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Intraoperative electron radiation therapy after salvage surgery in gynecological cancers and retroperitoneal sarcomas: outcomes and adverse effects

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ABSTRACT

Background: Salvage surgery is considered an option for isolated recurrences of retroperitoneal and pelvic tumors, in patients who have undergone previous radiotherapy. In order to increase local control intra operative electron radiation therapy (IOERT) can be used in these patients to administer additional radiation dose. We evaluated the outcomes and adverse effects in patients with retroperitoneal sarcoma and gynecologic tumors after salvage surgery and IOERT.

Materials and methods: Twenty patients were retrospectively analyzed. Twenty-three IOERT treatments were performed after surgery. Six (30%) were sarcoma and 14 (70%) were gynecological carcinoma. Administered dose depended on previous dose received with external beam radiotherapy (EBRT) and proximity to critical structures. The toxicities were scored using the Common Terminology Criteria for Adverse Events version 4.0.

Results: The median age of the patients was 51 years (range 34–70). After a median follow-up of 32 months (range 1–68), in the sarcoma group the local control rate was 66.6%; while in the gynecological group the local control rate was 64.3%. In relation to late toxicity, one patient had a Grade 2 vesicovaginal fistula, and one patient presented Grade 4 enterocolitis and enteric intestinal fistula.

Conclusions: IOERT could have a role in the treatment of retroperitoneal sarcomas in primary tumors after EBRT, as it may suggest a benefit in local control or recurrences after surgical resection in those at high risk of microscopic residual disease. The addition of IOERT to salvage resection for isolated recurrence of gynecologic cancers suggest favorable local control in cases with concern for residual microscopic disease.

Key words: retroperitoneal sarcoma; gynecologic tumors; intraoperative radiation therapy; IOERT; local recurrence; toxicity

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Introduction

The treatment of retroperitoneal and pelvic primary tumors involves a multimodality approach. It may include a combined treatment involving chemotherapy (Ch), external beam radiation therapy (EBRT), brachytherapy, and/or surgery. In primary tumors, radical surgery is the treatment of

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choice. However, there is a non-negligible percentage of incomplete resections with microscopically focally involved margins or macroscopic residual tumor, so that after surgery intra operative radiation therapy (IORT) [1] could be associated with an increase in local control.

In focal recurrences of retroperitoneal and pelvic tumors salvage surgery is currently considered the only curative option, particularly for patients that have already undergone a first-line radiotherapy. However, surgery alone cannot achieve satisfactory local control, subsequent failures have been reported in more than 50% of all patients [1–3]. After surgery, for patients with close or positive margins, IORT can be useful to improve local control and be used safely to deliver additional radiation doses to patients previously treated with EBRT [4–6].

After breast-conserving surgery IORT can be used, under clinical trial, as accelerated partial breast irradiation or as a boost in patients requiring a tumor bed boost [7–9]. The American Brachytherapy Society recommends administering IORT as a boost in primary sarcomas with positive or close resection margins, or in the case of local recurrence after EBRT [10–15]. IORT could also be considered for isolated recurrences in gynecologic cancer with residual microscopic disease after surgical resection [16, 17]. Furthermore, it could be considered as the primary treatment after chemoradiotherapy (ChRT) followed by surgery in locally advanced cervical cancer [18]. But the indication for IORT after surgical resection in recurrent localized ovarian cancer is still controversial.

IORT consists of a single fraction treatment with low energy photons or electrons on a surgically exposed area. IORT has been used as the primary management, as well as in the salvage setting, for many solid tumors of different locations. The objective of this study was to analyze the outcomes and adverse effects in patients with retroperitoneal sarcoma and gynecologic tumors after salvage surgery and intra operative electron radiation therapy (IOERT).

Materials and methods

Patient and tumor characteristics

The present study had institutional review board approval. All the patients signed an informed consent form. We analyzed 20 patients who underwent salvage surgery and IOERT between January 2014 and February 2019 for a total of 23 treatments (multiple sites treatment in 3 patients). All the patients were discussed and selected in a multidisciplinary oncologic board. Positron emission tomography /computed tomography (PET-CT) was performed to exclude p with metastatic disease, and pelvic magnetic resonance imaging (MRI) to exclude patients with multiple recurrence foci.

Patients received treatment with IOERT after surgical resection. The results of surgical procedures were classified by pathological anatomy intraoperatively before IOERT in: R0, free surgical margins; R1, resection with focally microscopically involved margins; and R2, visible or palpable residual tumor. The indications for IOERT in our series were:

- primary retroperitoneal sarcoma treated with surgery with positive or suspected close resection margins (R1 or R2), or in cases of local recurrence where EBRT has been previously administered;
- as primary treatment in patients with locally advanced cervical cancer treated with ChRT followed by surgery with positive or suspected close margins (R1 or R2);
- treatment for recurrences of gynecologic cancer (cervix, endometrial and ovarian) with suspected residual microscopic disease (R1 or R2).

Characteristics of the patients and previous treatment to IOERT are shown in Table 1.

Treatment characteristics

A dedicated 10 MeV mobile electron linear accelerator (LIAC) (S.I.T. Sordina IORT Technologies S.p.A., Italy) was used to deliver IOERT. The electron beam is delivered through transparent polymethylmethacrylate (PMMA) applicators (tubes) with different diameters (3 to 10 cm). To spare underlying tissues from radiation, a shielding disc available in various diameters was used when needed. The protective disc consists of a steel disc that is inserted in a polytetrafluoroethylene (PTFE) sleeve. The orientation of the disc is such that the sleeve is facing upwards (towards the tumor bed) to efficiently shield secondary electrons backscattered and avoid undesired overdosage of the superjacent tissue. In most of the patients the size of the shielding disc was 1 cm in diameter larger than the applicator selected, the last depend-

Table 1. Patient and tumor characteristics

	n = 20 (%)
Sex	
Male	3 (15)
Female	17 (85)
Histology	
Cervix	
Squamous carcinoma	8 (40)
Adenocarcinoma	1 (5)
Endometrium	
Endometroid adenocarcinoma	2 (10)
Carcinosarcoma	1 (5)
Clear cell adenocarcinoma	1 (5)
Ovary	
Serous-papillary carcinoma	1 (5)
Sarcoma	
Liposarcoma	4 (20)
Leiomyosarcoma	1 (5)
Retroperitoneal desmoid tumor	1 (5)
Primary tumor location	
Cervix	9 (45)
Endometrium	4 (20)
Sarcoma	6 (30)
Ovary	1 (5)

ing on the needs of the area to be treated based on previous tumor size, and the effective field size for the energy used. The most common applicator diameter was 5 cm (range 3–8), and only flat tubes were used. The applicator size was chosen in order to ensure a proper coverage for a given target volume around the surgical sutured breech, depending on the tumor size and location. We defined the Planning Target Volume as a perimeter expansion of 2 cm beyond the former macroscopic tumor edge. The most used energy of the electron beams was 4 MeV (range 4–10), and it was chosen according to the depth of the tumor bed. The applicator was placed directly in contact with the target volume. The median prescribed dose was 10 Gy (range 8–20, mode 10). The doses of IOERT prescribed in retroperitoneal sarcoma or in recurrences were 10–20 Gy, depending on the type of surgical resection (R1 or R2) and if they had previously received EBRT. The prescribed dose in locally advanced cervical carcinoma was 10–12 Gy. The prescribed dose in recurrences of gynecological carcinomas was 8–15 Gy, since they had previously received EBRT and also depended on the type of surgical resection (R1 or R2).

A clinical follow-up was performed by surgeons and radiation oncologists every 3 or 6 months, with tumor markers and imaging tests (CT scan, PET-CT and/or MRI) according to each individual case.

Study endpoints and statistical analysis

The objective of this study was to analyze local recurrence (LR), regional recurrence (RR) and distant recurrence (DR). LR was calculated between the date of IOERT and the date of the first in-IOERT field recurrence regardless of any previous DR. RR was defined from the date of IOERT to the date of first outside-IOERT field recurrence within the anatomical site (pelvic or retroperitoneum). DR was measured from the date of IOERT to the date of the first recurrence outside the pelvis or retroperitoneum. Acute and chronic toxicities attributable to IOERT were scored according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Grades 1–5). The mean, standard deviation, median, range and frequencies of the prognostic variables were analyzed. The statistical analysis was carried out through the IBM SPSS version 25.0.

Results

Patient's characteristics

The median age of the patients was 51 years (34–70). The median follow-up was 32 months (1–68). Five patients (25%) were treated for primary tumors with IOERT: four (20%) for locally advanced cervical carcinoma and one (5%) for sarcoma. The remaining 15 (75%) were tumor recurrences: five (33.3%) sarcomas, five (33.3%) cervical carcinomas, four (26.7%) endometrial carcinomas and one (6.7%) ovarian carcinoma. Characteristics of the patients and tumor previously to IOERT are shown in Table 1.

Treatment characteristics

Retroperitoneal sarcomas

Six patients with retroperitoneal sarcoma were treated. One with primary stage IIB liposarcoma treated with tumor excision in two locations achieving R0 with the subsequent IOERT in both

lesions to a total dose of 15 and 20 Gy. Five patients were treated for recurrent sarcoma. Of these, one received Ch prior to ressection and the other received EBRT. All patients were treated with tumor recurrence resection in the retroperitoneum (4) and the right pelvis (1), achieving R0 resection in two patients and R1 in the other 3 patients. The total prescribed doses ranged from 10 to 20 Gy.

Residual tumor after locally advanced cervical cancer

Two patients with stage IIb disease were treated with concomitant ChRT with residual disease. One of them underwent radical hysterectomy achieving R0 followed by 10 Gy IOERT to the right parametrium. The other patient underwent radical hysterectomy with double adnexectomy with R1, for which she received 10 Gy of IOERT in the area of the vaginal cuff. Two patients with locally advanced cervical carcinoma (stage IIIb) underwent concomitant ChRT followed by pelvic exenteration for residual disease. R0 was achieved in one patient, and she received 12 Gy IOERT in two locations (obturator fossa and pelvic floor). The other patient received 12 Gy IOERT in the vaginal cuff.

Cervical cancer recurrences

Five patients previously treated with ChRT and brachytherapy developed tumor recurrence. One patient was treated with radical hysterectomy, two with hysterectomy and adnexectomy and two with pelvic exenteration. All the patients received IOERT in the vaginal cuff and the patient with two tumor locations was also irradiated in the right parametrium. Five of the six resections were R1, and one was R0. The IOERT prescribed dose ranged from 8 to 10 Gy.

Ovarian cancer recurrence

One patient had a left parametrium recurrence from a serous-papillary ovarian carcinoma. After R0 lymph node excision, 15 Gy IOERT was administered.

Endometrial carcinoma recurrences

Four patients presented lymph node recurrence, of whom three previously received Ch followed by tumor excision. In these three cases, the locations of recurrence were in the right iliac fossa (R0), left iliac fossa (R2) and in the right pelvis (R0). All received 10 Gy IOERT after resection.

The remaining patients underwent tumor excision (R0) followed by 12 Gy IOERT in the right iliac fossa.

The treatment characteristics are listed in Table 2.

Patient outcomes

The local control rate was 66.6% for the patients with sarcomas. The patients treated with retroperitoneal liposarcoma presented a loco-regional and distant recurrence with a progression-free interval (PFI) of 34 months. Surgical resection of the recurrences was performed, and the patients are currently alive. For the five patients with sarcoma recurrences, three (60%) had no recurrence while one (20%) had LR with a PFI of 15 months and with subsequent surgical rescue; the other patient (20%) presented RR with a PFI of 4 months. After surgical rescue the patient presented DR and finally underwent treatment with Ch. Of the patients with recurrent sarcoma, 4 out of 5 are alive and one died from a non-related cause.

The local control rate of the gynecological cancers was 64.3%. The local control rate of the locally advanced cervix carcinoma was 100%. Three out of four patients did not show local or distant recurrence and are still alive. The remaining patient presented DR with a PFI of 5 months, currently undergoing Ch, without reported LR. The local control rate of the patients with recurrent cervical carcinoma was 40%. One was treated in two locations presenting DR with a PFI of 6 months, requiring systemic treatment with Ch. Three patients presented locoregional recurrence with a PFI of 3 to 16 months, subsequently undergoing Ch. The remaining patient did not have any recurrence. Two out of five patients are still alive, the remaining three have died from disease progression. The local control rate of the patients with recurrence of endometrial carcinoma was 50%. One presented LR with a PFI of 10 months, undergoing salvage surgery, subsequently presenting DR. One patient presented local-regional recurrence with a PFI of 6 months, undergoing surgery and finally presented DR. One patient presented DR with a PFI of 10 months, requiring Ch. The remaining patient did not present any recurrence and is the only one alive. The local control rate of the patient with recurrence of ovarian carcinoma was 100%. The patient presented a DR with a PFI of 21 months, for

which she underwent Ch and finally died from disease progression.

The current status of the treatments and patients is recorded in Supplementary File — Tables S1 and S2).

Adverse effects

No complications related to surgery (dehiscence of the suture, infection, major bleeding, intestinal obstruction or death) were observed. We observed two cases of chronic toxicity, both in patients with recurrent locally advanced cervical carcinoma (in Tab. 2). One had a Grade 2 vesicovaginal fistula, and the other patient developed Grade 4 enterocolitis and an enteroenteric fistula that required surgery, and currently suffers from short bowel syndrome. It should be noted that both patients had previously undergone surgery followed by EBRT, and brachytherapy. No deaths attributable to toxicity were observed.

Table 2. Treatment characteristics

Patients	Ch	EBRT	Total dose [Gy]	Type of surgery	Surgical resection margin	IOERT location	Total dose [Gy]
Locally advanced							
Cervical carcinoma							
1	Yes	Yes	45	Radical hysterectomy	R0	Right parametrium	10
2	Yes	Yes	45	Radical hysterectomy	R1	Vaginal cuff	10
3	Yes	Yes	45	Pelvic exenteration	R0	Vaginal cuff	12
4	Yes	Yes	45	Pelvic exenteration	R0	Pelvic floor	12
Cervical recurrences							
1	Yes	Yes	50	Radical hysterectomy	R1	Vaginal cuff	8
2	Yes	Yes	50	Radical hysterectomy	R1	Right parametrium	8
3	Yes	Yes	50	Hysterectomy with adnexectomy	R1	Vaginal cuff	8
4	Yes	Yes	50	Pelvic exenteration	R1	Vaginal cuff	10
5	Yes	Yes	45	Hysterectomy with adnexectomy	R0	Vaginal cuff	10
6	Yes	Yes	45	Pelvic exenteration	R1	Vaginal cuff	10
Endometrial recurrences							
1	No	Yes	50	Nodal exeresis	R0	Right iliac fossa	12
2	Yes	Yes	50	Nodal exeresis	R0	Right iliac fossa	10
3	Yes	Yes	50	Nodal exeresis	R0	Right pelvis	10
4	Yes	No	–	Nodal exeresis	R2	Left iliac fossa	10
Ovarian recurrence							
1	No	No	–	Nodal exeresis	R0	Left parametrium	15
Locally advanced							
Sarcoma							
1	No	No	–	Tumor exeresis	R0	Retroperitoneum	20
2	No	No	–	Tumor exeresis	R0	Retroperitoneum	15
Sarcoma recurrences							
1	Yes	No	–	Tumor exeresis	R1	Retroperitoneum	12
2	No	Yes	45	Tumor exeresis	R0	Right pelvis	10
3	No	No	–	Tumor exeresis	R1	Retroperitoneum	12
4	No	No	–	Tumor exeresis	R1	Retroperitoneum	20
5	No	No	–	Tumor exeresis	R0	Retroperitoneum	15

Ch — chemotherapy; EBRT — external beam radiation therapy; R0 — free surgical margins; R1 — resection with focally microscopically involved margins; R2 — visible or palpable residual tumor; IOERT — intra operative electron radiation therapy

Discussion

Treatment of patients with primary or recurrent carcinoma involves a multidisciplinary approach, including surgery, radiotherapy (EBRT, brachytherapy or IOERT) and/or systemic therapy, depending on the patient functional status, tumor type and previous treatments. In patients with recurrences who have previously received EBRT with or without brachytherapy, radical surgery with the intention of a complete resection with clear margins should be considered as the main option. But if close or positive margins are present, focal radiation therapy should be considered as additional treatment. IOERT consists of a single fraction treatment with electrons on a surgically exposed area. It has been used as a primary treatment as well as in the salvage setting for solid tumors of different locations.

Retroperitoneal sarcoma (RPS)

IOERT can be used as a boost for patients undergoing preoperative or postoperative EBRT in primary tumor or as monotherapy in recurrences [11–14]. The traditional IOERT dosage ranges from 10–20 Gy. However, doses of less than 15 Gy are recommended to reduce potential toxicities including bowel damage and neuropathy [12]. Stucky et al. [15] examined the LC of surgical resection combined with preoperative EBRT and IOERT for RPS in 63 patients. Thirty-seven (59%) underwent EBRT plus IOERT and 26 (41%) had surgery alone. The 5-year LC rate was 89% for EBRT plus IOERT and 46% for surgery alone ($p = 0.03$). Petersen et al. [21] analyzed 87 patients with primary (43) or recurrent (44) intrapelvic or RPS treated with surgical resection and IOERT. The 3- and 5-year estimated LC rate was 77% and 59%, respectively. Roeder et al. [22] studied 156 patients with RPS (69 primary and 87 recurrent) treated with IOERT and 114 patients received additional EBRT. The LR rates at 3 and 5 years were 57% and 50%, respectively.

IOERT may have a role in the treatment of these sarcomas. Especially in primary tumors the dose increase after EBRT could contribute to a better local control. And in recurrences after surgical resection in those cases with high risk of residual disease that have been previously treated with EBRT [6].

Locally advanced cervical tumors with persistent disease

IORT has been considered a viable alternative in patients with FIGO stages IIB in order to deliver a boost to the surgical bed at risk after the removal of the persistent tumor [1, 23]. Martinez-Monge et al. [18] reported a series of 31 patients presenting resectable locally advanced cervix carcinoma treated with ChRT followed by surgery and IORT.

The 10-year in field control rate was 92.8% and the 10-year probability of pelvic control reached 78.6%. Toxicity attributable to IOERT was detected in 14% of the patients, mainly transient pelvic pain and neuropathy in one case. Foley et al. [24] analyzed 32 patients treated with IOERT after surgery where 21 (65.6%) had primary locally advanced or recurrent cervical cancer. Seventeen of the thirty-two (53%) developed recurrent disease. Seven (41%) developed LR (pelvis), 6 (35%) RR (abdomen), and 4 (24%) distant failure after IORT. The 5-year actuarial LC rate was 73% for patients with microscopic residual disease and 71% for patients with gross residual disease. Grade 3 or 4 treatment-related (surgery, IORT, EBRT, and Ch) toxicity was seen in 15 patients (46.9%), one patient developed grade 3 peripheral neuropathy. They concluded that the volume of residual disease before IOERT is an important prognostic indicator, LR being more common in patients with gross residual disease at the moment of IOERT. IOERT is not a standard treatment. However, in some cases with residual disease the local control can be increased after surgical resection. Neuropathy appears to be a relatively common side effect when IOERT is used in the pelvis. IOERT after chemoradiation and surgery for the primary treatment of locally advanced cervical cancer should not be used off-protocol [6].

Recurrence in gynecological cancers

Defining the best therapeutic strategy for gynecological cancer recurrence is complex and challenging. IOERT could be a therapeutic option [5, 25]. Women with recurrent endometrial cancer can present an isolated vaginal recurrence, pelvic recurrence, or disseminated metastatic disease [26, 27]. In some cases of recurrence in the form of adenopathy, they could benefit from surgical salvage and IOERT [23]. Sole et al. [28] performed a review of 35 patients with lymph-node oligometastases of

gynecological cancer, where 18 were endometrial carcinoma cases who underwent radical surgery followed by IORT in cases of close margins R1, with a median follow-up of 55 months (2–148) the 5-year loco-regional control, disease-free survival (DFS) was 79% and 44%, respectively.

Dowdy et al. [17] described a series of 25 patients with recurrence of endometrial cancer treated with EBRT followed by surgical resection and IORT. The median survival was 57 months, LR within the IORT field and DR were observed in 4 (16%) and 6 patients (24%), respectively. Complications included peripheral neuropathy, functional ureteral obstruction, and fistula formation.

The main locations of the recurrences of cervical cancer are the central pelvis (cervix or vaginal vault), pelvic walls, parametria and nodal areas (pelvic or para-aortic). IORT has been used in the surgical bed after complete resection or on the remaining unresectable recurrence, mainly due to infiltration or adherence to vascular or other anatomical structures [23]. Barney et al. [16] analyzed 86 patients, where 73 (85%) had recurrent tumors. The 3-year LC was 56%. Sixteen patients experienced peripheral neuropathy, 4 ureteral strictures, and 4 intestinal perforations or fistulas. Arians et al. [29] analyzed 36 patients, where half of them had recurrent cervical cancer. The LC rate was 0% at 2 years and the reported neurological toxicity was 11%. Mahé et al. [30] analyzed 70 patients who had received IORT for pelvic recurrence of cervical carcinoma with a LC rate of 21%. The reported IORT toxicities were peripheral neuropathy (5/70) and ureteral stenosis (4/70).

In another study [31] in which 31/62 patients had recurrent cervical carcinoma, they presented a LC at 5 years of 65%. Due to the heterogeneity of the data, it is difficult to make a strong recommendation, as the available evidence reflects diverse results regarding LC. Possibly, adding IOERT to debulking surgery could provide a benefit of LC, especially in those cases in which the resection is incomplete or there is microscopic involvement of the margins.

The benefit of adding IORT to surgical resection of recurrent ovarian carcinoma is even more controversial [23]. Yap et al. [19] analyzed 22 patients with ovarian carcinoma after surgery and IORT. The locoregional relapse rate was 32%. Nine patients (41%) experienced Grade 3 toxicities from their treatments. Gao et al. [32] analyzed 45 patients with a local failure of 32%, although the majority occurred out-field (10/14). Peripheral neuropathy was observed in 11% of patients and hydronephrosis in 4% of cases. Barney et al. [33] published a series of 20 cases of ovarian cancer recurrence. The IOERT zones were the pelvis (14/20), para-aortic and inguinal lymph-nodes (6/20). The probability of global-LC at 5 years was 59% and neural toxicity was reported in three cases (15%).

The addition of IOERT to salvage resection for isolated recurrence of gynecologic cancers has not been evaluated prospectively. Retrospective data do not conclusively suggest that the addition of IOERT improves outcomes, but suggest favorable local control in cases with concern for residual microscopic disease. Prospective studies are needed to determine which subgroups of patients with recurrent gynecologic cancer may benefit from IOERT.

Limitations to study

Our series presents a small and heterogeneous number of patients, but in comparison with the other studies, our recruitment was carried out in a short time, from January 2014 to February 2019. Because of the retrospective study design, clinical interpretation of our statistical results should be made with caution.

Conclusions

IOERT could have a role in the treatment of retroperitoneal sarcomas in primary tumors after EBRT, as it may suggest a benefit in local control or in recurrences after surgical resection in those at high risk of microscopic residual disease. And the addition of IOERT to salvage resection for isolated recurrence of gynecologic cancers has not been evaluated prospectively. Retrospective data do not conclusively suggest that the addition of IOERT improves outcomes but suggest favorable local control in cases with concern for residual microscopic disease. Prospective studies are needed to determine which subgroups of patients with recurrent gynecologic cancer may benefit from IOERT.

Conflict of interests

All authors declare that they have no conflict of interest.

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All the patients signed informed consent form.

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