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Second Re-Irradiation as A Salvage Treatment in A Patient with Recurrent Endometrial Cancer

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Abstract

The management of loco-regional recurrences from endometrial cancer is challenging since there are limited data regarding to management of recurrent endometrial cancer. Therapeutic options are often limited particularly for the patients who received adjuvant radiotherapy (RT). Patients who present with loco-regional recurrence after curative surgery and adjuvant RT are ideal for salvage surgery; However, the salvage surgery is associated with higher rates of mortality and morbidity. Re-irradiation could be an option for selected patients. However, pelvic re-irradiation is challenging and is often approached reluctantly by radiation oncologist due to the tolerance limits of nearby normal tissues which may lead severe chronic toxicities. Herein we report a case of recurrent endometrial cancer who underwent second re-irradiation in addition to multiple cytoreductive debulking surgery.

Introduction

During the last few decades, there have been major advancements in diagnosis, staging, and treatment of endometrial cancer which has translated into improved clinical outcomes and better survival times. Despite this a significant proportion will relapse locally, requiring multidisciplinary management. Patients who received adjuvant radiotherapy (RT) at the beginning of the disease are candidates of salvage surgery; however, this is not always possible. Re-irradiation poses a therapeutic dilemma, as the desire for local control must be balanced against with the deleterious effect of re-irradiation[1]. However, for carefully selected patients, even second re-irradiation may be a reasonable approach[2,3]. There is limited data in the literature regarding to re-irradiation in patients with recurrent endometrial carcinoma. Furthermore, there is extremely rare evidence with respect to the second re-irradiation in loco-regional recurrences of endometrial carcinoma. Herein we report a case of recurrent endometrial cancer patient who received third course of RT in addition the multiple surgical procedures.

Case report

A 68-year-old woman was admitted to our university with a complaint of abdominal pain. From her past medical history it was learned that, the patient had undergone a surgical staging procedure including an abdominal hysterectomy with bilateral salpingo-oophorectomy, with pelvic and para-aortic lymph nodes dissection, and pelvic washing 6 years ago. The histopathology was endometriod adenocarcinoma, and the disease was staged as stage

IA grade 3 according to the International Federation of Gynecology and Obstetrics System (FIGO) for endometrioid carcinoma, and the patient underwent vaginal cuff brachytherapy (BRT) to a dosage of 2750 cGy in 5 fractions to 5mm depth, and chemotherapy (CT) consisted of five cycles of paclitaxel (175 mg/m^2) and carboplatin (AUC 6) on a q21-day schedule. The planned CT cycles were 6; however, because of severe neuropathy the patient could not complete the 6th course of the CT.

Pelvic magnetic resonance imaging (MRI) revealed an 8x6x7 cm cystic lesion in the uterine tumor bed, with solid components, in addition to a 2,5x 1.8 cm paravaginal cyst located on the distal lateral vagina wall (Figure 1). Whole body positron emission tomography/computed tomography (PET/BT) scan confirmed high fluorodeoxyglucose uptake in the mass located in uterine tumor bed (SUVmax: 22.34), and another mass located superior to the previous mass (SUVmax: 4.38). There was no associated lymphadenopathy or other signs of metastatic spread. The karnofsky performance status (KPS) was approximately 90%. The patient underwent cytoreductive debulking surgery (CRDS), and ureteral J stent placement, and the histopathology revealed high grade papillary serous carcinoma. Then we applied external pelvic radiotherapy (EPRT) to a dosage of 5040 cGy in 28 fraction using 3-dimesional conformal radiotherapy (3D-CRT) with field in field technique (Figure 2). During RT, the patient developed acute grade 1 gastrointestinal (GI),

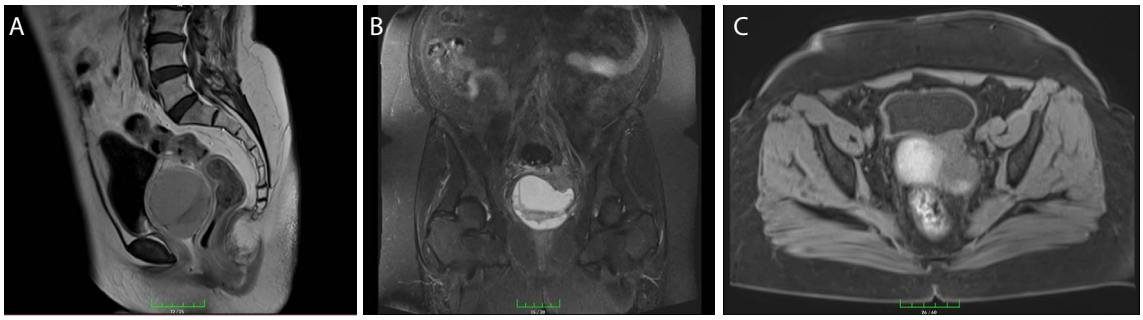

Figure 1: Pelvic MRI showing an 8x6x7 cm cystic lesion in the uterine tumor bed, with solid components (a) sagittal view (b) coronal view (c) axial view.

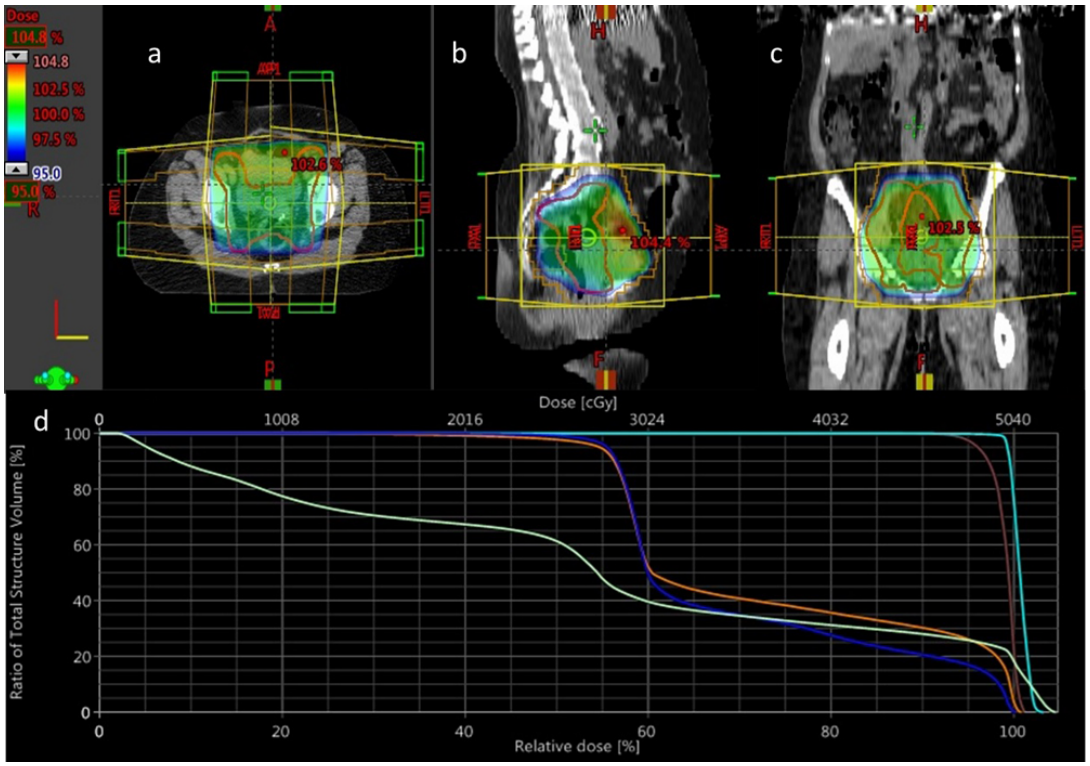

Figure 2: External pelvic radiotherapy (EPRT) treatment plan (a) axial view (b)sagittal view (c) coronal view; and (d) dose volume histogram (DVH) (cyan: bladder, brown: rectum, dark blue left femoral head, orange: right femoral head; light green: intestine).

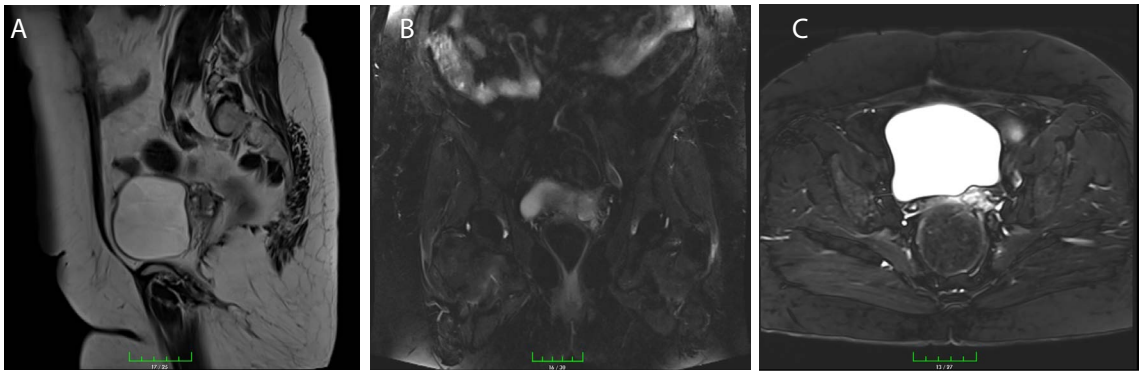

Figure 3: Pelvic MRI showing a 2.4x2x 3 cm recurrent mass about located in recto-vaginal area posterior to left side of the bladder wall (a) sagittal view (b) coronal view (c) axial view.

and genitourinary (GU) toxicities, which responded oral medications. After EBRT we suggested our patient dose escalation with stereotactic body radiotherapy (SBRT), in order to control the pelvic recurrent disease; however, our patient did not eager to receive boost treatment. Also, she did not want to receive systemic chemotherapy.

Six months later during routine follow-up we observed a 2.4x2x 3 cm recurrent mass about located in recto-vaginal area posterior to left side of the bladder wall (Figure 3). At that time KPS was still 90%. The patient underwent second re-irradiation to a dosage of 2500 cGy in 5 fractions using SBRT with cyberKnife® (Accuray Inc., Sunnyvale, CA, USA). The patient had grade 1 acute GI and GU toxicity, and grade 1 chronic GU toxicity. The patient again refused both surgery (pelvic exenteration) and chemotherapy.

Nine months after the second re-irradiation, we detected a recurrent 2.1x1.3x2.8 cm mass located postero-lateral wall of the bladder. PET/BT scan showed that there was no distant metastasis. The patient underwent CRDS, and although she was offered systemic treatment, she refused it again. The histopathology revealed high grade serous carcinoma. Three months later pelvic MRI showed a recurrent mass in recto-vaginal area posterior to left side of the bladder wall. The patient declined Pelvic exenteration and systemic therapy. The patient again underwent CRDS; however, histopathology revealed fibrotic changes, and chronic inflammation.

The patient underwent routine follow-up procedure. Nineteen months after the last CRDS, she is still alive with the stable pelvic mass which was confirmed as chronic inflammation. We did not observe any enlargement during follow-up in that mass. She had grade 1 chronic GU toxicity.

Discussion

Pelvic re-irradiation for endometrial cancer is challenging and is often approached reluctantly by radiation oncologist due to the tolerance limits of nearby normal tissues which may lead severe chronic toxicities. However pelvic re-irradiation including second re-irradiation in endometrial cancer patients with limited local recurrences has the potential to provide worthwhile symptom palliation and/or temporary tumor growth arrest, thereby contributing to the ever increasing armamentarium of options that increase the survival of patients with incurable cancer and try to prolong the time period where independent living is possible. The most critical issue in planning re-irradiation is to select the suitable patient. On the other hand, the most challenging part of second re-irradiation is the unavailability of organ at risk (OAR) limitations of pelvic structures even in first re-irradiation. The RT dose is limited by the tolerance of normal tissue surrounding the tumor. Exceeding the tolerance dose can cause severe damage and can be lethal in some cases. We reported a case of recurrent endometrial cancer who received second re-irradiation in addition to multiple cytoreductive debulking surgeries without any severe unmanageable chronic toxicity.

Abusaris et al. reported a large series of 23 patients who underwent second re-irradiation for palliative purpose[4]. Fourteen out of 23 patients had a recurrent tumor in the pelvic region. In this study, symptomatic response was observed in 81% of the patients after the third radiation. The median cumulative maximum dose to the tumor and its regions was 133 Gy3 (range: 82–496 Gy_3). Neider et al reported three cases who underwent second re-irradiation to pelvic region from a single institution database[3]. The diagnoses of the patients were sacral bone metastases, recurrent rectal and pelvic nodal metastases. The maximum cumulative equivalent dose in 2-Gy fractions (EQD2) was 142 Gy. The purpose of the second re-irradiation was to palliate the symptoms for all of the patients. The authors reported a good symptomatic response for all patients without clinically relevant severe side effects. Feddock et al. investigated the clinical efficacy and toxicity of pelvic re-irradiation using permanent interstitial brachytherapy (^{198}Au or ^{131}Cs) for local recurrences of pelvic malignancies

from 42 patients[5]. The most common primary sites at the time of diagnosis were uterine corpus (n=12). Nine out of 42 patients underwent a second salvage re-irradiation with re-implantation of the same lesion in the vagina. The median cumulative lifetime EQD2 was 152 Gy (range 115–172). Only three (33%) of these tumors were still controlled at the time of death or of last follow-up.

In the current study, different from the other reported patients, the aim of the second re-irradiation was to cure the patient instead of palliating tumor related symptoms, since our patient was asymptomatic. In our case the median cumulative dose was 135.13 Gy_3 (BRT dose: 5.5 Gyx 5 fraction=46.75 Gy; EPRT dose: 1.8 Gyx 28 fraction= + 48.38 Gy; and SBRT dose 5Gyx 5 fraction= 40 Gy, for biological equivalent dose (BED) $\alpha/\beta=3$). Our median cumulative dosage was lower than the both Neider's and Feddock's study, and comparable with the Abusaris's study. We controlled the recurrent disease after the third course of RT without systemic therapy.

Abusaris et al. reported 4% of acute grade 3 pain and 7% of the patient's acute grade 3 dysuria. None of the patients in that study experienced grade 4 late toxicity. Grade 3 late skin toxicity was experienced in 4% of the patients. The authors recommended safe dose constraints of OAR as 100 Gy3 for rectum, 90 Gy3 for bowel and 110 Gy3 for bladder[4]. The low percentage of late high toxicity in this study could be related to short follow-up time (median overall survival times from the third radiation was 7 months (3.5-49.5 months). However, the authors selected reasonable dose limits when compared the recommended dose limits for first re-irradiation[6]. Neider et al. did not report any severe chronic toxicity[3]. In this study the authors used the normal tissue tolerance limits from the suggested doses by Abusaris et al. In the study by Feddock et al. all nine second re-irradiated patients demonstrated soft tissue necrosis, which was persistent beyond 3 months and was symptomatic in only two of them[5]. However, in this study the mean EQD2 dose, which was 152 Gy, was higher than other studies.

In the current case we observed only grade 1 acute GI and GU toxicities in addition to chronic grade 1 urinary toxicity. Our dose limits were similar with to the dose limits defined by Abusaris et al. Six months after the second re-irradiation the patient had a gross hematuria; however, this was because of urinary infection, which responded to oral medications. During routine follow-up she had microscopical hematuria, which did not deteriorate her quality of life. She is still free of disease after 19 months from the last debulking surgery.

In the current case the first histopathology was endometrioid adenocarcinoma grade 3, and the second one was papillary serous carcinoma. Our pathological slices were consulted many different pathologist, who are dealing with gynecologic oncology. However, the histopathologies were reported to be as adenocarcinoma grade 3 for the first one and papillary serous carcinoma for the second one as well, meaning that the first one and the second one were different. We can explain this by two ways. The first hypothesis is that there might have been a change regarding to biological behavior of the tumor cells, as in the case of brain tumors. The second explanation may be is that the recurrent tumor is the second primary tumor such as primary peritoneal papillary serous carcinoma. Nevertheless, our case is an interesting one not just because of our aggressive treatment for the aggressive disease, but also the histopathological differences that might have been very difficult to explain.

In the current case we used EBRT and SBRT for the re-irradiation and second re-irradiation, respectively. There are other local treatment options including intraoperative radiotherapy (IORT), and brachytherapy (BRT) for the management of recurrent disease. Recently Aridgides et al reported their institutional experience of interstitial BRT in recurrent pelvic cancer patients[7]. Their results demonstrated that that interstitial BRT was a safe and effective treatment for primary or recurrent pelvic malignancies. They found high local control rates in addition to preservation of both bladder and rectal function in 97% of the patients. Moreover, the authors from University of Louisville reported their experience of interstitial BRT for recurrent previously irradiated gynecologic tumors; the 2-year local control was 72% without any unmanageable toxicity[8]. From the results of the relevant studies it can be concluded that interstitial BRT allows permits effective tumor dose delivery while sparing nearby critical organs that have been previously irradiated.

Advances in the imaging and treatment techniques enhanced to re-irradiate the pelvic recurrences in a previously irradiated field, by allowing to decrease the dosages received by nearby healthy tissues and to escalate the dosages received by the recurrent mass. The most important obstacle is the lack of enough evidence with respect to the tolerance dose limits of nearby tissues/organs. In the current case we applied second re-irradiation course in addition to multiple surgeries without any severe side effects. Second re-irradiation may be a reasonable treatment option in selected patients with loco-regional recurrent endometrial cancer. There is a need of determination of cumulative dose constraints and practice recommendations regarding suitable minimum time intervals. With the increasing evidence, reluctance to retreat is expected to diminish, and an increasing number of patients will thus be able to benefit from re-irradiation.

Ethics

Informed Consent: written signed consent was obtained by patient.

Authorship Contributions

Surgical and Medical practices: G.Y., K.O., H.Y., C.C., **Concept:** G.Y., **Design:** G.Y., **Data Collection and Processing:** G.Y., C.Y., O.V.G., **Analysis and Interpretation:** G.Y., C.C., **Literature Search:** G.Y., **Writing:** G.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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