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Customized treatment of recurrent gynaecological cancer - the need for intraoperative radiation therapy

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Summary

Objective: The objective of this retrospective study was to analyze the experience with intraoperative radiation therapy (IORT) at the present institution and to evaluate its contribution to the management of patients with recurrent gynecological cancer. *Materials and Methods:* Retrospectively this study reviewed data of patients with a gynecological malignancy considered for treatment with IORT at Freiburg University Medical Center between 2005 and 2012. For this purpose, an analysis of medical records, radiation oncology records, operation reports, and follow-up data was conducted. *Results:* During the period of this study, 31 women with gynecological cancer underwent tumor resection in combination with IORT. The median age of the patients at the time of IORT was 62 years (range 38-85). Most patients had undergone surgery at the time of initial diagnosis (87%). More than one-third of the patients received prior radiation therapy. In addition to that, 52% of the patients had already received chemotherapy. The majority of patients suffered from the first relapse of their disease. The local recurrence was predominantly located at the pelvic side wall (32%) or in intra-abdominal lymph nodes (32%). In 12 patients the authors did not apply the planned IORT. Intraoperative complications were rare and IORT was tolerated without severe side-effects. Follow-up was 14 months (range 1-65), progression free survival (PFS) was five months (range 3-31). *Conclusions:* In carefully selected patients, IORT and cytoreductive surgery contributed to local control and disease palliation. The authors therefore consider IORT an important aspect of modern cancer treatment.

Key words: Intraoperative radiation therapy (IORT); Recurrent gynecological cancer; Surgery.

Introduction

The prognosis of patients with recurrent gynecological cancer is poor: The five-year survival rate among patients suffering from a pelvic recurrence is 0-25%, depending on the primary tumor site. For patients with cervical cancer it is ≤ 5% [1, 2]. Local failure is described as the most important site for recurrence, despite radical surgery [3]. The loco regional recurrence of cervical or endometrial cancer is the principle cause of death in 60% of patients [1, 2]. However, studies show that optimizing local control, as, for instance by pelvic exenteration, significantly improves survival rates and quality of life [4-6]. Moreover, women who had undergone optimal surgical debulking are found to have a reduced risk of distant metastases [1, 3, 7].

To achieve local control in situations of disease recurrence, external beam radiation therapy (EBRT) with or without chemotherapy is often recommended. However, the dosage of the radiation therapy is often limited due to prior EBRT. An aggressive EBRT often tends to exceed the tolerance of surrounding tissues and can lead to severe treatment-related complications [8]. If an EBRT is possible, the radiation dose depends on the amount of radiation used, and the time interval passed since the previous treatment. Furthermore, the anatomical location of the recurrence in relation to surrounding organs is deemed to play a role [1, 9].

Another treatment option is surgery. However, only a selected group of women benefit from extensive tumor resection or exenterative surgery for recurrent disease [5]. Furthermore, microscopic or macroscopic residual tumor might not be treatable with ERBT because of the location and its surrounding tissues or due to prior EBRT [5]. In those cases, intraoperative radiation therapy (IORT) serves as a further treatment option. By mobilization or shielding of normal tissues from the radiation field, a higher dosage can be directed to the area with the highest risk of local recurrence, while minimizing damage to surrounding tissues. The combination of surgery with IORT achieves better long-term local control and overall survival than surgery alone [3, 7, 10]. Still, the success of this combined treatment depends on the skill of the surgeon [11]. Patients with optimal surgical resection at the time of IORT had a higher disease-free and overall survival compared to those with gross residual disease. Furthermore, their risk for distant metastasis was reduced significantly (33 *vs.* 82 %) [12].

IORT can be realized through different techniques. Electron beam radiation is delivered by a linear accelerator and directed to the radiation field with a cone of size suitable for

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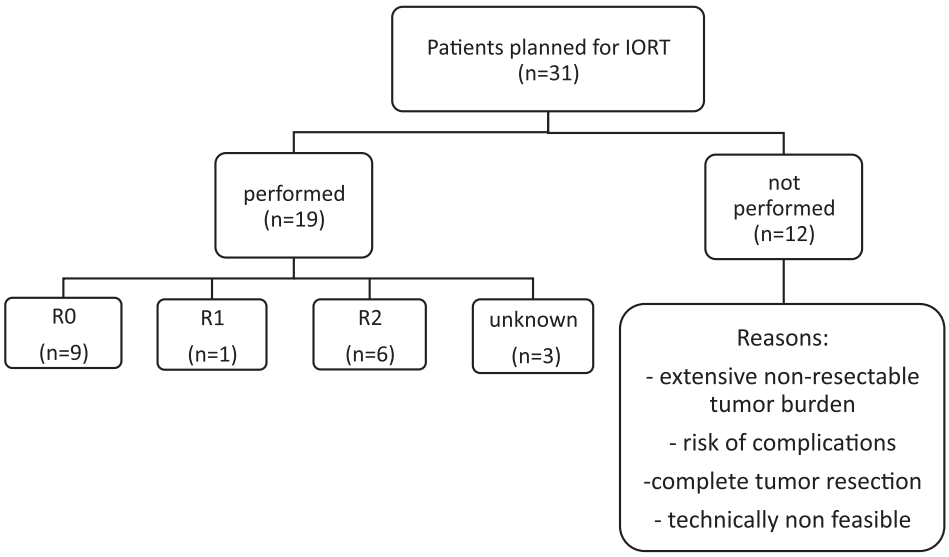

Figure 1. — Overview of both treatment groups.

the tumor bed. A common range of electron energies is between six to 18 MeV. A different technique is a high-dose-rate (HDR) brachytherapy, which uses a flexible applicator that can be adapted to match the tumor bed. In this case, the source of radiation is Iridium-192. In both cases, the radiation has to be administered in a shielded operating theatre for radiation protection. In recent years, mobile linear accelerators have been developed, which can be used in standard operation rooms without any other special fixed shielding systems.

Generally, IORT is well tolerated. Data suggest no increase in severe complications with the use of IORT compared to surgery alone [13]. The main dose-limiting toxicity of pelvic IORT is described to be peripheral neuropathy and ureteral stenosis. [14]

The objective of this retrospective study was to analyze the experience with IORT at the present institution and to evaluate the contribution of IORT to the management of patients with recurrent gynecological cancer.

Materials and Methods

Retrospectively this study reviewed data of patients with a gynecological malignancy considered for treatment with IORT at Freiburg University Medical Center between 2005 and 2012. For this purpose, an analysis of medical records, radiation oncology records, operation reports, and follow-up data was conducted.

The patients selected for this study were required to satisfy the following criteria before they were eligible for IORT: diagnosis of loco-regional recurrence or locally advanced gynecological cancer with no evidence of distant metastases. Another selection criterion was the absence of co-morbidities that would preclude aggressive surgical treatment. For these patients, surgery alone was not expected to provide acceptable local control. External beam radiation therapy (EBRT) was not available as a treatment option for these patients, either because it would have exceeded the dose tolerated by surrounding tissues or because of prior EBRT.

The eligibility of patients for IORT was initially evaluated at the tumor board and multi-disciplinary approval was obtained. Pretreatment evaluations included medical history, physical examination including gynecological examination, routine laboratory studies, and computed tomography or magnetic resonance imaging to estimate the extent of the local recurrence and to exclude distant metastases. Patients gave informed consent.

Follow-up data were obtained through routine follow-up in the present hospital (mean 22 months, range 1-65 months). The follow-up data included physical examination, gynecological examination, imaging and tumor markers when appropriate (e.g. CA 12-5).

During the operations, which took place in a dedicated shielded operation room, the surgeon and the radiation oncologist defined the IORT fields (i.e. tumor bed) after resection of the tumor. The histology was confirmed by frozen section. IORT was administered in case of positive surgical margins and in cases, in whom a postoperative EBRT was not feasible or in cases of negative margins to avoid postoperative EBRT.

The dedicated operation room contained a radiation unit. For directing the electron beams to the tumor bed, circular cones in different sizes and with straight and beveled ends were used. After identifying the IORT field, uninvolved organs and tissues were packed out of the radiation field and delicate structures (e.g. ureter) were shielded with lead strips. During radiation, which only took two to three minutes, the surgical team left the operation room. The patients were monitored by camera and surveillance of the vital parameters. IORT was administered with a median of 15 Gray (range 8-18Gy).

Results

During the period of this study, between 2005 and 2012, 27 women with gynaecological cancer underwent tumor resection in combination with IORT (Figure 1). Of these 27 women, four were scheduled for IORT treatment twice during this period, thus a total of 31 cases were eligible for IORT. In 30 cases, a localized recurrence of the cancer was diagnosed. One patient suffered from locally advanced pri-

Table 1. — *Patient characteristics.*

		n	%
Patients		31	100
Age (years)	median	62	
	range	38-85	
Origin of cancer	ovarian	7	22.6%
	ovarian+uterus	1	3.2%
	cervical	5	16.1%
	uterus	8	25.6%
	leiomyosarcoma	5	16.1%
	vulva	2	6.5%
	fallopian tube	1	3.2%
	malignant mixed Müllerian tumor	1	3.2%
	granulosa cell tumor	1	3.2%

Table 2. — *Prior therapy (EBRT, ICRT, and IORT).*

		n	%
Surgery	yes	27	87.1%
	no	1	3.2%
	unknown	3	9.7%
Radiation	EBRT	10	32.3%
	ICRT	7	22.6%
	IORT	2	6.5%
	none	15	48.4%
	unknown	3	9.7%
Chemotherapy	yes	16	51.6%
	no	12	38.7%
	unknown	3	9.7%

mary vulvar carcinoma as primary disease. The median age of the patients at the time of IORT was 62 years (range 38-85).

The site of the primary tumor was the ovary in seven patients (23%), the uterus in eight patients (26%), the cervix in five patients (16%). Five patients were diagnosed with leiomyosarcoma of the uterus (16%), two patients suffered from a vulvar carcinoma (6.5%), and one patient each from a fallopian tube cancer, a malignant mixed Müllerian tumor, a granulosa cell tumour, and one patient from a coincidence of an ovarian and endometrial carcinoma. For details see Tables 1 and 2.

Most patients had undergone surgery at the time of initial diagnosis (87%). More than one-third of the patients received prior radiation therapy, i.e. EBRT in 31%, ICRT (intracavitary radiation therapy) (23%) or IORT (7%). Of these patients, eight had even received a combination of the three radiation modalities. In addition to that, 52% of the patients had already received chemotherapy.

Most of the patients had their first relapse (45%), seven patients suffered from their second relapse (23%), and only one patient had a primary diagnosis of an advanced vulvar carcinoma. The local recurrence was predominantly located at the pelvic side wall (32%) or the intra-abdominal lymph nodes (32%) (Table 3). Surgery

Table 3. — *Diagnosis at time of IORT.*

		n	%
Location of recurrence	pelvic wall	10	32.3
	vaginal stump	2	6.5
	pelvic floor	2	6.5
	lymph nodes	10	32.3
	multifocal intra-abdominal recurrence	3	9.7
	mesentery fat	1	3.2
	unknown	3	9.7
Number of recurrence	primary diagnosis	1	3.2
	1st	14	45.2
	2nd	7	22.6
	3rd	5	16.1
	4th	1	3.2
	unknown	3	9.7

consisted of local tumor excision (45%), extensive tumor resection (16%), exenteration (3%), lymph node dissection (19%), radical vulvectomy (3%) or explorative laparotomy (3%). With these operations, the authors achieved a macroscopically complete tumor resection in 55% of the patients. Out of all patients 7% had a microscopic residual tumor and in 26% of the patients, a macroscopic tumor burden remained at the end of the operation. Nineteen patients were treated with IORT with a median dose of 15 Gy (range 8-18 Gy). The most common target of the IORT was the pelvic sidewall. In 12 patients the authors did not apply the planned IORT due to complete tumor resection (n=6), an extensive non resectable tumor burden (n=1), tumor burden in several different locations (n=2), the risk of complications (n=1) or because it was not technically feasible (n=1). The median duration of surgery was 290 minutes. Intraoperative complications consisted of one bowel lesion, one ureter lesion, and two patients with a blood loss exceeding 500 cc. IORT was tolerated without severe side-effects. The authors diagnosed a postoperative thrombosis in one patient. Furthermore, two patients suffered from bowel obstruction, which was treated conservatively. As all patients received multimodal therapies, it was difficult to assign single side-effects or complications to IORT. They did not observe complications historically associated with IORT (e.g. neuropathy and ureteral stenosis) (Table 4).

After tumor resection and IORT, six patients received external beam radiotherapy (31,6%), two patients received chemotherapy, and two patients anti-hormonal treatment. For six patients, no further therapy was necessary after surgery. In the non-IORT group, three patients had EBRT (25%), three had chemotherapy (25%) and five patients received no further treatment (41.7%) (Table 5).

Follow-up was 14 months (range 1-65), progression-free survival (PFS) was five months (range 3-31). The median PFS for the non-IORT group was seven months (range 3-

Table 4. — *Surgical data.*

		n	%
Extent of surgery	local excision	14	45.2
	gross total	5	16.1
	exenteration	1	3.2
	lymphadenectomy	6	19.4
	vulvectomy	1	3.2
	explorative laparotomy	1	3.2
	unknown	3	9.7
Residual tumor	R 0	17	54.8
	R 1	2	6.5
	R 2	8	25.8
	unknown	4	12.9
IORT field	pelvic sidewall	11	57.9
	pubic bone	1	5.3
	pelvic floor	1	5.3
	para-aortic region	2	10.5
	para-iliacal region	3	15.8
	unknown	1	5.3
IORT dose (Gy)	median	15	
	range	8-18	
operation time (min)	median	290	
	range	60-624	
Intra- and postoperative	complications		
	obstructive ileus	2	6.5
	thrombosis	1	3.2
	ureter lesion	1	3.2
	blood loss > 500ml	2	6.5
	bowel lesion	1	3.2
	none	21	67.7
	unknown	3	9.7

Table 5. — *Postoperative treatment.*

	IORT (n=19)	non-IORT (n=12)
Chemotherapy	2 (10.5%)	3 (25 %)
Radiation	6 (31.6%)	3 (25 %)
Anti-hormonal therapy	2 (10.5%)	0
No therapy	6 (31.6%)	5 (41.7%)
Unknown	3 (15.8%)	1 (8.3%)

31) and for the IORT group it was five months (range 3-14). This may be due to missing follow-up data. The authors had no information about the progression of the disease in 13 of 31 patients (42%). In patients with no residual disease, the median PFS was seven months, regardless whether they received IORT or not. In patients with complete tumor resection receiving IORT, the median PFS was ten months.

Discussion

The authors presented a retrospective analysis of patients with a relapse of a gynecologic malignancy eligible for treatment with IORT at Freiburg University Medical Center between 2005 and 2012. This group of patients is commonly known to have a poor prognosis [5], and EBRT alone often provides insufficient local control [15]. Furthermore, most patients falling into this group generally have already received multimodality therapy, including surgery, EBRT, and chemotherapy. In the present study, more than one-third of the patients had already received radiation therapy. This implies, that the dose of EBRT necessary to secure local control exceeds the radiation tolerable to surrounding structures [8, 9]. For these patients, IORT is a valuable therapy option, especially because it achieves a better outcome than surgery alone [10]. Data suggests an improved outcome for patients with microscopic residual tumor burden at time of IORT [12, 16]. Therefore, loco-regional control depends on the skill of surgeons, because complete gross resection improves long-term local control and decreases risk of toxicity as lower doses of IORT can be utilized [11, 12]. With the residual disease at the time of IORT being the main prognostic factor for local control [1, 3, 7], a thorough patient selection is essential [17]. The present findings are coherent with this literature review as the longest median PFS was observed in with complete tumor resection at the time of IORT.

Given the poor prognosis and high risk of tumor-related morbidity toxicities are acceptable. The present authors did not observe severe complications that were clearly associated with IORT but rather with surgery itself.

Limitations of the study include first of all the small size of the sample that was analyzed retrospectively. There was no systematic re-evaluation of these patients. Although the present patients were treated uniformly in the same IORT-dedicated surgical theatre with the same radiation equipment and under similar conditions, the heterogeneity of the patients represents an obvious limitation. The patients differed according to their primary tumor site, the treatment received prior to and after the IORT, and the location and size of recurrence. Furthermore, the authors were not able to obtain follow-up data for more than one-third of the patients. Therefore, and because of the small cohort and subsequent third and fourth line therapies, efficacy data for IORT cannot be provided. Moreover, the long time span of the present retrospective analysis might have produced confounding effects due to improvements in diagnosis and changes in treatment regime.

To conclude, IORT and cytoreductive surgery contribute to local control and disease palliation in carefully selected patients. Future studies, which would have to be multi-institutional to achieve adequate patient numbers, should focus on defining guidelines for patient selection. The present results suggest that the combined approach is particularly suitable for women who received prior conventional radiotherapy and were therefore not eligible for further external beam treatment. Furthermore, these pa-

tients should always be assessed regarding the operability, as the residual tumor burden is the most important factor of success of local control achieved by IORT. For a selected group of patients, IORT can prolong the progression-free interval and can therefore delay the necessity for further treatment. Moreover, it enables us to set aside a line of chemotherapy, which can then be used later on in the course of the disease. Though efficacy data cannot be provided due to the aforementioned limitations, the authors consider IORT an important aspect of modern, tailor-made cancer treatment.

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