American College of Radiology
ACR Appropriateness Criteria®

DEFINITIVE THERAPY FOR EARLY STAGE CERVICAL CANCER

Expert Panel on Radiation Oncology–Gynecology: William Small Jr, MD[1]; Jonathan B. Strauss, MD, MBA[2]; Anuja Jhingran, MD[3]; Catheryn M. Yashar, MD[4]; David K. Gaffney, MD, PhD[5]; Higinia Rosa Cardenes, MD, PhD[6]; Beth A. Erickson-Wittmann, MD[7]; Norleena Gullett, MD[8]; Elizabeth Kidd, MD[9]; Larissa Lee, MD[10]; Nina A. Mayr, MD[11]; David Moore, MD[12]; Ajmel A. Puthawala, MD[13]; Gautam G. Rao, MD[14]; Mahesh A. Varia, MD[15]; Andrew O. Wahl, MD[16]; Aaron H. Wolfson, MD[17]; William Yuh, MD.[18]

Summary of Literature Review

Introduction

Although detection and treatment of cervical cancer are improving, the disease continues to impose a significant burden of morbidity and mortality. Worldwide, cervical cancer remains the fourth-leading cause of cancer death in women, and is especially common and onerous in the developing world where it is the second-leading cause of cancer death [1]. Advances in imaging, radiotherapy (RT), systemic therapy, and our understanding of disease biology offer new approaches to improve oncologic outcomes and reduce treatment-related toxicity. This document is based on a thorough literature review supplemented by expert opinion regarding the optimal practice in treating early stage cervical cancer.

Staging

Cervical cancer staging has been recently updated by the International Federation of Gynecology and Obstetrics (FIGO) [2]. This staging system remains primarily clinical in nature and restricts the incorporation of information gleaned from modern imaging. It reflects the lack of medical resources in some areas and also helps to preserve the applicability of historical series to current practice. However, FIGO does endorse the use of computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) and allows their findings to be used to guide therapy. An in-depth discussion of staging for cervical cancer can be found in the ACR Appropriateness Criteria® for "Pretreatment Planning of Invasive Cancer of the Cervix."

CT is an essential component for 3-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT) planning and has some utility in assessing the extent of cervical cancer spread. CT outperforms chest radiograph in evaluating pulmonary metastasis and the presence of pleural effusions. CT has only modest sensitivity and specificity in identifying parametrial invasion due to difficulty in differentiating between tumor and normal parametrial structures [3]. Similarly, the identification of involved lymph nodes is only moderately accurate with CT, likely owing to its reliance on a size-based criterion alone [4]. MRI provides superior soft-tissue delineation compared to CT and thus yields more a precise assessment of tumor size and local extension, including parametrial invasion, than either CT or physical examination [3]. MRI does not appear to exceed CT in accuracy of assessing cervical stromal invasion [5]. PET, especially when used in combination with CT, appears to offer a notable improvement in the detection of involved lymph nodes and distant metastatic disease [6]. However, a series evaluating the correlation between PET/CT identification of involved para-aortic lymph nodes and pathologic examination in women with stage IB or II disease found a false-negative rate of 8% for PET/CT [7]. The false-negative rate of PET/CT for involved para-aortic lymph nodes appears to be even higher in locally advanced disease [8]. Surgical staging may thus have a role in early stage cervical cancer, leading to changes in the treatment plan by detecting radiographically occult nodal metastases, more accurately defining appropriate

[1]Principal Author, The Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, Illinois. [2]Research Author, Northwestern University, Chicago, Illinois. [3]Co-author, University of Texas, MD Anderson Cancer Center, Houston, Texas. [4]Co-author, University of California San Diego, San Diego, California. [5]Panel Chair, University of Utah Medical Center, Salt Lake City, Utah. [6]Panel Vice-chair, Indiana University Medical Center, Indianapolis, Indiana. [7]Medical College of Wisconsin, Milwaukee, Wisconsin. [8]Indiana University Medical Center, Indianapolis, Indiana. [9]Stanford Cancer Center, Stanford, California. [10]Harvard Radiation Oncology Program, Boston, Massachusetts. [11]Ohio State Comprehensive Cancer Center-James Cancer Hospital, Columbus, Ohio. [12]Indiana University School of Medicine, Indianapolis, Indiana, American College of Obstetricians and Gynecologists. [13]Long Beach Memorial Medical Center, Long Beach, California. [14]University of Maryland School of Medicine, Baltimore, Maryland, American Society of Clinical Oncology. [15]University of North Carolina School of Medicine, Chapel Hill, North Carolina. [16]University of Nebraska Medical Center, Omaha, Nebraska. [17]University of Miami, Miami, Florida. [18]Ohio State University, Columbus, Ohio.

Reprint requests to: Department of Quality & Safety, American College of Radiology, 1891 Preston White Drive, Reston, VA 20191-4397.

volumes for radiation therapy, and, possibly imparting a therapeutic advantage by clearing a reservoir of disease [9,10]. Surgical clearance may be most appropriate in the treatment of bulky pelvic lymphadenopathy. Surgical staging may delay the start of RT due to wound healing, but the advent of laparoscopic nodal staging may allay this concern.

Treatment: Surgery versus Radiotherapy

Cervical cancer stage IB1 or below can be appropriately treated with either surgery or definitive RT. Only a single randomized trial has compared surgery to RT in early stage disease. Landoni et al [11] randomized women with IB or IIA cervical cancer to surgery with or without postoperative RT versus definitive RT alone. Postoperative RT was administered to 64% of women in the surgery arm. The two treatment arms yielded identical overall survival (OS) and disease-free survival (DFS), although severe morbidity was higher in the surgery arm (28% vs 12%), likely due to contributions from both treatment modalities. No trial has compared surgery to chemoradiotherapy. Both surgery and RT remain viable treatment options in early stage disease and the choice may depend on institutional experience. Surgery, which allows for better preservation of ovarian and sexual function and eliminates the risk of radiation-induced malignancies, may be preferable in younger women. Definitive RT or chemoradiotherapy is preferred in patients likely to require postoperative RT in order to avoid compounding treatment-related morbidity.

Radiotherapy Technique

Definitive RT for cervical cancer is typically delivered with external beam RT (EBRT) to the pelvis to approximately 45-50 Gy interdigitated with brachytherapy and lymph node boosts (if necessary). Although no randomized data evaluating the role of brachytherapy exist, it is considered to be an integral component of definitive RT, delivering high doses to the central tumor while preferentially sparing normal tissue [12,13]. Retrospective data from Barillot et al [14] as well as early patterns-of-care studies [15] show local control in patients receiving brachytherapy to be far superior to that for patients receiving EBRT alone. Additionally, the combination of EBRT and brachytherapy is associated with less toxicity as compared to EBRT alone.

EBRT has classically been delivered using 2-field or 4-field arrangements with field borders and blocks defined using bony landmarks in order to encompass the primary cervical disease, local extension and regional lymph nodes. Incorporation of CT imaging allowed the use of 3D-CRT, in which contoured volumes could be used to define blocks or multileaf collimators (MLCs) and dose homogeneity could be fine-tuned. More recently, IMRT has been used to reduce the volume of normal tissue receiving high-dose RT compared to supine 3D-CRT. Dosimetric analyses suggest that IMRT decreases the dose to small bowel, bladder, rectum, and bone marrow [16,17]. Early clinical data also suggest that this improvement in dose distribution translates into a reduction in acute toxicity [18]. However, multiple reports also show that tumor regression and normal tissue motion may lead to underdosing of target structures or overdosing of adjacent critical structures if not adequately considered in RT planning [19,20].

Other positioning techniques or patient instructions have been considered to facilitate small-bowel sparing. Specifically, the use of the prone position, pelvic compression, and belly board may displace small bowel out of the RT field [21]. The presence of a full bladder may exert a similar effect on small bowel, although consistent daily bladder filling may be difficult to achieve and may be limited by the patient's discomfort as the treatment progresses [22]. An in-depth discussion of considerations in pelvic radiotherapy technique can be found in the "ACR Appropriateness Criteria® Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer".

Stereotactic body RT (SBRT) has been shown to be a useful treatment option in other tumor sites, especially in early stage lung cancer. There are preliminary data on its use in treating cervical cancer [23], but, given target definition, tumor motion, and the proven track record of brachytherapy, SBRT should not be considered a substitute for brachytherapy [24]. (See Variant 1.)

Radiotherapy versus Chemoradiotherapy

Historically, RT alone had been used to treat locally advanced or bulky cervical cancer. Several randomized trials have evaluated the utility of adding concurrent chemotherapy to that regimen; some of these trials included women with IB2-IIA disease [25-28]. Most showed an advantage in OS for the addition of concurrent chemotherapy, using a cisplatin-based regimen. By contrast, a National Cancer Institute-Canada (NCIC) trial randomized women to RT with or without concurrent weekly cisplatin chemotherapy and found no statistically significant advantage in progression-free survival (PFS) or OS [27]. The notable discrepancy between the results

of the NCIC trial and those of several others that support chemoradiotherapy may be explained by statistical variation, the presence of anemia in the chemoradiotherapy arm or the absence of para-aortic lymph node surgical staging. Alternatively, chemotherapy may be compensating for the extended treatment time in most trials, whereas the NCIC trial achieved shorter average treatment duration. A Cochrane meta-analysis of all randomized trials comparing RT to chemoradiotherapy found a 6% survival advantage in favor of the latter [29]. Moreover, there was a trend towards larger benefit for the addition of chemotherapy in stages IB-IIA as compared to more advanced stages. An advantage of chemoradiotherapy was present for both cisplatin-based and nonplatinum-based chemotherapy regimens. Likely due to an NCI alert issued in 1999 recommending concurrent cisplatin-based chemoradiotherapy, weekly cisplatin is by far the most commonly used agent [30]. Caution is advised with the use of chemotherapy doublets containing cisplatin as well as fluorouracil (5-FU), gemcitabine, or taxol; each of these regimens is more toxic than cisplatin alone, especially when used concurrently with extended-field RT (EFRT). No randomized data exist concerning the use of chemoradiotherapy in stage IB1 or below.

Induction Chemotherapy Followed by Surgery

In countries with limited RT resources, bulky cervical cancer is often treated with induction chemotherapy followed by hysterectomy. Three randomized trials included women with bulky stage IB who were disease randomized to chemotherapy followed by surgery versus RT alone [31-33]. These trials yielded mixed results, with some suggesting an advantage for induction chemotherapy and surgery over definitive RT and one showing equivalency. A meta-analysis that included these trials and trials of women with higher-stage disease also supported the superiority of chemotherapy followed by surgery over RT [34]. However, the validity and applicability of these studies have been challenged. The RT in these trials was of poor quality due to inadequate dose, protracted delivery schedules, and the absence of concurrent chemotherapy. Interestingly, a meta-analysis of induction chemotherapy followed by surgery versus surgery alone failed to show clear a benefit for the induction chemotherapy arms [35]. For these reasons, the appropriateness of induction chemotherapy followed by surgery remains uncertain, and it should be performed only in the context of a clinical trial. The issue most relevant to modern therapy is whether concurrent chemoradiotherapy or induction chemotherapy followed by hysterectomy is preferred. This issue is currently being evaluated in two phase III clinical trials: EORTC 55994 and NCT 00193739. In the interim, consensus supports the use of chemoradiotherapy as the preferred treatment modality for tumors above stage IB1 [36]. (See Variant 2.)

Extended-Field Radiotherapy

The role of EFRT to the para-aortic lymph node chain with definitive RT alone was supported by the Radiation Therapy Oncology Group® (RTOG®) 79-20 [37]. Women with bulky IB/IIA (greater or equal to 5 cm or with positive pelvic nodes) or IIB tumors were randomized to receive pelvic RT alone or EFRT. Although no differences in locoregional recurrence or DFS were evident, a benefit in 10-year OS emerged. This difference appears to be due to a reduction in the rate of distant metastatic disease and an improvement in the rate of salvage after local recurrence. This prompted the comparison between pelvic RT administered concurrently with chemotherapy versus EFRT alone in RTOG® 90-01 [25]. The mature analysis of this trial showed a large benefit in both DFS and OS for the pelvic RT plus chemotherapy arm. Interestingly, there was an improvement as well in the risk of distant metastasis in the pelvic RT with concurrent cisplatin and 5-FU chemotherapy. The role of prophylactic EFRT in addition to concurrent chemotherapy is unclear given the significant acute and late toxicity associated with combination treatment [38,39]. RTOG® 0116, a multi-institutional study evaluating the toxicity of EFRT with concurrent cisplatin, found an acute grade 3/4 toxicity rate excluding grade 3 leukopenia of 81% and a late grade 3/4 toxicity of 40%.

Patient-specific risk factors for toxicity such as obesity, diabetes mellitus, and smoking may be important considerations when selecting the appropriate RT fields. More conformal means of delivering RT, such as IMRT, may have a role in reducing toxicity [17]. Additionally, the advent of PET, which can identify some nodal metastases occult to CT imaging, may reduce the benefit of prophylactic RT to an uninvolved nodal chain.

When not using EFRT, the superior border of pelvic RT fields has traditionally been the L4/L5 interspace. This bony landmark was thought to correlate to the top of the common iliac chain. The use of 3D-CRT has shown that the bifurcation of the aorta is frequently superior to L4/L5. Ideally, the pelvic field should be designed with 3D-CRT so as to include the common iliac vessels. If 3D-CRT is unavailable, then the L3/L4 interspace may be a preferred field border. This is supported by an analysis of regional recurrences after definitive RT for cervical cancer from the M.D. Anderson Cancer Center, which suggested that most regional recurrences occurred immediately superior to the pelvic field border at approximately L4/L5 [40].

Adjuvant Hysterectomy

A single randomized trial evaluated the incremental benefit of extrafascial hysterectomy after definitive RT. In GOG 71, women with bulky IB cervical cancer were randomized to receive RT alone to 80 Gy or RT to 75 Gy followed by hysterectomy [41]. Although there was a trend towards better local control in the hysterectomy group, there was no benefit in OS. This trial has been criticized for the relatively low dose used in the RT alone arm, the protracted RT schedule and the absence of concurrent chemotherapy. The subsequent GOG study, GOG 123 [26,42], confirmed the benefit of concurrent chemoradiotherapy in this patient population. Since GOG 71 did not demonstrate a survival benefit for the addition of "adjuvant" extrafascial hysterectomy, the authors indicated that "It is reasonable to conclude on the basis of these results and our results that the elimination of hysterectomy from both regimens would not have affected the increase in survival associated with the use of cisplatin. Therefore, RT in combination with treatment with cisplatin should be adequate for patients with bulky stage IB cervical cancer."

Given the dearth of randomized data, there are no clear guidelines as to when, or in whom, RT or chemoradiotherapy should be followed by extrafascial hysterectomy. It should probably be limited to patients with bulky residual disease at the time of the brachytherapy (generally after 45 Gy EBRT + chemotherapy), to patients whose anatomy prevents an adequate implant, and perhaps to some patients with adenocarcinomas, although level one evidence is lacking. Some investigators have evaluated the role of post-treatment biopsy, MRI, or PET to identify patients with residual disease who may benefit from surgery while sparing most patients the added morbidity [43-45]. This remains an area of active investigation.

Adjuvant Chemotherapy

Pelvic control rates have improved with modern therapeutic techniques, leaving development of distant metastatic disease an ever more important competing risk. This is especially true in lymph-node-positive disease. Also, conflicting evidence points to a possibly higher likelihood of distant metastases for nonsquamous (notably adenocarcinoma and adenosquamous) histologies, suggesting a role for systemic therapy [46,47]. Even in higher risk subsets of early stage cervical carcinoma, the utility of adjuvant chemotherapy remains unclear. A randomized trial investigating the role of intensification of the chemotherapeutic regimen in locoregionally advanced cervical cancer compared concurrent single-agent cisplatin versus concurrent and adjuvant cisplatin and gemcitabine [48]. This trial found an OS advantage for the cisplatin plus gemcitabine arm (hazard ratio = 0.68) at the cost of a significant increase in toxicity; grade 3/4 toxicity rates were 86.5% in the experimental arm vs. 46.3% in the cisplatin-alone arm. It remains to be seen whether these findings can be replicated in early stage disease, and whether the benefit is attributable to the addition of gemcitabine or to additional cycles of cisplatin. Due in part to benefits of extended adjuvant chemotherapy in the SWOG trial, the Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration supports this as a promising area of research [29]. The utility of adjuvant chemotherapy after chemoradiotherapy in the setting of high-risk postoperative cervical cancer is currently under study by the RTOG® (Phase III Randomized Study of Concurrent Chemotherapy and Pelvic Radiation Therapy with or without Adjuvant Chemotherapy in High-Risk Patients with Early-Stage Cervical Carcinoma Following Radical Hysterectomy. Available at: http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0724.) Until more data are collected, adjuvant chemotherapy may be most appropriately used in the setting of a clinical trial.

Hemoglobin Level

A clear association is seen between hemoglobin (Hgb) level and prognosis in cervical cancer treated with RT or chemoradiotherapy [49]. Whether anemia has a causative relationship with disease recurrence — possibly through hypoxic radioprotection or induction of a more malignant phenotype — or whether anemia represents an epiphenomenon associated with, but not responsible for, poor prognosis is unclear. A multi-institutional retrospective analysis suggests that average weekly nadir of hemoglobin (AWNH) is highly predictive for outcome [50]. In this study, transfusion compensated for the negative prognostic effects of anemia, rendering women who received transfusions with prognoses similar to those with comparable baseline AWNH levels. Transfusion may be especially important in women with lower tumor perfusion on MRI [51]. However, to this date, no randomized data support therapeutic transfusion, and the minimum acceptable Hgb is unclear. The role of erythropoietin to raise Hgb levels appears to be limited after a phase III trial closed prematurely due to concerns about elevated risk of thromboembolic events [52]. Although analysis was quite limited due to low accrual prior to study closure, there was no suggestion of benefit with regard to PFS or OS in the experimental arm. In fact a

nonstatistically significant detrimental effect was noted in the PFS (58% vs 65% at 3 years) and OS (61% vs 75% at 3 years) in the arm receiving erythropoietin compared with the standard arm [52].

Brachytherapy

Brachytherapy is an integral component of the definitive treatment of cervical cancer using RT or chemoradiotherapy. Intacavitary brachytherapy, typically performed using a tandem and ovoids or a tandem and ring, is the most standard approach. Classically, two-dimensional dosimetry is performed using the Manchester nomenclature or comparable formalism. More recently, the GEC-ESTRO created guidelines recommending 3D dosimetry incorporating delineation of the target volume and organs at risk in order to improve target coverage and normal tissue sparing [53]. MRI simulation or fusion of MRI images with CT simulation may be beneficial to identify the extent of tumor spread. Early experience with MRI planning has yielded favorable outcomes [54]. In circumstances where insertion of an intracavitary brachytherapy is not feasible or is inadequate to cover the central tumor volume (eg, vaginal extension, anatomic distortion due to tumor, or bulky disease) the use of interstitial brachytherapy may be advantageous. Consideration should be given to performing interstitial brachytherapy under laparoscopic guidance to perform lysis of adhesions, identify possible carcinomatosis, and avoid visceral puncture. However, some reports suggest that laparoscopy does not reduce toxicity [55,56]. Brachytherapy can be performed using low-dose-rate (LDR), high-dose-rate (HDR), or pulsed-dose-rate (PDR) delivery of RT. A recent meta-analysis of available randomized trials supports the equivalency of LDR and HDR with regard to local control, OS, and late complications to the rectum or bladder [57]. Every effort should be made to perform treatment planning for each brachytherapy insertion and to carefully balance the doses needed for tumor control with those recommended to minimize normal tissue toxicity [58]. (See Variant 3.)

Overall Treatment Time

Several retrospective series consistently show an association between prolongation of overall treatment time of RT and a reduction in local control and survival [59,60]. The nonrandomized nature of these studies prohibits concluding a causative relationship with certainty, but these findings are likely the result of accelerated repopulation of tumor clonogens during treatment breaks. These results have not been verified in a randomized trial, in part due to an absence of equipoise, and most reports predate the widespread use of chemoradiotherapy. However, overall treatment time appears to be one of the most powerful predictors of outcome and should be a key driver in the design of the treatment paradigm. Unfortunately, survey data suggest this goal is often not met in clinical practice [12].

Postoperative Radiotherapy

An in-depth discussion of the role of postoperative RT or chemoradiotherapy can be found in the ACR Appropriateness Criteria® topic on "Role of Adjuvant Therapy in the Management of Early Stage Cervical Cancer."

Cervical Cancer after Supracervical Hysterectomy

The scenario of a cervical cancer presenting in the cervical stump after prior supracervical hysterectomy comprises approximately 5% of newly diagnosed cases [14]. Therapy is complicated by the frequent inability to place a tandem, the displacement of small bowel into the low pelvis, and the likely presence of adhesions tethering organs at risk to radiation aimed at target tissue. If surgery is not feasible, definitive RT or chemoradiotherapy is indicated. In circumstances where intracavitary brachytherapy is not feasible, interstitial brachytherapy by experienced users should be considered. Referral to an experienced center may be preferred, since EBRT without brachytherapy is less likely to achieve durably tumor control. In circumstances where brachytherapy is not feasible, treatment with EBRT alone – including IMRT – is appropriate. SBRT should be reserved for use on a clinical trial, given the limited clinical data and concerns about organ motion. The use of MRI to guide treatment planning, obtained prior to implant or after needle insertion (with MRI-compatible template) is strongly encouraged. Only a few retrospective series describe outcomes after RT in this setting, and none routinely used concurrent chemotherapy. Treatment of cancer of the cervical stump may be associated with increased toxicity due to anatomic shifts after hysterectomy; the use of 3D-CRT or IMRT may ameliorate this risk to some degree, although care should be taken to account for intrafraction motion and setup uncertainty. Prone position and full bladder instructions should also be considered [21]. Outcomes vary by stage, but 5-year OS ranges from 82%-91% for stage I, 73%-78% for stage II, 38%-69% for stage III, and 0%-37% for stage IV [14,61]. (See Variant 4.)

Follow-up

The majority of the panel supported performing cervical cytology and physical examination every 3-6 months for the first 5 years and then annually. Chest radiograph is considered reasonable. Although its role is under investigation, a PET/CT at 3 months to evaluate the extent of residual disease is favored [44].

Salvage Therapy

Treatment for persistent or recurrent disease after definitive RT or chemoradiotherapy is challenging. Workup should include biopsy to prove the nature of the recurrence and staging examinations to rule out metastatic disease. If feasible, surgery presents the best option for cure; the type of surgery — radical hysterectomy versus exenteration — should be dictated by the extent of disease. Interstitial brachytherapy may be indicated, especially if the first course of RT was compromised due to prolongation of treatment course, marginal miss of tumor, inadequacy of dose, or suboptimal brachytherapy technique. Other options include systemic therapy such as chemotherapy and use of emerging biologic agents.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin.* 2011;61(2):69-90.
2. Pecorelli S, Zigliani L, Odicino F. Revised FIGO staging for carcinoma of the cervix. *Int J Gynaecol Obstet.* 2009;105(2):107-108.
3. Kim SH, Choi BI, Lee HP, et al. Uterine cervical carcinoma: comparison of CT and MR findings. *Radiology.* 1990;175(1):45-51.
4. Bellomi M, Bonomo G, Landoni F, et al. Accuracy of computed tomography and magnetic resonance imaging in the detection of lymph node involvement in cervix carcinoma. *Eur Radiol.* 2005;15(12):2469-2474.
5. Mitchell DG, Snyder B, Coakley F, et al. Early invasive cervical cancer: tumor delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 Intergroup Study. *J Clin Oncol.* 2006;24(36):5687-5694.
6. Choi HJ, Roh JW, Seo SS, et al. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. *Cancer.* 2006;106(4):914-922.
7. Boughanim M, Leboulleux S, Rey A, et al. Histologic results of para-aortic lymphadenectomy in patients treated for stage IB2/II cervical cancer with negative [18F]fluorodeoxyglucose positron emission tomography scans in the para-aortic area. *J Clin Oncol.* 2008;26(15):2558-2561.
8. Leblanc E, Gauthier H, Querleu D, et al. Accuracy of 18-fluoro-2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult para-aortic node involvement in patients with a locally advanced cervical carcinoma. *Ann Surg Oncol.* 2011;18(8):2302-2309.
9. Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. *Cancer.* 2008;112(9):1954-1963.
10. Hasenburg A, Salama JK, Van TJ, Amosson C, Chiu JK, Kieback DG. Evaluation of patients after extraperitoneal lymph node dissection and subsequent radiotherapy for cervical cancer. *Gynecol Oncol.* 2002;84(2):321-326.
11. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet.* 1997;350(9077):535-540.
12. Eifel PJ, Moughan J, Erickson B, Iarocci T, Grant D, Owen J. Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study. *Int J Radiat Oncol Biol Phys.* 2004;60(4):1144-1153.
13. Erickson B, Eifel P, Moughan J, Rownd J, Iarocci T, Owen J. Patterns of brachytherapy practice for patients with carcinoma of the cervix (1996-1999): a patterns of care study. *Int J Radiat Oncol Biol Phys.* 2005;63(4):1083-1092.

14. Barillot I, Horiot JC, Cuisenier J, et al. Carcinoma of the cervical stump: a review of 213 cases. *Eur J Cancer.* 1993;29A(9):1231-1236.
15. Lanciano RM, Won M, Coia LR, Hanks GE. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 patterns of care studies. *Int J Radiat Oncol Biol Phys.* 1991;20(4):667-676.
16. Mell LK, Tiryaki H, Ahn KH, Mundt AJ, Roeske JC, Aydogan B. Dosimetric comparison of bone marrow-sparing intensity-modulated radiotherapy versus conventional techniques for treatment of cervical cancer. *Int J Radiat Oncol Biol Phys.* 2008;71(5):1504-1510.
17. Portelance L, Chao KS, Grigsby PW, Bennet H, Low D. Intensity-modulated radiation therapy (IMRT) reduces small bowel, rectum, and bladder doses in patients with cervical cancer receiving pelvic and para-aortic irradiation. *Int J Radiat Oncol Biol Phys.* 2001;51(1):261-266.
18. Hasselle MD, Rose BS, Kochanski JD, et al. Clinical outcomes of intensity-modulated pelvic radiation therapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2011;80(5):1436-1445.
19. Beadle BM, Jhingran A, Salehpour M, Sam M, Iyer RB, Eifel PJ. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2009;73(1):235-241.
20. Chan P, Dinniwell R, Haider MA, et al. Inter- and intrafractional tumor and organ movement in patients with cervical cancer undergoing radiotherapy: a cinematic-MRI point-of-interest study. *Int J Radiat Oncol Biol Phys.* 2008;70(5):1507-1515.
21. Adli M, Mayr NA, Kaiser HS, et al. Does prone positioning reduce small bowel dose in pelvic radiation with intensity-modulated radiotherapy for gynecologic cancer? *Int J Radiat Oncol Biol Phys.* 2003;57(1):230-238.
22. Ahmad R, Hoogeman MS, Bondar M, et al. Increasing treatment accuracy for cervical cancer patients using correlations between bladder-filling change and cervix-uterus displacements: proof of principle. *Radiother Oncol.* 2011;98(3):340-346.
23. Higginson DS, Morris DE, Jones EL, Clarke-Pearson D, Varia MA. Stereotactic body radiotherapy (SBRT): Technological innovation and application in gynecologic oncology. *Gynecol Oncol.* 2011;120(3):404-412.
24. Mayr NA, Huang Z, Sohn JW, et al. Emerging application of stereotactic body radiation therapy for gynecologic malignancies. *Expert Rev Anticancer Ther.* 2011;11(7):1071-1077.
25. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol.* 2004;22(5):872-880.
26. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med.* 1999;340(15):1154-1161.
27. Pearcey R, Brundage M, Drouin P, et al. Phase III trial comparing radical radiotherapy with and without cisplatin chemotherapy in patients with advanced squamous cell cancer of the cervix. *J Clin Oncol.* 2002;20(4):966-972.
28. Roberts KB, Urdaneta N, Vera R, et al. Interim results of a randomized trial of mitomycin C as an adjunct to radical radiotherapy in the treatment of locally advanced squamous-cell carcinoma of the cervix. *Int J Cancer.* 2000;90(4):206-223.
29. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev.* 2010(1):CD008285.
30. Gaffney DK, Du Bois A, Narayan K, et al. Practice patterns of radiotherapy in cervical cancer among member groups of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Oncol Biol Phys.* 2007;68(2):485-490.
31. Benedetti-Panici P, Greggi S, Colombo A, et al. Neoadjuvant chemotherapy and radical surgery versus exclusive radiotherapy in locally advanced squamous cell cervical cancer: results from the Italian multicenter randomized study. *J Clin Oncol.* 2002;20(1):179-188.
32. Chang TC, Lai CH, Hong JH, et al. Randomized trial of neoadjuvant cisplatin, vincristine, bleomycin, and radical hysterectomy versus radiation therapy for bulky stage IB and IIA cervical cancer. *J Clin Oncol.* 2000;18(8):1740-1747.
33. Choi YS, Sin JI, Kim JH, Ye GW, Shin IH, Lee TS. Survival benefits of neoadjuvant chemotherapy followed by radical surgery versus radiotherapy in locally advanced chemoresistant cervical cancer. *J Korean Med Sci.* 2006;21(4):683-689.
34. Neoadjuvant chemotherapy for locally advanced cervical cancer: a systematic review and meta-analysis of individual patient data from 21 randomised trials. *Eur J Cancer.* 2003;39(17):2470-2486.

35. Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. *Cochrane Database Syst Rev.* 2010(1):CD007406.
36. Monk BJ, Koh WJ. What is the standard therapy for bulky stage IB cervical cancer? *Int J Gynecol Cancer.* 2009;19(3):480.
37. Rotman M, Pajak TF, Choi K, et al. Prophylactic extended-field irradiation of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. Ten-year treatment results of RTOG 79-20. *JAMA.* 1995;274(5):387-393.
38. Grigsby PW, Heydon K, Mutch DG, Kim RY, Eifel P. Long-term follow-up of RTOG 92-10: cervical cancer with positive para-aortic lymph nodes. *Int J Radiat Oncol Biol Phys.* 2001;51(4):982-987.
39. Small W, Jr., Winter K, Levenback C, et al. Extended-field irradiation and intracavitary brachytherapy combined with cisplatin chemotherapy for cervical cancer with positive para-aortic or high common iliac lymph nodes: results of ARM 1 of RTOG 0116. *Int J Radiat Oncol Biol Phys.* 2007;68(4):1081-1087.
40. Beadle BM, Jhingran A, Yom SS, Ramirez PT, Eifel PJ. Patterns of regional recurrence after definitive radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2010;76(5):1396-1403.
41. Keys HM, Bundy BN, Stehman FB, et al. Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: a randomized trial of the Gynecologic Oncology Group. *Gynecol Oncol.* 2003;89(3):343-353.
42. Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. *Am J Obstet Gynecol.* 2007;197(5):503 e501-506.
43. Nijhuis ER, van der Zee AG, in 't Hout BA, et al. Gynecologic examination and cervical biopsies after (chemo) radiation for cervical cancer to identify patients eligible for salvage surgery. *Int J Radiat Oncol Biol Phys.* 2006;66(3):699-705.
44. Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA.* 2007;298(19):2289-2295.
45. Wang JZ, Mayr NA, Zhang D, et al. Sequential magnetic resonance imaging of cervical cancer: the predictive value of absolute tumor volume and regression ratio measured before, during, and after radiation therapy. *Cancer.* 2010;116(21):5093-5101.
46. Huang YT, Wang CC, Tsai CS, et al. Long-term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. *Int J Radiat Oncol Biol Phys.* 2011;80(2):429-436.
47. Lea JS, Coleman RL, Garner EO, Duska LR, Miller DS, Schorge JO. Adenosquamous histology predicts poor outcome in low-risk stage IB1 cervical adenocarcinoma. *Gynecol Oncol.* 2003;91(3):558-562.
48. Duenas-Gonzalez A, Zarba JJ, Patel F, et al. Phase III, Open-Label, Randomized Study Comparing Concurrent Gemcitabine Plus Cisplatin and Radiation Followed by Adjuvant Gemcitabine and Cisplatin Versus Concurrent Cisplatin and Radiation in Patients With Stage IIB to IVA Carcinoma of the Cervix. *J Clin Oncol.* 2011;29(13):1678-1685.
49. Winter WE, 3rd, Maxwell GL, Tian C, et al. Association of hemoglobin level with survival in cervical carcinoma patients treated with concurrent cisplatin and radiotherapy: a Gynecologic Oncology Group Study. *Gynecol Oncol.* 2004;94(2):495-501.
50. Grogan M, Thomas GM, Melamed I, et al. The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer.* 1999;86(8):1528-1536.
51. Mayr NA, Wang JZ, Zhang D, et al. Synergistic effects of hemoglobin and tumor perfusion on tumor control and survival in cervical cancer. *Int J Radiat Oncol Biol Phys.* 2009;74(5):1513-1521.
52. Thomas G, Ali S, Hoebers FJ, et al. Phase III trial to evaluate the efficacy of maintaining hemoglobin levels above 12.0 g/dL with erythropoietin vs above 10.0 g/dL without erythropoietin in anemic patients receiving concurrent radiation and cisplatin for cervical cancer. *Gynecol Oncol.* 2008;108(2):317-325.
53. Potter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol.* 2006;78(1):67-77.
54. Dimopoulos JC, Potter R, Lang S, et al. Dose-effect relationship for local control of cervical cancer by magnetic resonance image-guided brachytherapy. *Radiother Oncol.* 2009;93(2):311-315.
55. Engle DB, Bradley KA, Chappell RJ, Conner JP, Hartenbach EM, Kushner DM. The effect of laparoscopic guidance on gynecologic interstitial brachytherapy. *J Minim Invasive Gynecol.* 2008;15(5):541-546.

56. Shah AP, Strauss JB, Gielda BT, Zusag TW. Toxicity associated with bowel or bladder puncture during gynecologic interstitial brachytherapy. *Int J Radiat Oncol Biol Phys.* 2010;77(1):171-179.
57. Viani GA, Manta GB, Stefano EJ, de Fendi LI. Brachytherapy for cervix cancer: low-dose rate or high-dose rate brachytherapy - a meta-analysis of clinical trials. *J Exp Clin Cancer Res.* 2009;28:47.
58. Jones ND, Rankin J, Gaffney DK. Is simulation necessary for each high-dose-rate tandem and ovoid insertion in carcinoma of the cervix? *Brachytherapy.* 2004;3(3):120-124.
59. Perez CA, Grigsby PW, Castro-Vita H, Lockett MA. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. *Int J Radiat Oncol Biol Phys.* 1995;32(5):1275-1288.
60. Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma. *Int J Radiat Oncol Biol Phys.* 1995;32(5):1301-1307.
61. Miller BE, Copeland LJ, Hamberger AD, et al. Carcinoma of the cervical stump. *Gynecol Oncol.* 1984;18(1):100-108.

Clinical Condition: **Definitive Therapy for Early Stage Cervical Cancer**

Variant 1: **50-year-old woman with FIGO clinical stage IB1 poorly differentiated squamous cell carcinoma of the cervix. No evidence of lymph node metastasis on imaging.**

Treatment	Rating	Comments
Treatment		
Surgery	8	
Radiotherapy	8	
Chemoradiotherapy	6	
Radiotherapy Technique		
3D-CRT	9	
2D radiotherapy	5	May be appropriate in resource-poor settings.
IMRT	5	
Brachytherapy		
EBRT and brachytherapy	9	
EBRT alone	2	
EBRT and SBRT	2	
Overall Treatment Time		
<56 days	9	
56-70 days	5	
>70 days	1	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Definitive Therapy for Early Stage Cervical Cancer**

Variant 2: **45-year-old woman with FIGO clinical stage IB2, 6 cm diameter, moderately differentiated adenocarcinoma, PET negative for nodal or distant metastatic disease. Hemoglobin (Hgb) at presentation 7 gr/dl.**

Treatment	Rating	Comments
Treatment of Cervical Primary		
Chemoradiotherapy to 85-90 Gy	9	
Chemoradiotherapy to 75 Gy followed by extrafascial hysterectomy	5	
Radiotherapy alone	3	
Induction chemotherapy followed by surgery	2	
Upper Field Border if Using RT Alone (LN -)		
Bifurcation of aorta	8	
Bony landmark of L4/L5	7	
Mid para-aortic chain (~L1/L2)	4	
Extended field RT to T11/T12	2	
Upper Border of Field if Using Chemoradiotherapy (LN -)		
Bifurcation of aorta	8	
Bony landmark of L4/L5	7	
Bony landmark of L5/S1	3	
Mid para-aortic chain (~L1/L2)	2	
Hemoglobin		
Transfuse to maintain Hgb 10-11.9 during RT	8	
Transfuse to maintain Hgb $\geq$12 during RT	4	
Do not transfuse during RT	2	
Administer erythropoietin during RT	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Definitive Therapy for Early Stage Cervical Cancer**

Variant 3: **30-year-old woman with FIGO clinical stage IIA, 5 cm diameter, poorly differentiated adenosquamous carcinoma with uterine extension, PET positive left external iliac-obturator node without evidence of distant metastatic disease.**

Treatment	Rating	Comments
Treatment of Primary		
Chemoradiotherapy	9	
Chemoradiotherapy followed by additional chemotherapy	5	
Neoadjuvant chemotherapy followed by local treatment	2	
Radiation therapy alone	2	
Node Dissection Prior to Start of Radiation Therapy		
No node dissection	7	
Para-aortic node dissection	6	
Pelvic and para-aortic node dissection	5	
Radiotherapy Boost to Undissected Pelvic Node (include brachytherapy contribution)		
Boost involved node to 60-65 Gy	9	
No boost	3	
Top of the Radiation Field in a Patient with PET Positive Pelvic Node and Negative Common/Para-aortic Nodes with no Node Dissection.		
Bifurcation of aorta	8	
L3/L4	7	
L4/L5	5	
L2/L3	5	
L1/L2	5	
Type of Chemotherapy		
Concurrent chemotherapy	9	
Concurrent chemotherapy followed by additional chemotherapy	5	
Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy	2	
If Treating Higher than L4/L5		
Concurrent chemotherapy	8	
No chemotherapy	2	
Type of Concurrent Chemotherapy		
Weekly cisplatin	9	
Cisplatin and 5-FU	5	
Cisplatin and gemcitabine	3	
Weekly taxol	3	

Cisplatin and taxol	3	
Type of Intracavitary Brachytherapy		
LDR	9	
HDR	9	
PDR	9	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Variant 4: **55-year-old woman status postsupracervical hysterectomy 20 years earlier, now with a FIGO clinical stage IB2, 5 cm diameter, well-differentiated squamous cell carcinoma, PET negative for nodal regional or distant metastatic disease. Tandem cannot be placed in the residual cervix.**

Treatment	Rating	Comments
Treatment of Primary		
Chemoradiotherapy	9	
Surgery followed by RT or chemoradiotherapy	5	
Surgery	3	
Radiation therapy alone	2	
If Conformal Radiotherapy Selected		
EBRT and brachytherapy	9	
Prone with belly board	8	
Supine	8	
Bladder full for simulation and daily treatment	8	
EBRT alone (including IMRT)	4	
EBRT and SBRT	2	
Interstitial Brachytherapy		
CT for treatment planning	9	
MRI for treatment planning before implant	8	
Laparoscopic guidance	8	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		