American College of Radiology
ACR Appropriateness Criteria®

ADVANCED CERVICAL CANCER

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Summary of Literature Review

Introduction

The management of advanced cervix cancer continues to evolve. The disease remains a severe worldwide public health problem. It is the second leading cause of cancer death in women worldwide with the majority of women presenting with advanced stage disease. The availability of advanced imaging, new radiotherapeutic modalities, and novel chemotherapeutic agents has gradually modified the standard of care for women with advanced cervix cancer.

Staging

Cervix cancer remains a clinically staged neoplasm. The Federation of Gynecology and Obstetrics (FIGO) recently updated the staging system for carcinoma of the cervix [1].

Due to historical precedence and lack of uniform availability of imaging, FIGO elected to continue using a clinical staging system. FIGO readily endorses the use of imaging such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) imaging for patient care. MRI has been demonstrated in numerous studies to be an excellent modality for assessing the extent of the primary neoplasm due to its excellent soft-tissue resolution, in contrast to CT. MRI is excellent for revealing parametrial infiltration and vaginal extension in addition to tumor size [2]. CT and MRI are not particularly useful for evaluating the sensitivity of lymph node involvement. A recent study demonstrated sensitivities of 36% and 35% for CT and MRI, respectively in women surgically staged for cervix cancer [3]. MRI is the preferred modality for evaluating endometrial involvement [2]. PET/CT has been shown to be superior to MRI in evaluating lymph node extension in cervix cancer [4,5]. Similarly, for evaluating extent of disease, PET/CT has favorable diagnostic accuracy for assessing metastatic disease [6,7]. The prognostic importance of PET imaging in detecting the regional or metastatic spread of cervix cancer has been documented [8,9]. (See the ACR Appropriateness Criteria topic on "Pretreatment Planning of Invasive Cancer of the Cervix".)

Treatment of the Primary in Advanced Cervix Neoplasms

The preferred modality for treating advanced cervix cancer is chemoradiotherapy. (See Variant 1.) Monk and Koh [10] in a recent review advocated that for tumors greater than IB1, the preferred primary treatment is chemoradiotherapy. Another relatively common treatment in countries where radiotherapy (RT) is not widely available is neoadjuvant chemotherapy followed by surgery. The Gynecologic Oncology Group (GOG) 141 was a prospective trial in 291 women comparing 3 cycles of vincristine and cisplatin followed by surgery to surgery alone. The hazard rates were 1.00 for recurrence and 1.01 for overall survival. The GOG concluded that there was no evidence of any objective benefit with neoadjuvant chemotherapy as delivered in this trial [11]. A randomized trial performed in China in 142 patients with stages IB2-IIB also failed on Cox hazard analysis to show a survival

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benefit for neoadjuvant therapy compared to surgery alone [12]. In this trial the overall clinical response rate was 69%. Worldwide, many women do not have access to RT. A recent meta-analysis of neoadjuvant chemotherapy and surgery compared to surgery alone in five trials evaluating data on over 900 women showed no survival advantage for the neoadjuvant chemotherapy design [13].

Neoadjuvant chemotherapy has demonstrated high response rates in cancer of the cervix, allowing local therapy to be delivered in a substantial proportion of women. In one recent experience in 39 women with stage IIIB cervix cancer the pathologic complete response rate was 34% [14]. A large meta-analysis has been done evaluating over 3,000 patients treated in 21 different randomized trials. In the 18 trials comparing neoadjuvant chemotherapy followed by radical RT versus the same RT alone, trials that employed a cisplatin dose intensity of ≥25 mg/m^2, and chemotherapy cycles of a fortnight or less tended to have improved survival [15], whereas trials that used a cisplatin dose intensity of <25 mg/m^2, and chemotherapy cycles longer than a fortnight tended to have impaired survival. This may be due to accelerated repopulation triggered by the early institution of chemotherapy. In the five trials comparing neoadjuvant chemotherapy followed by surgery versus RT, there was a highly significant reduction in the risk of death with neoadjuvant chemotherapy, but significant trial heterogeneity was noted.

In the developed world, the preferred modality for treating advanced cancer of the cervix is chemoradiotherapy. (See Variant 1.) A large trial is ongoing by the European Organisation for Research and Treatment of Cancer (EORTC) comparing chemoradiotherapy to neoadjuvant chemotherapy and surgery. Neoadjuvant chemotherapy followed by RT has been addressed in multiple trials, and in several studies this has resulted in inferior survival rates. The Cochrane meta-analysis concluded that this strategy could jeopardize survival unless a quick, dose-intense regimen is used [16]. This may be due to accelerated repopulation triggered by the early institution of chemotherapy [17].

The preferred dose of whole pelvic RT is approximately 45 Gy [18]. (See Variant 1.) Most clinical trials have used external-beam doses similar to this with an allowance for boosting areas of positive lymph nodes or positive margins. There have been no pure phase III dose escalation trials. In the absence of involved pelvic lymph nodes, the majority of respondents treat a large pelvic field with the upper border at the junction of L4-5 or the bifurcation of the iliac arteries from the aorta. The preferred external-beam modality has not been tested. In other words, two-dimensional RT versus three-dimensional therapy versus intensity-modulated radiation therapy (IMRT) has not been tested in a prospective fashion. Retrospective reviews point to the limitations of using boney landmarks alone, particularly with regard to nodal coverage. IMRT is not felt by the panel to be indicated for the routine treatment of cervix cancer at this time due to significant organ motion issues. Common beam arrangements for the three-dimensional treatment of cervix cancer include AP/PA and four-field approaches. When AP/PA fields are used, a high-energy beam is preferred. When lateral fields are used, three-dimensional planning can help to avoid marginal misses of the uterus and pelvic lymph nodes.

Nodal Treatments

The treatment of lymph nodes continues to evolve. The decision about performing surgical resection depends on the physician's choice, patient's performance status, location of tumor, and tumor size. The optimal dose for sterilization of lymph nodes in advanced cervix cancer continues to be refined. Most radiation oncologists prefer a dose of 60 Gy or greater with limited fields and with strict constraints placed on normal tissues. (See Variant 1 and Variant 2). Multiple investigators favor boosting positive lymph nodes with IMRT in an attempt to reduce the volume of normal tissue receiving high doses. No prospective trials have evaluated three-dimensional conformal RT boosts versus IMRT in this setting. It is unclear if surgical debulking or dose escalation will impact survival in patients with positive nodes as Grigsby et al concluded, as these patients fail more often from metastatic disease than from failure to control their nodal disease [19].

Chemotherapy

The optimal choice of chemotherapy is not defined. (See Variant 1.) In 1999, the National Cancer Institute of the United States released a clinical alert indicating that cisplatin-based chemotherapy improved overall survival in women with advanced cervix cancer. This was due to the simultaneous publication of five clinical trials, which all revealed a benefit for the combination of chemoradiotherapy with cisplatin-based treatment [20-24]. These treatments had a hazard rate favoring the chemoradiotherapy arm for risk of recurrence ranging from 0.54 to 0.74, with an overall improvement in survival increasing from 9% to 18% depending on the specific trial. More recently, a Cochrane meta-analysis demonstrated that survival was improved not only by cisplatin-based chemotherapy but also by trials using non-cisplatin-containing regimens [25,26]. Nevertheless, the National

Comprehensive Cancer Network (NCCN) guidelines favor the incorporation of cisplatin-based chemotherapy [26]. The optimal dose and scheduling of cisplatin is not established. However, the worldwide standard is currently 40 mg/m^2 of cisplatin administered weekly for 5-6 cycles [18].

Brachytherapy

In addition to external beam RT, the optimal management of advanced cervix cancer incorporates brachytherapy [27]. (See Variant 1 and Variant 3.) Eighty to 90 Gy low-dose-rate equivalent to Point A or to the high-risk clinical target volume as defined by the GEC-ESTRO guidelines is preferred [28]. Multiple trials have assessed the survival and toxicity of high-dose-rate brachytherapy versus low-dose-rate brachytherapy. A current meta-analysis evaluating five randomized trials and over 2,000 patients revealed no difference between high- and low-dose-rate brachytherapy for overall survival, local recurrence, and late complications in clinical stages I, II, and III [29]. Additionally, pulsed-dose-rate brachytherapy is used by several centers and is felt to have a biological efficacy to that of low-dose-rate brachytherapy [30]. Most radiation oncologists prefer tandem and ovoid brachytherapy devices (Viswanathan unpublished Gynaecological Cancer Intergroup (GCIG) survey). However, in the 1996-1999 Patterns of Care Study (PCS) study, 68.7% used tandem and ring for high-dose RT and 18.2% tandem and ovoids [31]. Dosimetry should be performed for every insertion to define and limit the doses to the critical organs at risk, including the bladder and rectosigmoid [32]. Interstitial brachytherapy is used by some radiation oncologists for patients with bulky disease, anatomical distortion, or vaginal extension of disease [33,34]. The panelists were supportive of image-guided brachytherapy (IGBT) as espoused by Potter et al [35]. In experienced hands, brachytherapy is able to be accomplished in more than 95% of cases. In instances where brachytherapy is not possible, external-beam boosting to the primary is preferred, delivering a dose from 64 to 75 Gy. No trials have evaluated the optimal beam arrangements using three-dimensional conformal RT versus IMRT versus particle therapy. Given the proximity of sensitive normal structures — namely bladder, rectum, and sigmoid — multifield arrangements are preferred.

Role of Hysterectomy after Definitive Radiation Therapy

Initial retrospective reports indicated a local control benefit for a simple hysterectomy after RT in patients with tumors >6 cm in diameter [36]. More recent retrospective reports have challenged the addition of adjuvant hysterectomy [37,38]. The GOG performed a randomized trial evaluating the benefit of adjuvant hysterectomy in 282 patients with stage IB tumors >4 cm in diameter [39]. There was no survival benefit for hysterectomy; consequently, it is not routinely supported by the panelists. (See Variant 4.) Additionally, the combination of surgery and RT has been shown to be more toxic than RT alone [40].

Follow-up of Patients

Standard follow-up of patients with advanced cervix cancer includes a clinical evaluation every 3 months for 2 years and then less often [26]. The majority of panelists favor obtaining a PET/CT scan at 3 months to evaluate the extent of disease. Surveillance imaging can lead to successful salvage of asymptomatic recurrences and is cost-effective following definitive therapy [41]. For patients who have a residual mass, appropriate workup and biopsy are recommended.

Treatment of Recurrence

For patients who have a recurrence at the primary in the central pelvis, the preferred management after full-dose chemoradiotherapy is evaluation by an experienced gynecologic oncologist for consideration of exenteration. (See Variant 4.) Favorable response rates have been observed with relatively low morbidity in several series for patients who have a central recurrence only [42,43]. For patients who have a recurrence involving the pelvic sidewall, there is little enthusiasm for extended surgical procedures. Other management strategies for patients with recurrent cervical cancer after full-dose chemoradiotherapy include repeat chemoradiotherapy. This may be more beneficial if significant time has elapsed since the primary treatment. Interstitial brachytherapy may be a particularly useful modality in this setting. The panelists felt that a repeat course of brachytherapy for recurrent disease may be beneficial if poor-quality RT was performed, such as prolonged treatment course, inadequate treatment fields, or suboptimal brachytherapy [44]. It may be worthwhile to consider sensitizing chemotherapy such as platinols, taxanes, or fluoropyrimidines, depending on previous chemotherapy. Another option for treating recurrent disease is chemotherapy alone. The GOG has documented that the most active single agent is cisplatin [45]. The combinations of cisplatin and topotecan have demonstrated an improvement in overall survival, and recently bevacizumab has shown promising activity in recurrent or metastatic cervix cancer [46,47].

Conclusions

- The combined use of imaging, advanced radiotherapeutic modalities, and chemotherapy has led to better treatment for cancer of the cervix.
- MRI and PET/CT are superior modalities for evaluating extent of disease.
- IMRT and IGBT are widely used to reduce dose to normal tissue.
- The addition of chemotherapy concurrently with RT has resulted in a large improvement in overall survival.
- PET scanning before and after chemoradiation can be pivotal in evaluating extent of disease and in detecting persistent or recurrent disease.
- Comparative clinical trials continue to be necessary to monitor our progress in the treatment of advanced cervix cancer.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Advanced Cervical Cancer**

Variant 1: **35-year-old woman with a 3 cm tumor and 5 cm left common iliac lymph node at the level of L5 by CT.**

Treatment	Rating	Comments
Staging Method		
FDG-PET/CT whole body	9	
MRI abdomen and pelvis	8	
Surgical	6	
Examination under anesthesia	5	
Cystoscopy	4	
Proctoscopy	4	
Treatment of Primary		
Chemoradiotherapy	9	
Induction chemotherapy followed by local treatment	2	
RT alone	1	
Radical hysterectomy	1	
Treatment of Lymph Nodes		
3D conformal RT	7	
IMRT	7	
Laparascopic lymph node dissection then RT	6	
Retroperitoneal lymph node dissection then RT	5	
Robotic lymph node dissection then RT	5	
Open laparatomy for lymph node dissection then RT	2	
Transperitoneal lymph node dissection then RT	1	
Type of Chemotherapy		
Concurrent	9	
Concurrent and adjuvant chemotherapy	5	
Neoadjuvant chemotherapy and concurrent CRT	2	
Neoadjuvant chemotherapy then surgery	2	
Adjuvant chemotherapy after surgery and nodal debulking (no RT)	1	
Chemotherapy		
Cisplatin	9	
Cisplatin and 5-FU	7	
5-FU	2	
Carboplatin and taxol	2	
Gemcitabine and cisplatin	2	
Other	2	

Initial Dose of Radiotherapy to the Pelvis		
<40 Gy	2	
40-45 Gy	7	
46-50 Gy	7	
>50 Gy	3	
Location of Upper Field Border for a Positive Common Iliac Lymph Node Patient with Negative Para-Aortic Lymph Nodes by PET/CT		
L1/T12	8	
L2/1	7	
L2/L3	5	
T12/L1	5	
L3/L4	3	
Dose to the Para-aortic Region when Treating Electively		
<40 Gy	1	
40-45 Gy	8	
46-50 Gy	6	
>50 Gy	1	
Dose of Brachytherapy (Cumulative Point A Low-Dose Equivalent)		
≤80 Gy	1	
81-85 Gy	8	
>85 Gy	7	
Type of Intracavitary Brachytherapy		
Low-dose-rate	9	
High-dose-rate	9	
Pulsed-dose-rate	6	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Advanced Cervical Cancer**

Variant 2: **40-year-old woman with a 5 cm, IIA adenocarcinoma with a 2 cm para-aortic lymph node.**

Treatment	Rating	Comments
External Beam Arrangement		
Four-field 3D conformal RT to the pelvis and para-aortic region	7	
Four-field 3D conformal RT to the pelvis and AP/PA to the para-aortic region	7	
Four-field 3D conformal RT to the pelvis and IMRT to para-aortic region	7	
AP/PA to the pelvis and para-aortic region	5	
IMRT to the pelvis and para-aortic region	3	
Nodal Boost Type		
3D conformal RT	8	
IMRT	8	
None	1	
Cumulative Nodal Boost Dose after 45 Gy		
<55 Gy	5	
56-65 Gy	7	
66-70 Gy	3	
>70 Gy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 3: **42-year-old woman with a stage IIIB squamous cell carcinoma 9 cm in size with bilateral hydronephrosis. After the initial 45 Gy, a 5 cm tumor remained.**

Treatment	Rating	Comments
Treatment		
Chemoradiotherapy	8	
RT	5	
Chemoradiotherapy followed by adjuvant hysterectomy	3	
Radical hysterectomy	1	
Type of Boost		
Tandem and ovoid	8	
MRI based image guided brachytherapy	8	
Tandem and ring	7	
Interstitial	7	
3D conformal RT	4	
IMRT	4	
Proton or other particle therapy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Advanced Cervical Cancer**

Variant 4: **28-year-old woman after chemoradiotherapy for a node-negative stage IIB squamous carcinoma that was 7 cm in size initially. Three months after definitive chemotherapy, a 2 cm residual mass is noted. She received 45 Gy to the pelvis followed by two low-dose-rate implants to a cumulative dose of 85 Gy to Point A.**

Treatment	Rating	Comments
Biopsy	9	
MRI pelvis without and with contrast	8	
FDG-PET/CT whole body	8	
CT abdomen and pelvis with contrast	6	
Re-evaluation in one month	1	
Simple hysterectomy	1	
Radical hysterectomy	1	
Management Options after Positive Biopsy		
Exenteration	8	
Chemotherapy	5	
Interstitial implant	4	
Radical hysterectomy	3	
RT	2	
Chemoradiotherapy	2	
Simple hysterectomy	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		