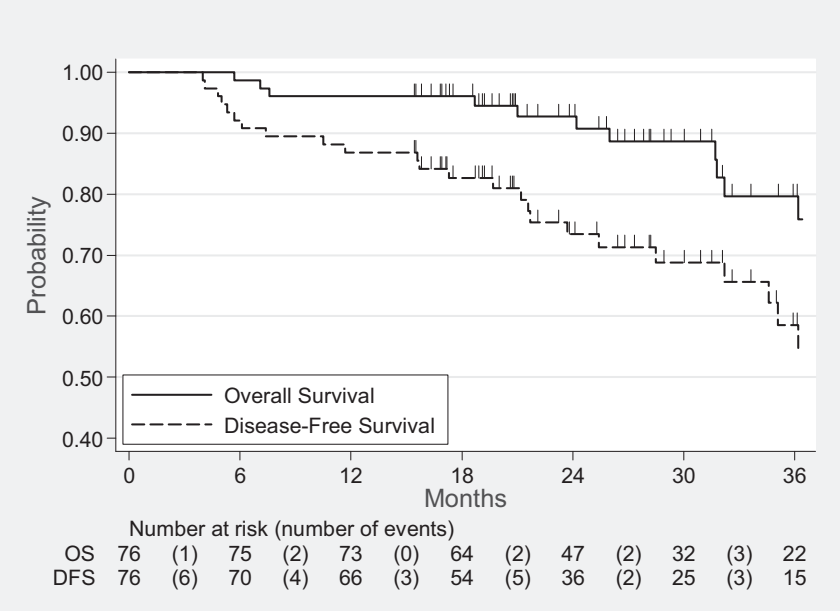

Fig. 1 – Survival curves.

observed. The overall Grades 1–2 late toxicity was less than 3%.

The Mann–Whitney *U*-test was used to examine the differences in the doses delivered to the OARs of the patients who presented with acute and late side effects. However, the dosimetric parameters presented in Table 2 were not predictive of the secondary effects.

5. Discussion

This work sought to report data regarding IMRT as an adjuvant treatment to surgery for endometrial cancer with an unfavorable prognosis. At the median follow-up time of 29 months, the OS rate was 96% at 12 months and 89% at 24 months. The DFS rate was 87% at 12 months and 74% at 24 months. An age above 60 years was associated with significantly lower OSs (HR: 8.9; CI: 1.1–68) ($p = 0.036$) and higher recurrence rates (HR: 3.5; CI: 1.2–10.2) ($p = 0.022$). Four women (5.2%) developed in-field local vaginal recurrences, and four other women presented with regional pelvic recurrence components. The only sites of recurrence in nine patients were distant metastases. No late severe toxicity was observed, and the rate of overall Grade 2 late toxicity was less than 3%.

The group of patients with Type II and Type I Grade III histology presented with lower OSs than did the Type I Grades

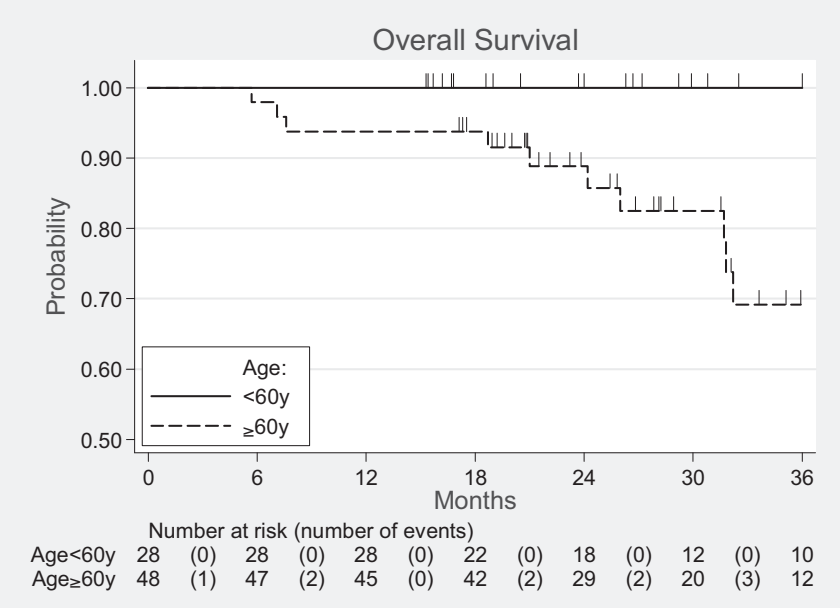

Fig. 2 – Overall survival and age.

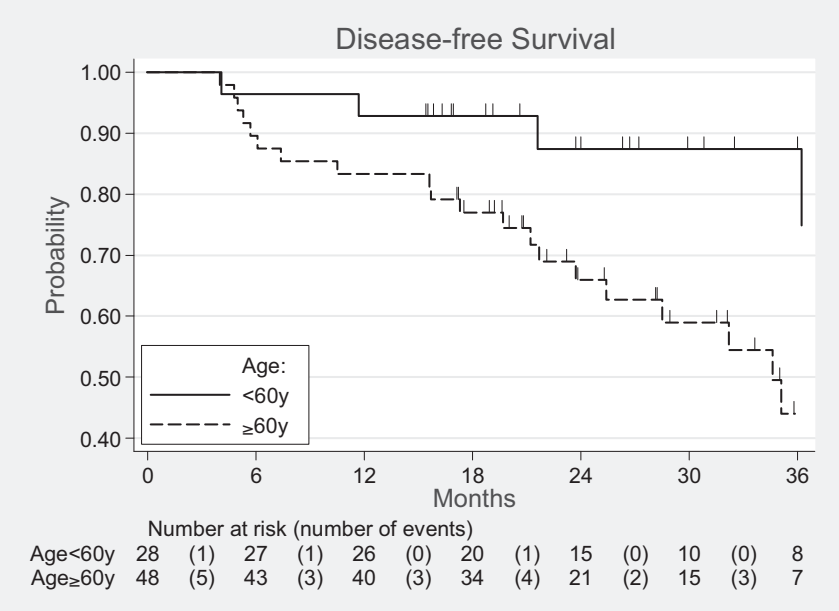

Fig. 3 – Disease-free survival and age.

I–II histology patients (HR: 3.3; CI: 1.1–11) ($p = 0.046$). Five patients (6.6%) developed in-field local vaginal recurrences; in four cases, these recurrences were associated with distant disease, and two (2.6%) cases developed out-of-field vaginal recurrence. Four patients (5.2%) developed pelvic node recurrence, and all of these cases were associated with distant metastases. Eleven patients (14.4%) presented with distant metastatic recurrence only.

According to the ICRU 83 recommendations,[19] the D2, D50, D95 and D98 PTV values were highly homogeneous both in the patients who received 45 Gy and in those who received 50.4 Gy. These results confirm the conformability and safety of the IMRT technique. Similarly, the doses to the OAR remained low.

Regarding the doses to the small bowel, the median V40 and V45 were 77 cc and 7 cc, respectively, and the latter volume

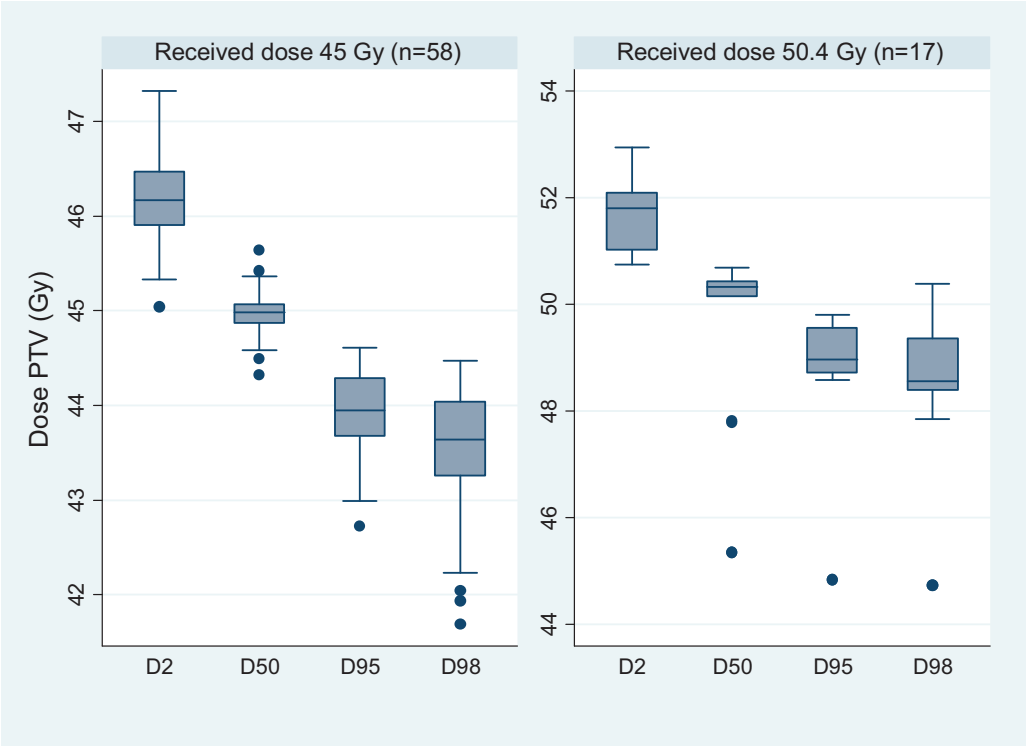

Fig. 4 – Doses delivered to the PTV.

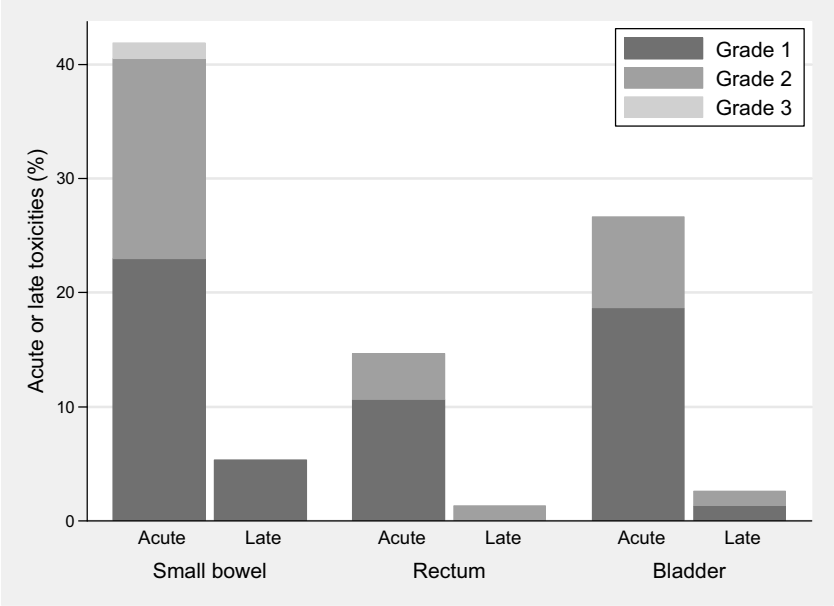

Fig. 5 – Acute and late toxicity.

Table 2 – Doses delivered to the different OARs.

Characteristics ($N = 76$)	Median (range)	Mean (sd)
Rectum ($n = 76$)		
D2cc (Gy)	45.21 (32.06–52.68)	45.17 (3.46)
D10cc (Gy)	42.10 (23.93–50.76)	40.48 (5.72)
D20cc (Gy)	36.01 (0.00–47.58)	33.99 (9.94)
D50cc (Gy)	17.34 (0.00–42.14)	15.72 (14.56)
Sigmoid colon ($n = 75$)		
D2cc (Gy)	44.97 (31.02–51.89)	44.59 (4.15)
D10cc (Gy)	42.68 (0.00–48.68)	39.42 (9.87)
D20cc (Gy)	38.71 (0.00–47.69)	34.22 (12.81)
D50cc (Gy)	26.74 (0.00–43.47)	22.49 (15.25)
Bladder ($n = 76$)		
D2cc (Gy)	45.31 (39.54–55.32)	46.11 (2.71)
D10cc (Gy)	44.44 (29.49–51.10)	44.30 (3.67)
D20cc (Gy)	43.08 (24.12–50.50)	42.06 (5.16)
D50cc (Gy)	36.12 (0.00–48.45)	34.66 (9.11)
Small bowel ($n = 76$)		
D2cc (Gy)	45.48 (42.38–53.09)	46.36 (2.44)
D10cc (Gy)	44.72 (31.22–51.77)	45.12 (3.00)
D20cc (Gy)	43.97 (22.77–51.02)	43.92 (3.74)
D50cc (Gy)	42.17 (12.53–50.14)	40.90 (5.21)
V40 (cc)	76.75 (3.68–308.27)	89.19 (64.14)
V45 (cc)	6.76 (0.00–801.67)	29.54 (94.96)
V50 (cc)	0.00 (0.00–61.52)	2.49 (9.00)
Left femoral head ($n = 76$)		
V40	0.00 (0.00–4.80)	0.33 (0.86)
V50	0.00 (0.00–0.00)	0.00 (0.00)
Right femoral head ($n = 76$)		
V40	0.00 (0.00–4.44)	0.21 (0.74)
V50	0.00 (0.00–0.00)	0.00 (0.00)

was defined to contain all of the possible organ locations on the planning CT scan. Thus, all of the dosimetric parameters presented in Table 2 can be considered safe when initiating adjuvant IMRT for endometrial cancer.

IMRT in the treatment of GYN malignancies is an interesting option as an adjuvant to surgery, despite the small number of relevant publications available in the literature. The results of NCT01641497 and NCT01672892 trials could provide more information about the use of IMRT techniques in postoperative GYN cancer.

Conventional radiation treatments of the postoperative pelvic area are not free of intestinal and urinary consequences, particularly when used to treat elderly populations. Classically, conformal radiotherapy is associated with high rates of Grades 1–2 acute and late urinary (45.6 vs. 31.7%; $p = 0.001$) and GI (25.8 vs. 14.6; $p = 0.006$) morbidity.[24] Keys et al.[4] showed relatively high and severe rates of hematologic, gastrointestinal, genitourinary and cutaneous toxicities in radiotherapy cohorts versus no additional treatment cohorts.

Likewise, gastrointestinal (GI) sequelae are among the most common acute and chronic side effects in GYN patients, with 1–25% rates of severe late toxicity.[9,10,25,26] In contrast to conventional treatments, IMRT significantly spares the OAR (Table 2). In our series, the small bowel median V40 and V45 of 77 cc and 7 cc, respectively, could not be obtained using conventional 3D conformal therapy alone. These results can explain the absence of Grade 3 or higher GI toxicity.

Several retrospective studies have reported on the use of IMRT or 3D conformational radiation techniques as adjuvant GYN treatments. Yang et al.[27] reported a better conformity and lower integral dose to OARs with IMRT and Helical Tomotherapy compared with 3D conformal therapy. Roeske et al.[14] described a twofold reduction in the volume of the small bowel treated (17.4% vs. 33.8%) in 10 patients.

The two randomized trials[11,28] evaluating IMRT in postoperative endometrial cancer patients showed an incidence of GI acute toxicity (Grade 2 or greater) of 28% in the RTOG0418 trial and 27% in the RTCMI-ENDOMETRE trial, respectively.

In the present work, the Grades 1, 2, and 3 acute gastrointestinal toxicity (AGIT) rates were 22.7%, 17.3%, and 1.3%,

respectively. Shih et al.[29] found 59%, 21%, and 2% rates of Grades 1, 2, and 3 AGITs, respectively, in 46 patients. Vandecasteele et al.[30] observed Grades 1 and 2 AGITs in 39% and 54% of patients, respectively, in a series of 41 patients, and Beriwal et al.[31] reported 27% and 70% rates of Grades 1 and 2 toxicities, respectively, in a study that included 47 patients. Barillot et al.[28] reported 27.1% of Grades 1–2 acute intestinal toxicity without Grade 3. Bibault et al.[32] showed 49% of Grades 1–2 AGIT in 47 endometrial cancer patients treated by postoperative Helical Tomotherapy.

Regarding chronic gastrointestinal toxicity (CGIT), our results do not differ from those of other IMRT studies. We reported a 5.3% rate of Grade 1 CGIT and no cases with Grade 2 or higher. Beriwal et al.[31] described 25% and 2% rates of Grades 1 and 3 CGIT, respectively. Vandecasteele et al.[30] reported a 32% rate of Grade 1 and a 4% rate of Grade 2 CGIT.

Moreover, the late genito-urinary toxicity (GUT) rates observed here do not contradict those observed in the preliminary literature. We observed G1-2 acute GUT in 26.7% of cases and no G3 toxicity. Mundt et al.[17] reported a rate of 30% in 40 patients, Beriwal et al.[31] reported a rate of 20%, and Vandecasteele et al.[30] reported rates of G1, G2, and G3 of 49%, 12%, and 2%, respectively. Barillot et al.[28] reported 19% acute Grade 2 urinary toxicity, Bibault et al.[32] reported 21.3% of Grade 1–2 GUT, and no urinary toxicity rates were reported in a phase II RTOG 0418 3D conformal trial.[11]

Our series revealed that the 2-year related OS, DFS and local control rates were 96%, 89%, 87%, and 74%, respectively. These findings are similar to the preliminary results that are available in the literature.[17,29–31,33,34] The in-field vaginal-nodal recurrence rate (11.8%) observed here did not differ from those of historical series[3–6] or those of recent IMRT publications;[17,31,33–35]; only Shih et al.[29] showed a lower rate on in-field vaginal recurrence. Eleven patients (14.4%) developed only metastatic disease at the 29-month follow-up. Among these patients, seven had Type II histology, and one had a Grade 3 Type I histology. Similarly, Beriwal et al.[31] reported 3-year OSs and DFSs of 90% and 84%, respectively, in 47 patients. Bouchard et al.[33] reported a 27-month DFS of 100% among 15 patients. Chen-Hsi Hsieh et al.[34] observed 3-year DFS and OS rates of 94% and 88%, respectively, and a 6.5% rate of local failure in 31 patients. Shih et al.[29] reported a 5-year relapse rate of 9%. The five-year DFS rate was 88%, and the OS rate was 97%.

6. Conclusion

To the best of our knowledge, this study is the largest to prospectively evaluate the outcomes of adjuvant IMRT and TA techniques in endometrial cancer. We systematically used pre-treatment mega-voltage CT scans. The patients were only treated after the online and planning CT scan data could be overlaid. No late severe toxicity was observed, and the rate of Grades I–II late side effects was less than 5%. This is in contrast to the high rates of severe late side effects reported after conventional 3D radiation treatments. The safety of the present procedure allows its use in the treatment of elderly populations who are increasing in the western countries. The results from our study are in line with the ICRU 83 prescriptions and treatment delivery recommendations. Despite the use of high-precision radiation treatments, nine (11.8%) patients developed in-field local or regional recurrence, and 11 (14.4%) exhibited recurrences that involved only distant metastases. These results underline the role of systemic treatments to inhibit the dissemination process while reducing the pelvic recurrence rate. Increasing the pelvic radiation dose should be further investigated in prospective trials because the rate of side effects observed in this study was low.

Conflict of interest

Eric Lartigau PhD has been acting chief Medical at Accuray from April 2014 until September 2014.

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