The Role of Intraoperative Radiation Therapy in the Management of Recurrent and Locally Advanced Gynecologic Cancers

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Abstract: For patients with locally advanced primary or recurrent gynecologic cancers, prognosis is poor. Doses of external beam radiation therapy required to treat either gross or microscopic disease in patients previously irradiated or treated surgically exceed doses that are tolerated by normal anatomic structures. Intraoperative radiation therapy allows maximal tumor control achievable with radiation while minimizing radiation exposure of dose-limiting surrounding structures. Intraoperative radiation therapy is a unique treatment modality, allowing direct visualization of the target volume during a planned surgical procedure. Intraoperative radiation therapy has the potential to improve both long-term local control and overall survival especially in patients with para-aortic and/or pelvic sidewall recurrences.

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The prognosis for women with locally advanced primary or recurrent gynecologic malignancies is poor especially when the tumor extends to the pelvic sidewall or involves lymphatic dissemination to pelvic or para-aortic lymph nodes. In as many as 60% of patients with cervical or endometrial cancer, local failure is the primary cause of death.[1,2] Exenterative surgery may be curative for only a selected group of patients with locally recurrent disease confined to the pelvis.[1] The role of intraoperative radiation therapy (IORT) in the management of these malignancies may be beneficial in the treatment of some of these malignancies. Significant progress in the technical, clinical, and experimental application of IORT has been made in the last 30 years. The use of IORT has been greatly facilitated by the design of dedicated linear accelerator operating rooms, high-dose brachytherapy suites, and mobile linear accelerators. Intraoperative radiation therapy has increasingly become a treatment modality option for patients with pelvic, abdominal, head and neck, thoracic, and most recently, breast cancers.[3–9]

Dose constraints to normal structures limit the amount of tolerable external beam radiation therapy (EBRT) than can be safely delivered to the pelvis. Doses of radiation required to control microscopic or gross residual disease often exceed the dose that can be safely tolerated by normal structures.[2,3] Radiation doses of 45 to 54 Gy, delivered in fractions of 1.8 Gy, can be safely administered.[1] After gross surgical resection, radiation doses required to treat residual disease, which may be in excess of 60 Gy, are too high and carry the risk of unacceptable toxicity.[4,5] A high degree of toxicity is seen especially in cases where the tissue to be irradiated has been previously surgically manipulated or radiated.[3]

Intraoperative radiation therapy is a unique treatment modality, allowing direct visualization of the target volume during a planned surgical procedure, that is, the tumor bed of

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interest is radiated during the planned operation. Intraoperative radiation therapy permits direct visualization of the target volume, which in turn results in more precise mapping of the field to be irradiated.[2,6,7] Intraoperative radiation therapy allows shielding of normal structures away from the radiation field. Thus, the total dose of radiation that can be safely delivered can be increased while the radiation to normal tissue and its associated morbidity can be diminished.[6,8] Intraoperative radiation therapy can sufficiently deliver high doses of radiation with minimal exposure to other organs such as the bladder, rectum, small bowel, ureters, and kidneys.[7]

Single-dose IORT has 2 to 3 times the biologic effect of fractionated radiation therapy.[1] For example, a dose of 15 Gy of IORT is equivalent to 30 to 45 Gy of fractionated EBRT.[1] Once all resectable tumor is debulked, IORT can be used to sterilize the remaining tumor nests.[6] Although newer radiation technologies are briefly mentioned here, such as intensity-modulated radiation therapy, the primary focus of this review is delivery of radiation therapy intraoperatively.

PATIENT SELECTION

Patient candidacy for IORT should be evaluated by a multidisciplinary team, including gynecologic and radiation oncologists.[5] The patient's initial assessment should include a history and physical examination, as well as evaluation of pelvic tumor involvement, which in some cases may require an examination under anesthesia.[5] Workup should also include pertinent laboratory evaluation, including a comprehensive blood count, liver function tests, and blood chemistries.[1,5] Imaging studies may include chest and abdominal/pelvic computed tomography (CT), pelvic magnetic resonance imaging, and integrated CT and positron emission tomography, so as to delineate the anatomy of the tumor to be treated and exclude distant metastases.[1,5]

Intraoperative radiation therapy is most appropriate as part of a multimodality therapy for locally advanced cancers when anatomic and normal tissue location constrain. Selection criteria of patients with gynecologic malignancies who may be appropriate candidates for treatment with IORT have been delineated and include the following:[1–5]

- Patient's medical condition must permit major surgery
- Surgery alone would not result in acceptable local control. Microscopically positive margins would likely exist if surgery alone were to be performed.
- Patients with distant metastases are excluded (including peritoneal seeding).

The anatomic location to be treated should be amenable to direct intraoperative treatment of the tumor bed, with minimal exposure of normal structures.[4,5] Dose-limiting tissue, such as the small bowel, for example, can be temporally displaced at the time of IORT to optimize the therapeutic ratio between curative intent and complications.[2] In summary, ideal patients for IORT are those whose tumors are amenable to complete surgical resection or resection down to microscopic residual disease without evidence of metastatic disease.

RADIATION THERAPY DELIVERY TECHNIQUE

Several studies have documented the short- and long-term tolerance, as pertinent to volume and dose, of normal tissues irradiated with IORT.[9,10] Single large fractions of radiation (10–20 Gy) can be safely delivered at the time of surgery.[9,10] Previously, patients eligible for IORT were transported from the operating room to the radiation suite while under general anesthesia for this type of treatment. The design of dedicated linear accelerator operating rooms has been a major innovation in the field, leading to wider adoption of the treatment modality.

The primary goal of IORT is to irradiate the exposed tumor or tumor bed directly delivering a higher dose to the tumor, while minimizing dose to normal structures.[9] By delivering the radiation during a surgical procedure, IORT allows shielding of normal tissue away from the radiation beam. Furthermore, delivery of radiation at the time of surgery facilitates a more precise treatment with more accurate delineation of high-risk areas at the time of IORT delivery.[9,10]

Given that IORT is delivered at the time of surgery, it is given as a single fraction.[9] Biologically, this dose is likely equivalent to at least a dose 2 to 3 times greater than the equivalent dose given by conventional fractionated radiation.[9] The dose is calculated based on the following factors: tumor burden remaining after surgery, depth of target volume, location of dose-limiting structures, and degree of previous irradiation in the patient.[1,4,5]

The IORT dose is usually calculated at the 90% isodose line.[5] Electron energies range from 6 to 18 MeV.[10] The electron energy level selected varies based on the tissue thickness. The dose delivered depends on the amount of residual disease and radiation therapy the patient may have received in the past or will receive.[1,4,5] For example, if the patient has been treated with EBRT in the past with a dose of 45 to 50 Gy or will be irradiated postoperatively at this dose, microscopic residual disease can be treated with IORT doses of 10 to 15 Gy.[1,4,5,9,10] Doses of 10 to 20 Gy result in high rates of local control in patients with solid tumors, especially in the setting of microscopic residual disease.[9,10] These dose levels, per preclinical and clinical studies, represent the maximal tolerated dose for bone, soft tissue, ureters, and peripheral nerves.[9,10] Higher doses in the order of 15 to 20 Gy may be necessary to irradiate gross residual disease.[5,10] Doses in excess of 15 Gy may be appropriate in the treatment of patients previously irradiated with high-dose EBRT or in those who cannot receive full-dose EBRT.[4,5,9]

The applicability of IORT has been limited by limitations and perceived constraints of the intrinsic inefficiency that results with delivery of IORT in nondedicated facilties.[9] While still under anesthesia, patients were transported with an open abdomen from the operating room to the radiation oncology suite where they were treated with nondedicated linear accelerators.[9] The design of dedicated facilities has simplified treatment, with dedicated IORT suites within or

adjacent to the operating room.[5,9,10] These dedicated suites obviate the need to transport the patient and ensure continued sterility of the surgical field.[9] These efforts, however, have been limited by the cost associated with the design of a dedicated treatment suite, such as retrofitting the operating room with appropriate shielding, purchasing a linear accelerator dedicated for IORT use, and constructing a separate suite adjacent to the operating room, for example.[5,9]

The development of new technologies offers a more cost-effective alternative.[9] For example, mobile IORT and high-dose rate IORT (HDR-IORT) units allow for the delivery of this technology, circumventing the need for room construction or specific shielding requirements.[9] The HDR-IORT units, for example, use an iridium-192 source. These units are remote afterloading devices that use flexible applicators of different sizes that can adjust to any curved surface in the abdomen, pelvis, chest, and other locations.[9] Other innovative radiation technologies include stereotactic body radiation therapy, intensity-modulated radiation therapy, intensity-modulated arc therapy, and image-guided radiation therapy (IGRT), which can be delivered either during or immediately after surgery. In stereotactic body radiation therapy, a specially designed coordinate system is used for the exact localization of tumor lesions to treat this target with a high degree of precision. Stereotactic body radiation therapy involves the delivery of a single high-dose radiation treatment or a few fractionated radiation treatments (usually up to 5 treatments).[9] Intensity-modulated radiation therapy uses advanced computer programming to plan a precise dose of radiation in 3 dimensions before every treatment. Three-dimensional planning permits simultaneous treatment of multiple tumor lesions with different doses of radiation while minimizing radiation exposure to normal structures. Intensity-modulated radiation therapy results in a higher degree of accuracy in conformation of the radiation to the planned target while sparing normal tissue. Advantages of intensity-modulated radiation therapy are particularly evident when target volumes have complex shapes and concave regions or are adjacent to critical normal structures.[9] Intensity-modulated arc therapy uses multiple irregular fields shaped with conventional multileaf collimators during gantry rotation. Intensity-modulated arc therapy is planned as a series of static fields, every 5 to 10 degrees apart but delivered with multiple superimposing arcs. Within each arc, the multileaf collimator shape is dynamically changed as a function of gantry angle so that the cumulative intensity distribution leads to the calculated dose distribution.[9] The IMAT method delivers a more uniform, higher concentration of radiation to different sites during a relatively short period.[9] The IGRT technique involves the acquisition of 2- or 3-dimensional images before each treatment, tracking the location of the tumor and surrounding organs. For example, when IGRT is used in the treatment of prostate cancer, gold marker (fiducial) tracking is used with megavoltage portal imaging, fluoroscopy, abdominal ultrasound, or CT. In this setting, IGRT provides accurate localization of the prostate gland, which can vary on a daily basis.[9]

There are relative advantages and disadvantages of IORT and HDR-IORT techniques. Both treatment and procedure times are generally shorter with IORT when compared with HDR-IORT. Intraoperative radiation therapy permits variation of electron energies, allowing treatment of both superficial and deeper seated targets. The HDR-IORT is appropriate for targets less than 0.5 cm in thickness. For example, the flexible Harrison-Anderson-Mick applicator used in HDR-IORT allows more conformal treatment along curved body surfaces (eg, large pelvic sidewall fields, lateral abdominal wall, and thoracic cage), which may be hard to treat using the rigid IORT cone applicators. However, separate matching fields can be used to treat larger curved target areas with IORT-based cone applicators. A comprehensive intraoperative radiation program should ideally include IORT, HDR-IORT, and perioperative brachytherapy resources. That is, these treatment modalities should be viewed as complementary and not competitive.[9]

RESULTS AFTER CONVENTIONAL TREATMENT

Primary Disease

To understand the role IORT plays in the management of patients with gynecologic malignancies, survival rates in historical controls with pelvic malignancies are briefly reviewed here. Patients diagnosed as having either locally advanced primary or locally recurrent gynecologic cancers have a poor prognosis.[5,11]

Stage I cervical cancer treated primarily by either radical hysterectomy or EBRT and brachytherapy has an estimated 5-year survival rate of 90%.[12] Patients with stage II cervical cancer have a 75% to 90% estimated 5-year survival rate.[12] Reported 5-year survival rates when the primary tumor extends to the pelvic sidewall is 50% to 65%.[12] Primary cervical cancer involving the lymph nodes carries a worse prognosis, especially if the para-aortic lymph nodes are involved.[13] In patients with grossly involved but resectable pelvic nodes, relapse-free survival is estimated to be 57%, whereas pelvic failure rate is approximately 20%.[12,13] Patients with unresectable pelvic nodes have a reported 0% relapse-free survival and pelvic failure rate of 56%.[12,13] For women with cervical cancer who have either microscopic or limited volume para-aortic nodal involvement, long-term survival rates range from 25% to 50%.[12,13] The doses of EBRT required to achieve macroscopic disease control exceed what is tolerated by normal structures such as the small intestines.[1]

In a study of 117 patients with stage IB and IIA cervical cancer treated by radical hysterectomy and pelvic lymph node dissection, 51 patients (44%) had palpably involved pelvic lymph nodes.[14] Twenty-nine of the 51 patients received EBRT in the adjuvant setting. Thirty-two of the 51 women developed recurrent disease.[14] The site of recurrence included an extrapelvic component in 73% of these women.[14] The investigators concluded that given that radiation doses required to treat large-volume disease often exceed those tolerated by normal tissue, resection of macroscopic nodal disease may be important in improving local disease control.[14]

Although only 5% to 10% of patients with primary endometrial cancer present with disease extending beyond the uterus, those with unresectable disease have a poor prognosis. Treatment with EBRT and brachytherapy is associated with a high rate of pelvic failure. Disease confined to the pelvis is associated with a 5-year survival rate of 12% and a local relapse rate of 37%.[15] For patients with pelvic sidewall disease, 5-year survival rate has been reported to be 0%.[15] Similar to patients with cervical cancer, the prognosis in women with endometrial cancer involving lymph nodes is poor. Patients with endometrial cancer and positive para-aortic lymph nodes treated with extended-field EBRT have a 5-year survival rate of 40% to 60%.[15]

In patients with early-stage endometrial cancer not treated with adjuvant radiation therapy, salvage rates are high after EBRT for local recurrences.[16,17] In the PORTEC trial, 32 patients randomized to no further treatment developed a vaginal recurrence, with a reported 87% salvage rate.[16]

Recurrent Disease

Failure to control local recurrence has been reported as the principal cause of death in as many as 60% of patients with recurrent cervical or endometrial cancer.[12] The estimated 5-year survival rate for cervical cancer patients who have a pelvic recurrence is 5% or less.[12] Patients with locally advanced disease may require exenterative procedures, with reported 5-year survival rates ranging from 20% to 50%.[1,4] Pelvic exenteration may result in a fatal complication in as many as 10% of patients and in recurrence in another 30% of patients.[12] Patients with recurrent uterine cancer involving the pelvis have been reported to have a 5-year disease-free survival rate of 20% and pelvic control rate of 17%.[18] In those with endometrial cancer confined to the vagina, the estimated 5-year disease-free survival and pelvic control rates are 40% and 59%, respectively.[18] Patients in this series who developed pelvic recurrences had a reported 5-year disease-free survival rate of 20% and pelvic control rate of 17%.[18]

RESULTS AFTER IORT

Intraoperative radiation therapy has been used to treat both patients with primary and recurrent gynecologic malignancies. However, most of the experience has been obtained from treating locally recurrent lesions or isolated nodal disease, with a much more limited experience in treating primary gynecologic cancers.[5]

Primary Disease

Patients with primary gynecologic malignancies extending to the pelvic sidewall or locally advanced nodal metastases are ideal candidates for IORT.[5] Table 1 summarizes survival data from several studies. In the series by Delgado et al,[7] 16 patients with locally advanced cervical cancer were treated with IORT delivered to the para-aortic region. Eleven of these patients (69%) had involvement of these nodes. Two patients (12%) received EBRT to the para-aortic area.[7] The doses of IORT given ranged from 15 to 20 Gy. Four of the 11 women with positive lymph nodes (36%) were alive and 2 (36%) had no evidence of disease at 10 to 36 months of follow-up.[7]

The Mayo Clinic experience includes 8 patients with primary locally advanced gynecologic cancers, 7 of whom were also treated with either preoperative or postoperative EBRT.[3,4,17] Sixty-two percent of these patients had a local relapse at 5 years; 43% had a central recurrence at 5 years, and 36% had a distant relapse also at 5 years.[1,3,4,19] The reported median survival time was 12 months. Fourteen percent of these patients survived at 5 years, with a similar percentage of patients disease-free at 5 years.[1,3,4,19–21]

In a phase II trial, patients with stage IIA-bulky (>4 cm) to stage IVA locally advanced cervical cancer were treated with EBRT and concurrent chemotherapy followed by surgery and IORT.[22] After chemoradiation therapy, 35 (83%) of 42 patients in the study underwent surgery and IORT. Eight (23%) of the 35 patients had a complete response; 27 of 35 had residual disease either microscopic (17 of 27) or gross (10 of 27).[22] The authors reported a 5-year disease-free survival rate of 46% and an overall survival rate of 49%.[22] Importantly, all recurrences were seen within 24 months from treatment.[22]

Maximal tumor resection has been shown to improve survival and local control.[5] In the phase II study previously discussed, both disease-free and overall survival were significantly improved when residual tumor was absent or limited to the cervix, 78% versus 16% and 81% versus 20%, respectively ($P < 0.001$).[22] In the Mayo Clinic series, a 5-year survival rate of 42% was reported in cases of microscopic residual tumor.[1] In contrast, only 11% of patients with gross residual disease survived the same time interval.[1]

TABLE 1. Survival with IORT for treatment of primary gynecologic cancers

Reference No.	Primary Site	No. Patients	Median Survival, mo	Overall Survival, %	Disease-Free Survival, %
3,4,19	Cervix = 4 Vagina = 2 Endometrium = 1 Uterine sarcoma = 1	8	12	14/5 yr	14/5 yr
20	Cervix = 8	8	27	63/2 yr	—
21	Cervix = 20	20	18	75/1–3 yr	—
22	Cervix = 35	35	—	49/5 yr	46/5 yr

TABLE 2. Disease recurrence after IORT therapy in recurrent locally advanced gynecologic cancers

Reference	Primary Site	No. Patients	Local Relapse, %	Central Relapse, %	Distant Relapse, %
[3,4,19]	All sites	55	43/5 yr	31/5 yr	48/5 yr
	Cervix	36	50/5 yr	40/5 yr	58/5 yr
	Endometrium	10	22/5 yr	___	33/5 yr
	Others*	9	50/5 yr	___	33/3 yr
[24,25]	Cervix	70	75/3 yr	___	33/3 yr
[26]	Cervix (previous EBRT)	14	60/4 yr	22/4 yr	20/4 yr
	Cervix (no previous EBRT)	24	16/4 yr	5/4 yr	11/4 yr
	Others†	10	44/4 yr	33/4 yr	67/4 yr
[27]	All sites‡	36	44/5 yr	___	51/5 yr
[28]	All sites§	17	67/5 yr	___	54/5 yr

*Three vagina, 4 uterine sarcoma, 2 ovary.
†Four endometrium, 4 ovary, 2 vulva.
‡Seventeen cervix, 11 endometrium, 5 vulva, 2 vagina, 1 fallopian tube.
§Nine cervix, 7 uterus, 1 vagina.

Furthermore, these patients were also more likely to have distant metastases. Thirty-one percent of patients with microscopic residual disease developed distant metastases compared with 78% of patients with a gross residual disease.[1] The group of women with a gross residual disease had a reported median survival of 19 months compared with 36 months for patients with only a microscopic residual tumor.[1]

Recurrent Disease

Initial experience at the Massachusetts General Hospital suggested that IORT had a role in the management of locally recurrent gynecologic cancers.[23] In this series, 5 patients with recurrent cervical cancer were treated with IORT. Three of these women had been previously treated with EBRT.[23] The authors documented a survival rate was 40%.[23] Tables 2 and 3 summarize a review of the literature of relapse rates and survival data, respectively, for locally advanced recurrent disease.

The Mayo Clinic has reported treatment results of 55 women treated with IORT for recurrent gynecologic cancers.[3,4,19] Either preoperative or postoperative EBRT was used to treat 36 (65%) of these patients. Reirradiation doses ranging from 9 to 50 Gy was also used to treat 9 (32%) of 28 patients who had recurrence of their tumor after previous treatment with radiation therapy. Preoperative chemotherapy was given to 11 (39%) of 28 patients. The agents included methotrexate, vinblastine, doxorubicin, and cisplatin.[3,4,19] Gross total resection was achieved in 7 patients

TABLE 3. Survival results after IORT treatment in patients with recurrent locally advanced gynecologic malignancies

Reference	Primary Site	No. Patients	Median Survival, mo	Disease-Free Survival, %	Overall Survival, %
[3,4,19]	All sites	55	20	21/5 yr	29/5 yr
	Cervix	36	15	21/5 yr	25/5 yr
	Endometrium	10	56	17/5 yr	38/5 yr
	Others*	9	14	22/5 yr	33/5 yr
[24,25]	Cervix	70	11	___	8/3 yr
[26]	Cervix (previous EBRT)	14	7	___	7/4 yr
	Cervix (no previous EBRT)	24	38		47/4 yr
	Others†	10	19		30/4 yr
[27]	All sites‡	36	___	47/5 yr	42/5 yr
[28]	All sites§	17	___	54/3 yr	54/3 yr

*Three vagina, 4 uterine sarcoma, 2 ovary.
†Four endometrium, 4 ovary, 2 vulva.
‡Seventeen cervix, 11 endometrium, 5 vulva, 2 vagina, 1 fallopian tube.
§Nine cervix, 7 uterus, 1 vagina.

(64%). Preoperative chemotherapy was shown to improve disease-free interval. The *P* value, however, did not reach statistical significance. The reported median IORT dose was 20 Gy for gross residual disease and 15 Gy for microscopic residual disease. At 5 years, local relapse rate was 43%, central relapse rate was 31%, and distant relapse rate was reported to be 48%.[3,4,19] At 5 years, the overall survival rate was 29%, and the disease-free survival rate was 21%. Median survival was documented to be 20 months.[3,4,19]

Mahe et al[24,25] have reported one of the largest series of patients with recurrent cervical cancer treated with IORT. Forty of 70 patients were treated with IORT only. Twenty patients also received chemotherapy with either 5-fluorouracil and cisplatin or a cisplatin-containing regimen. Mean IORT dose was 18 Gy. Reported median survival was 11 months, with a local control rate of 21% at a mean follow-up time of 15 months.[24,25] Three-year overall survival rate was 8%, with 1- and 2-year survival rates of 47% and 17%, respectively. Fifty (75%) of the 70 patients had a local recurrence, whereas distant relapse rate was seen in 33% of women. Forty of these patients did not receive EBRT, and 37 of them had gross residual disease at the time of IORT.[24] The poor results reported in this study may reflect inclusion of all patients without selecting for tumor volume or site of recurrence.[24–26]

Tran et al[27] reported the IORT experience of 36 consecutive patients treated with IORT for recurrent gynecologic cancers. Mean follow-up was 50 months. Systemic therapy and EBRT after IORT was given to 24% and 53% of patients, respectively. Five-year local control rate, distant metastasis–free survival rate, and disease-free survival rate were 44%, 51%, and 47%, respectively. For the 17 patients with recurrent cervical cancer in this series, 5-year local control rate, distant metastasis-free survival rate, and disease-free survival rate were 45%, 60%, and 46%, respectively.

Investigators from the University of Navarre, Spain, have reported their experience with IORT in the treatment of 31 patients with locally advanced or recurrent cervical cancer.[26] Patients were treated with cisplatin and 5-fluorouracil and EBRT (40–46 Gy) followed by surgery with or without IORT to high-risk areas for recurrent disease.[26] The authors reported a complete or quasi-complete pathologic response to treatment in 74% of surgical specimens. A partial response was seen in 26% of specimens. At a median follow-up of 27 months, actuarial disease-free survival was 80%, with a locoregional control rate of 93.4%.[26]

IORT-RELATED TOXICITY

Intraoperative radiation therapy studies have failed to show increased morbidity to the surgical procedure when IORT is performed, that is, the reported toxicities may be related to long-term complications from IORT but not the operation performed. In approximately 35% of patients, complications were noted when patients were treated with only preoperative EBRT.[5] This complication rate was comparable to the reported 32% associated risk in patients receiving both EBRT and IORT.[8] Table 4 lists some of the most common toxicities associated with IORT.

Peripheral nerves seem to be the most dose-limiting structures in the pelvis and para-aortic regions.[1,8] Painful neuropathy rates published in the literature range from 5% to 30%[1] In 1 study, a 48% complication rate in patients treated with IORT is documented.[3] Six (29%) of 21 patients had complications directly related to IORT. Two patients had a gastrointestinal tract toxicity, 1 patient had vascular tissue toxicity, 1 had soft tissue injury, 2 had peripheral neuropathy, and 2 patients had ureteral toxicity from IORT.[3]

In another study, grade 3 or higher toxicity was seen in 36% of patients.[4] Twelve patients had a gastrointestinal tract complication, 6 had soft tissue toxicity, 4 had hematological toxicity, 1 had bone toxicity, 1 had vascular toxicity, and 2 had peripheral nerve injury.[4] Cumulative data from the IORT experience at the Mayo Clinic suggests a 17% risk of grade 3 or higher toxicity.[19] These authors report gastrointestinal obstruction or fistula in 8% of patients, soft tissue injury in 3%, and ureteral obstruction in 3%.[19] Some investigators recommend placement of ureteral stents immediately before IORT as prophylaxis whenever tumor is adherent to the ureter before the planned surgical procedure.[1]

Tran et al,[27] in their series of 36 patients, report a grade 3 to 4 complication-free survival rate of 72%. Ten patients experienced grade 3 to 4 complications. These included postoperative wound infection in 4, vesicovaginal fistula in 1, pulmonary embolism in 1, lower extremity edema in 1, urinary tract infection in 1, small bowel perforation in 1, and bilateral hydronephrosis in 1. The reported median time to the development of a grade 3 to 4 complication was 14 days (range, 0–72 months).[27] Gemignani et al[28] reported 4 incidents of gastrointestinal obstruction (24%), 4 wound complications (24%), 3 abscesses (18%), 3 peripheral neuropathy events (18%), 2 rectovaginal fistulas (12%), and 2 ureteral obstructions (12%) in their series of 17 patients treated with IORT.

CONCLUSIONS

For patients with locally advanced primary or recurrent gynecologic cancers, prognosis is poor. Doses of EBRT required to treat either gross or microscopic disease in patients previously irradiated or treated surgically exceed doses that are tolerated by normal anatomic structures.[1–5] Intraoperative radiation therapy can be part of the treatment armamentarium,

TABLE 4. IORT toxicity

Toxicity Site	Rate, %
Peripheral nerves	5–30
Ureter	3
Gastrointestinal tract	8–16
Soft tissue	1–2
Vascular structures	<1
Hematologic	1–2
Bone	<1

From Haddock et al,[1,19] Garton et al,[3,4] del Carmen et al,[5] Mahe et al,[24,25] Martinez-Monge et al,[26] Tran et al,[27] and Gemignani et al.[28]

allowing maximal tumor control achievable with radiation while minimizing radiation exposure of dose-limiting surrounding structures.[5] Intraoperative radiation therapy has the potential to improve both long-term local control and overall survival in patients with para-aortic and/or pelvic sidewall recurrences.[1,3–5] The most encouraging results have been documented in cases where IORT is delivered to microscopic residual beds after surgical resection.[3]

The experience with IORT further validates the importance of optical surgical resection.[5] Higher 5-year disease-free and overall survival rates have been reported for patients treated with IORT who had microscopic disease after surgical resection when compared with patients who had gross residual disease left in situ.[1,4] Review of institutional experiences with IORT may result in establishment of guidelines for appropriate patient selection.[5] These criteria may be helpful in guiding the design of clinical trials in the future. The construction, execution, and evaluation of clinical trials are mandatory to adequately assess the role of IORT in the management of patients with gynecologic cancers.

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