Locally Advanced Uterine Cancer: A Multimodality Model or Muddle?

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A 54-year-old gravida 3 para 3 postmenopausal woman female has a 1-year history of intermittent vaginal bleeding. Pelvic examination reveals a bulky 6-cm mass at the cervical os obliterating the vaginal fornices. Computed tomography of the abdomen and pelvis shows a heterogeneously enhancing mass in the cervix extending into the lower uterine cavity and

Fig. 1. $^{18}$F-Fluorodeoxyglucose positron emission tomography/computed tomography imaging on coronal view reveals hypermetabolic retrocrural and periaortic lymph nodes (yellow arrow). (A color version of this figure is available at www.redjournal.org.)
vagina, with extensive retroperitoneal lymphadenopathy involving periaortic and aortocaval lymph nodes. The mass is biopsied, and pathology reveals a high-grade carcinoma. Ancillary testing shows human papillomavirus 16/18 negative, p16 focally positive, vimentin strongly positive, estrogen receptor weakly positive, hepatocyte nuclear factor $1\beta$ positive, and carcinoembryonic antigen with rare positivity. This is consistent with a diagnosis of endometrioid endometrial adenocarcinoma with a minor component of clear cell carcinoma. Positron emission tomography/computed tomography scan (Fig. 1) shows a hypermetabolic intrauterine mass and fluorodeoxyglucose-avid pelvic, periaortic, and retrocrural lymph nodes, including a 2.8-cm left periaortic lymph node. There are no distant metastases. Magnetic resonance imaging of the pelvis (Fig. 2) shows a mass centered in the cervix extending inferiorly into the superior vagina and superiorly into the fundus of the uterus, with bilateral parametrial extension and nodular enhancement of the left adnexa concerning for left fallopian tube involvement. There is no extension into the bladder or bowel.

**Question**

What would be your first line of treatment for her?

- Chemotherapy?
- Definitive (chemo)radiation therapy?
- Preoperative (chemo)radiation therapy?

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*What would you do? Follow the discussion on Twitter at #gyzone, and take the poll at www.redjournal.org/poll.*
Surgery is the mainstay of treatment for most patients with endometrial cancer, but for patients with bulky disease centered on the cervix, radiation may be a better choice. In general, cervical cancers are considered more radiation sensitive than endometrial cancer and thus more amenable to definitive radiation therapy. However, the efficacy of radiation in cervical cancer may be more a function of the favorable anatomy of cervical cancers that makes it possible to create highly conformal dose distributions with brachytherapy. Brachytherapy applicators can be safely positioned to traverse and abut the cervix, creating a highly conformal dose distribution. If 80 to 90 Gy can be safely delivered, high rates of disease control of all histologies, including endometrial cancer, may be expected.

It is particularly useful in these cases to perform magnetic resonance imaging after the implant is in place, to define a target volume including the endometrial cancer, cervix, and any gross residual disease (1). The treatment plan can be optimized to determine whether sufficient dose can be delivered to this target while respecting normal tissue tolerances (2). It is often difficult to deliver sufficient dose to disease that lies distal to the source in the uterine fundus, owing to inability to pass the tandem past the fundus and source anisotropy. In this particular case the fundal disease seems to be limited to the endometrial canal. As long as the tandem is positioned at the apex of the endometrial canal, the full extent of initial disease may be safely treated to definitive doses. This approach has the advantage of avoiding the toxicity of hysterectomy after radiation, which we know can increase the risk of rare but serious complications, such as fistula (3).

Nodal disease in this case could also be managed similarly to nodal metastasis in a patient with cervical cancer receiving definitive chemoradiation. Outcomes have improved in recent years for women with involved para-aortic nodes, likely owing to advances in radiation technique and imaging (4). The presence of retrocrural adenopathy in this case does put this patient at high risk of developing distant metastasis. External beam targets in this case would include an internal target volume including the entire uterus, upper vagina, and parametria, as well as pelvic and para-aortic nodal CTVs. An integrated and sequential boost delivered at 2 Gy per fraction could be used to bring the total dose to gross nodal disease to a definite dose of 60 to 66 Gy. Bowel toxicity can be reduced by using small expansions on the gross tumor volume with the use of daily image-guided radiation therapy, evaluating dose to the duodenum and adapting the treatment plan to reduce the target volume in response to treatment (5).

Conflict of interest: none.

References


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Chemo-radiation, Then on to Surgery

Preoperative radiation was quite common before the ascendancy of total hysterectomy as the initial approach to uterine cancer, and it continues to have a role in situations in which the standard surgical approach is likely to result in incomplete clearance of gross disease, such as parametrial involvement (1, 2).

Radiation alone does have the ability to clear disease, though in preoperative series the pathologic complete response rate is 16% to 33% (3, 4). Admittedly, these pathologic complete response rates are with fairly modest doses of radiation used in the preoperative setting: generally 50 to 65 Gy given with either external beam alone or in combination with a low- to moderate-dose brachytherapy boost. However, it is often difficult to cover the entire uterine cavity with a standard tandem and ovoid implant, clearly more optimized for cervical cancer, and often multiple tandems or other intrauterine channels are required for adequate coverage with a comprehensive brachytherapy boost.

Because of these issues, for this patient we advocate for preoperative extended field radiation therapy, using intensity modulated radiation therapy or similar technique to treat the uterus, pelvis, and PA chain to 45 to 50 Gy, with boosts to the nodal disease to 55 to 65 Gy depending on normal tissue tolerance. Concurrent, weekly cisplatin may be used at 40 mg/m², especially considering the bulky nodal involvement (5). A subsequent uterine brachytherapy boost to a total dose of 65 to 70 Gy may then be used if there is incomplete clearance of the parametrial disease on physical examination or magnetic resonance imaging. Hysterectomy should then be delayed for at least 4 to 6 weeks after radiation to allow for full response from radiation and for the resolution of acute radiation effects (6). Given the para-aortic disease, 3 to 6 cycles of carboplatin and paclitaxel will be recommended postsurgically to reduce the risk of distant recurrence.

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References


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Chemo First, Then Radiation, and Perhaps Surgery

This lady has a clinical stage IIIB endometrial cancer (involvement of vaginal wall) and image evidence highly suspicious for International Federation of Gynecology and Obstetrics stage IIIIC2 disease (para-aortic adenopathy) (1). In addition, magnetic resonance imaging also suggests parametrial spread of disease. Staging and/or debulking surgery is the standard initial therapy for endometrial cancer. In high-grade histology such as this case, an optimal outcome requires that staging surgery is comprehensive, and where extraterine disease is grossly apparent, all visible disease resected to R0 (no residual disease) (2). In this particular case initial surgery is inappropriate because R0 resection is highly unlikely and if attempted will be associated with unacceptable surgical morbidity. This patient will eventually require all 3 modalities of therapy utilized in treating endometrial cancer (chemotherapy, radiation therapy, and surgery). In my opinion the sequence of the modalities should be (a) chemotherapy, (b) radiation therapy, and depending on the response achieved from a and b, proceed with (c) surgery.

The reasons are as follows. First, systemic chemotherapy will shrink the local disease burden, treat the lymph node beds and treat possible disease in extraterine and extranodal locations that may not have been visible on the positron emission tomography/computed tomography scan. In Gynecologic Oncology Group protocol 33, gross intraperitoneal spread was highly correlated with pelvic and para-aortic nodal metastasis (3). Second, because of
shrinkage that is achieved by chemotherapy (4), when radiation is eventually started the target volume will be smaller, making radiation therapy more effective and potentially less toxic (5). Third, the only scenario that would justify radiation therapy as the first line of treatment would be troublesome (unmanageable) symptoms like severe pain and heavy vaginal bleeding, which she clearly does not have because her main symptoms are vaginal discharge and intermittent bleeding, which have been present for 1 year before presentation and therefore are unlikely to have been troublesome. Chemotherapy is the treatment modality that will drive this lady’s outcome.

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References


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