ROLE OF ADJUVANT THERAPY IN THE MANAGEMENT OF EARLY STAGE CERVICAL CANCER

Expert Panel on Radiation Oncology–Gynecology:
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Summary of Literature Review

Background on Surgical Management

For over 100 years, radical hysterectomy has been the preferred surgical method for treating early (International Federation of Gynecology and Obstetrics [FIGO] clinical stages I and II) cervical carcinoma. The first radical hysterectomy operation was described by John G. Clark, resident gynecologist under Howard Kelly at the Johns Hopkins Hospital in 1895. In a pathological examination of 20 cases treated by hysterectomy, Clark found that the disease had extended past the margins of resection in 15 cases. Influenced by the surgical doctrines of William Halsted, he developed an operative technique that is today recognized as the first true radical hysterectomy [1]. The operation was modified and popularized by Ernst Wertheim, whose experience was impressive in magnitude, completeness of patient follow-up, and descriptions of complications associated with the procedure [2]. Procedural modifications were later introduced by Okabayashi (isolation of the rectum and resection of the cardinal and uterosacral ligaments prior to the anterior dissection) and by Schauta (radical vaginal resection of the cardinal and uterosacral ligaments prior to the anterior dissection) [3,4]. Liu and Meigs [5] reinvigorated interest in primary surgical treatment of cervical cancer with reported 5-year survival rates >75% and no operative deaths among his last 100 patients. Representing variations in approach and extent, these radical operations shared the objective of a wide margin around the primary tumor. Later additions included routine dissection of the retroperitoneal lymph nodes to assess for the presence and patterns of metastasis. A classification system for radical hysterectomy procedures was first described by Piver et al [6] and recently updated by Querleu and Morrow [7].

Concomitant to the adoption of the radical hysterectomy as the standard operation for invasive cervical cancer was the recognition that patients undergoing an inadequate operation fared poorly — particularly when tumor involved the surgical resection margins of less than radical operations. Green and Morse [8] managed 84 women with invasive cervical cancer following a simple or subtotal hysterectomy over a 20-year period. The 5-year survival rate for 33 patients undergoing additional therapy within 4 months of their inadequate hysterectomy was 42% and only 18% for the 51 patients treated after 4 months. Davy et al [9] at the Norwegian Radium Hospital reported a 5-year survival rate of 77% for women with invasive cervical cancer who underwent simple hysterectomy and had negative margins and only 31% for women with tumor transected during the operation. Heller et al [10] reported that patients with stage IA disease did well (100% 5-year survival rate) regardless of whether or not adjuvant therapy was administered; however, the 5-year survival rate was poorer despite adjuvant radiation therapy (RT) for patients with stage IB (78%) or stage IIB (67%) disease. Among 64 patients with squamous cell carcinoma of the cervix, Hopkins et al [11] showed that patients who received postoperative radiation therapy (PORT) fared much better than patients who underwent observation (5-year survival rate of 88% vs 69% for the latter). Among 27 patients with adenocarcinoma of the cervix, the 5-year survival rate was only 42%. Outcomes from these series must be compared to what might have been achieved with radical surgical or RT alone, and do not take into consideration the additional expense and potential complications associated with multimodality therapy. For the patient who has undergone a substANDARD operation for invasive cervical cancer, one option is to perform a second operation to “complete” the radical hysterectomy (radical parametrectomy, radical upper vaginectomy, pelvic lymph node dissection) [12,13]. The other viable alternative would be to consider adjuvant RT with or without chemotheraphy.

Role of Adjuvant Radiation Therapy

The Gynecologic Oncology Group (GOG) in the United States registered 1,125 patients into a prospective clinical trial (GOG #49) with FIGO stage I cervical cancer preoperatively from May 1981 to February 1984 [14]. Of this group, 645 patients with squamous cell carcinoma...
A phase III randomized trial conducted by the GOG evaluated the effect of PORT in FIGO stage IB intermediate-risk patients with pathologically negative pelvic nodes. This trial (GOG protocol #92) accrued 299 patients, of whom 277 were eligible for randomization with 137 undergoing PORT versus 140 having no further treatment. Pelvic radiation dose was 46-50.4 Gy at 1.8-2.0 Gy per fraction over 4.5 to 6 weeks. Patients’ pathologic risk factors for recurrence were stratified by LVSI, deep cervical stromal invasion (DCSI), and “large” tumor diameter. Multivariate analysis found that the risk of relapse was significantly reduced by 44% in the radiation arm \( (P=0.019) \). Clinical tumor diameter was determined to be the most significant risk factor for recurrence. An updated review at over 9 years since closure of GOG #92 used an intent-to-treat approach and showed there were 67 failures, of which 24 had PORT versus 43 in the observation cohort. Both local \( (13.9\% \text{ vs } 20.7\%) \) and distant \( (2.9\% \text{ vs } 8.6\%) \) relapse rates were lower in the irradiated versus observation groups, respectively. After controlling for prognostic factors, patients in the adjuvant radiation group were 44% less likely to fail than those not receiving any additional treatment. Furthermore, only 8.8% of patients with non-squamous-cell carcinomas experienced recurrence after adjuvant RT versus 44% in the no-further-treatment cohort. Lastly, adjuvant irradiation significantly improved the progression-free interval when compared to observation \( (P=0.009) \). However, there was no statistical difference in OS between the two groups \( (P=0.074) \) \[17\]. (See Variant 1.)

A sentinel phase III randomized intergroup trial conducted jointly by the Southwest Oncology Group (SWOG) protocol #8797, Radiation Therapy Oncology Group \((\text{RTOG}^\text{®})\) protocol #91-12, and the GOG protocol #109 evaluated the addition of concurrent chemotherapy to adjuvant pelvic PORT in high-risk patients with FIGO pathological stages IA2, IB, or IIA cervical cancers following radical hysterectomy and pelvic lymphadenectomy with certain high-risk pathological findings \[18\]. There were 127 evaluable patients with PNM, PMI, or positive surgical margins in the combined modality therapy (CMT) arm versus 116 in the adjuvant radiation only group. Chemotherapy consisted of 4 cycles of cisplatin (CDDP) at 70 mg/m² intravenous (IV) infusion and 5-fluorouracil (5-FU) at 4,000 mg/m² over a 4-day continuous infusion. Chemotherapy was administered every 3 weeks beginning on day 1 of PORT. Both treatment groups received radiation to at least the whole pelvis to 49.3 Gy at 1.7 Gy per fraction. Elective para-aortic nodal irradiation to 45 Gy over 30 fractions was allowed for patients with positive common iliac nodes. Both progression-free survival (PFS) \( (P=0.003) \) and OS \( (P=0.007) \) were significantly improved with the addition of chemotherapy. Multivariate analyses demonstrated that pathological tumor size was the most predictive factor for both PFS and OS. The use of chemotherapy improved the outcome of patients with nonsquamous cell carcinomas. Also, the administration of at least 3 cycles was significantly associated with better PFS \( (P=0.03) \) and OS \( (P=0.03) \) \[19\]. A subsequent update of this latter study found an estimated 5-year OS of 80% in the CMT arm versus 66% in the irradiated-only cohort. Furthermore, the benefit of chemotherapy was particularly seen in patients with tumors >2 cm \( (P=0.009) \) as well as with at least two positive pelvic nodes \( (P=0.006) \) \[20\]. Thus, this latter trial established the standard of care of adjuvant chemoradiation for patients with FIGO stages I and II cervical cancer with high-risk pathological factors, namely positive surgical margins, PNM, and PMI. (See Variant 2.) However, for patients with early stage cervical cancer there are three risk factors for relapse for which the preferred choice between CMT and PORT has not been established in a prospective phase III clinical trial: large tumor size, DCSI, and LVSI in the presence of negative nodes or extracervical involvement. However, this patient population is currently being investigated by the GOG.

Another retrospective study reviewed the experience of 25 patients with FIGO stages IB, IIA, and IIB cervical cancer with at least two positive pelvic nodes and/or metastatic common iliac nodes who were treated with adjuvant CMT. Following radical hysterectomy, patients received one cycle of adjuvant chemotherapy (CDDP [60 mg/m²] and 5-FU [1500 mg/m²]) with either bleomycin [30 mg/m²] for squamous cell carcinoma or epirubicin [35 mg/m²] for adenocarcinoma) followed by extended field PORT to the pelvis (45 Gy total dose) and para-aortic region (40 Gy total dose) with weekly CDDP (30 mg/m²).
After completion of adjuvant chemoradiation, patients received five more cycles of adjuvant chemotherapy at 4-week intervals. With median follow-up of 30 months (range: 7-54 months), 16 patients (64%) were without evidence of disease, and no patient relapsed in the para-aortic region [21].

Finally, in a single institutional retrospective study, 65 patients with FIGO stages IB and IIA cervical cancer with DCSI (>50% of cervical wall), positive surgical margin, PMI, and/or PNM following radical surgery and pelvic lymphadenectomy were all given adjuvant chemotherapy alone. The drug regimen consisted of bleomycin (5 mg IV continuous infusion for 7 days), vincristine (0.7 mg/m² IV bolus on day 7), mitomycin C (7 mg/m² IV bolus on day 7), and CDDP (10 mg IV continuous infusion for 7 days). Patients received 3 cycles of chemotherapy every 4 weeks of chemotherapy for positive DCSI and 5 cycles for the presence of the other factors. The estimated 5-year disease-free survival (DFS) rates was 100% for patients with squamous cell carcinoma and DCSI, 71.4% for those with adenosquamous cell carcinoma and DCSI, 89.3% for those with squamous cell carcinoma and at least one of the other risk factors, and 71.4% for those with adenosquamous cell carcinoma and at least one of the other factors [22]. It must be noted that these latter two studies were retrospective in nature with a small number of patients. Consequently these had “unknown” selection criteria. Nonetheless, their results suggest further investigation of adjuvant chemotherapy alone in a well-controlled prospectively randomized trial in such subsets of cervical cancer patients.

**Postoperative Radiation Therapy Planning**

Clinical target volume (CTV) considerations are different in planning adjuvant RT for intermediate-risk patients with no extracervical disease extension but with pathologic risk factors in the cervix, high-risk patients with PNM, PMI, or positive parametrial margins, and incidental hysterectomy group patients as discussed above. Radiation treatment planning also requires consideration of techniques that will minimize morbidity resulting from the combination of surgery and PORT or chemoradiation therapy. CTV considerations include “small” or true pelvic field radiation therapy (TPRT) where the superior border of the pelvic field is lowered from the traditional L4-L5 interspace whole pelvic radiation therapy (WPRT) to 1-2 cm inferior to the inferior aspect of the sacroiliac joint, standard WPRT, and pelvic/para-aortic lymph node volumes (extended field radiation therapy [EFRT]). Other considerations in the planning process include radiation delivery techniques (traditional field arrangements, 3D conformal radiotherapy [3DCRT], and intensity-modulated radiation therapy [IMRT] or image-guided radiation therapy [IGRT]) as well as accessory devices that may be used to decrease treatment morbidity.

The standard of care for delivering pelvic PORT is derived from the two previously mentioned randomized phase III trials that addressed adjuvant irradiation for intermediate/high-risk patients with cervical carcinoma [17,18]. Although these reports did not elaborate on the techniques of delivery of PORT, they did describe the use of a four-field “box” technique to encompass the whole pelvis using bony landmarks to ensure adequate coverage of the tumor bed and pelvic nodal regions. Such nodal groups included the obturator nodes, external iliac nodes, hypogastric nodes, and presacral nodes.

Although no phase III trial has been designed to compare 3DCRT and IMRT, RTOG 0418 was opened as a phase II multi-institutional study to evaluate the role of IMRT for delivering adjuvant radiotherapy to patients that included stage I/II cervical carcinoma. In preparation for this trial, an international consortium of radiation oncologists collaborated to define a target delineation atlas that standardized IMRT treatment planning [23].

For the purpose of this discussion, it is assumed that there is no gross tumor volume (GTV) in the postoperative treatment of early-stage cervical cancer. However, GTV considerations should be addressed if surgical findings, postoperative restaging imaging, or post simple hysterectomy findings indicate the presence of residual disease. In general, the CTV dose is 45-50 Gy at 1.8-2.0 Gy per fraction, whereas GTV requires additional boost dose. Postoperative nodal CTV determination includes encompassing the bilateral internal, external iliac, common iliac, presacral, and para-aortic nodal lymph node regions as indicated. In addition, soft-tissue CTV determination includes upper vagina, parametrial/paravaginal soft tissues, and the spread patterns along the ligaments that support the cervix.

Currently, the determination of the extent of nodal and soft-tissue volumes is influenced by historical practices and institutional guidelines rather than randomized clinical trials. There are no randomized clinical trial data evaluating “small” TPRT versus conventional WPRT with or without treatment aids with the aim of reducing small-bowel dose.

Three retrospective studies have reported on the use of TPRT for intermediate-risk patients. Kridelka et al [24] in a pilot study of 25 stage IB lymph node negative patients considered to be at high risk for recurrence the patients were treated with 50.4 Gy of TPRT. The boundaries of the true pelvis were well described, with the superior border being located at the S1-S2 junction. They reported no major morbidity three cases of minor morbidity, and one case of mild rectal incontinence. One recurrence was observed in and out of the irradiated fields along the small-bowel mesentery, causing both small-bowel and bilateral ureteric obstruction. DFS was comparable to that of the GOG 92 study group.

Hong et al [25] retrospectively investigated whether postoperative TPRT is an appropriate treatment for node-negative, high-risk stage I-IIA cervical cancer patients. Seventy-nine patients (35%) received 30-50 Gy to the whole pelvis and a boost to the “low” pelvis (WPRT group). The other 149 patients (65%) received true pelvic RT only (TPRT group). This was not a randomized study. Parametrial involvement, lymph-vascular invasion, <50.4
Gy to the low pelvis, positive or close margins, and TPRT alone did not significantly affect survival. Three patients (2%) in the TPRT group and 6 patients (8%) in the WPRT group were found to have grade III or higher small-bowel complications \( (P=0.023) \). Five patients (3.6%) of the TPRT group and none of the WPRT group developed upper pelvis relapse. Three of these 5 patients had upper pelvic relapse alone. The authors concluded that TPRT alone appears to be an appropriate treatment method for this group of patients as compared with WPRT. TPRT significantly reduced the small-bowel complications. Although upper pelvic relapses were noted in the TPRT group, it was not shown in this small study to affect on OS.

Ohara et al [26] examined whether use of TPRT encompassing only the pericervical regions and adjacent lymphatic region would reduce the adverse events that occur with postoperative classic WPRT for cervical cancer. This retrospective study included 72 node-negative patients treated with TPRT and 46 patients of whom 34 had positive nodes treated with WPRT. Total dose was 50.0 or 50.4 Gy at 2.0 or 1.8 Gy per fraction. Acute side effects of diarrhea (grades 2-3) and leucopenia (grades 1-3) occurred significantly more often in the WPRT group (32% and 80%, respectively) than in TPRT group (9% and 52%, respectively). Late effects of ileus occurred at a significantly higher rate in the WPRT group than in the TPRT group (5-year rate, 16% vs 3%). The 5-year pelvic disease control rates were similar (TPRT group 93%, WPRT group 90%).

Techniques to Displace Small-Bowel out of the Pelvis to Diminish Postoperative Radiation Treatment Morbidity

A number of studies with small numbers of patients have reported different techniques to displace the small-bowel out of the postoperative pelvic field in an effort to diminish small-bowel morbidity. These techniques can be divided into an operative intervention group for internal devices and a nonoperative methods group.

Operative Internal Devices

Operative internal devices have included an autologous sling constructed from the peritoneum, the omentum, or the small-bowel mesentery or a polyglcan mesh sling. Others have used tissue expanders (TEs) or silicone breast type implants. These have had minimal success and are associated with morbidity from the surgical procedure itself.

Burnett et al [27] reported the use of a prosthetic silicone plastic device implanted in the pelvis that was inflated with 960-1200 ml of fluid prior to the start of PORT in 7 patients. They reported that all patients had radiologically documented exclusion of the small-bowel from the radiation field. One patient had pulmonary embolus in the immediate postoperative period. No clinical data on reduction in acute or late bowel morbidity or long-term follow-up information were provided.

Geller et al [28] recently reported the feasibility and morbidity of using saline-filled TE to reduce bowel morbidity in 10 patients considered to be at high risk for late morbidity. They observed small-bowel exclusion from the pelvis to varying degrees in all patients. Two patients had the TE removed prior to RT. Early complications included migration of TE during RT, development of vesico-vaginal fistula requiring immediate removal of the TE, and enterocutaneous fistula in a patient who developed pelvic abscess. Another patient had a rectovaginal fistula 18 months after removal of the TE. In their review of previous 4 studies of TE in 60 patients, the overall complication rate range was 5%-40%. They concluded that the TE placement can successfully isolate small-bowel from the pelvis, but its usage should be individualized, and that additional studies with a larger series of patients and longer follow-up are needed.

Nonoperative Methods

A variety of nonoperative and external devices have also been investigated to diminish the volume of small-bowel in pelvic RT. These methods include: prone position, Trendelenburg/inclined position, a belly board device (BBD), and full bladder during the delivery of RT fraction that help to displace small-bowel out of the pelvic radiation fields.

Belly Board Device

A BBD is used as an external compression device with the patient lying in a prone position while the lower abdomen is compressed against the flat part of this board. An opening in the board cephalad to the superior border of the pelvic field allows the displaced small-bowel to fall (“drop”) in this space.

Ghosh et al [29] studied the use of BBD with the patient in prone position and full bladder to reduce the small-bowel volume in pelvic radiation fields in 21 patients. The simulation films were visually analyzed, and the fields with the least amount of small-bowel in the target volume were chosen. BBD was most effective at minimizing small-bowel in the lateral fields, and prone position without the BBD spared the most volume of small-bowel. With median follow-up of 37 months, no bowel obstructions or fistula were observed. There were no acute gastrointestinal changes or requiring medical intervention for gastrointestinal morbidity in 86% of the patients.

Adli et al [30] performed a dosimetric study of IMRT with the patient in prone position and BBD to reduce the small-bowel dose in pelvic RT in 16 patients. Their preliminary data suggested that prone position with BBD can reduce the small-bowel dose with pelvic PORT. Furthermore, the dose reduction was dependent on the IMRT technique used.

Radiation Treatment Planning

Conventional Pelvic Radiation Therapy

Taylor and Powell [31] did a review of various radiation therapy techniques used in treating cervical cancer. They noted that there is a high risk of geographical miss and an
increase in normal tissue toxicity in treating cervical cancer patients with conventional 2-D RT. They concluded that 3DCRT and IMRT techniques can improve outcomes by accurate target coverage while reducing doses to organs at risk.

Zunino et al [32] reviewed the RT “box” technique for patients with FIGO stages IB-IVA cancer of the cervix using sagittal magnetic resonance imaging (MRI) (N = 35) and lymphangiography (N = 10). An anatomic study was performed on 30 cadavers to identify aortic bifurcation, lymphatic nodes, and uterus flexion. In 50% of the patients with FIGO IB, the posterior border of the lateral field was inadequate to encompass the planning target volume. The posterior border of the lateral field was inadequate in 49% of the cases, and the anterior border in 9% of the cases as assessed by sagittal MRI in 35 patients. The investigators concluded that the design of the lateral fields of the four-field technique for irradiation of the uterine cervix cancer based on anatomic bone references failed to encompass the planning target volume in a significant number of patients. They also emphasized the use of sagittal MRI view.

Gerstner et al [33] reported on the benefit of beam’s eye view (BEV) based 3D treatment planning compared to dose distribution derived from the conventional four-field pelvic box technique in 20 cervical cancer patients. The BEV conformal plans resulted in a 10% dose reduction of small-bowel volume included in the treated volume and reduced the risk of a geographical miss by 20%.

McAlpine et al [34] correlated radiation fields defined by bony landmarks to anatomic boundaries of lymph node dissection marked intraoperatively with surgical clips in 100 patients. Although 91% of patients would have adequate para-aortic lymph node coverage, they noted that the pelvic fields would miss 39% of common iliac nodes and 26% would receive inadequate coverage of one or both lateral boundaries of pelvic radiation.

3D Conformal Radiation Therapy and Pelvic Intensity-Modulated Radiation Therapy

Several investigators have reported studies of pelvic IMRT in gynecological patients that include dosimetric and some early clinical outcome studies. Mundt et al [35-38] have reported preliminary results showing a decrease in the small-bowel volume irradiated and a reduction in both acute and chronic gastrointestinal toxicities compared to historical series.

Taylor and Powell [31] performed a dosimetric study to compare four planning techniques (conventional with bony anatomy, conventional with virtual simulation, 3DCRT, and IMRT) in 40 consecutive patients receiving RT for cervical cancer. Dose-volume histograms for target volumes and the organs at risk were compared. Conventional fields based on bony landmarks provided inadequate coverage in 25% of patients, virtual simulation increased the volume of normal structures in the irradiated volume, and 3DCRT led to larger portals but permitted field shaping and shielding and more homogeneous dose. The IMRT dose distribution was more precise and conformal and reduced the dose to the normal organs.

Roeske et al [36] reported that IMRT decreased irradiated small-bowel volume at doses >30 Gy. They compared IMRT to standard four-field WPRT. At a 45 Gy prescription dose, the small-bowel volume >30 Gy was reduced from 34% to 17% (P = 0.0005). Portelance et al [39] noted statistically significant decreases in irradiated small-bowel volume with IMRT compared with conventional RT in cervical cancer patients. Heron et al [40] compared a four-field 3DCRT pelvic plan to a seven-field pelvic IMRT plan in 10 gynecological patients referred for adjuvant therapy. The volume of small-bowel receiving >30 Gy was reduced by 52% with IMRT compared with the 3DCRT plan. Igdem et al [41] compared a four-field box pelvic RT plan with a pelvic IMRT plan in 10 patients and noted that the average absolute volume of small-bowel receiving 45 Gy was significantly reduced from 318 cc to 33 cc.

Mundt et al [42] reported that IMRT significantly reduced the frequency and severity of acute gastrointestinal toxicity compared with conventional RT. In a follow-up analysis they also reported that intensity-modulated whole pelvic radiation therapy (IM-WPRT) was well tolerated in 40 patients with gynecological malignancies, with no patient developing grade 3 toxicity. Grade 2 acute gastrointestinal toxicity was less common in the IM-WPRT group (60% vs 91%, P = 0.002) than in the conventional WPRT group. Moreover, the percentages of IM-WPRT and WPRT patients requiring no or only infrequent antidiarrheal medications were 75% and 34%, respectively (P = 0.001) [43].

Mundt et al [35] further reported on chronic gastrointestinal toxicity in 36 gynecologic patients treated with IM-WPRT and compared this with patients who were treated with conventional WPRT prior to the implementation of pelvic IMRT. With a median follow-up of 19.6 months (IM-WPRT) and 30.2 months (WPRT), the IM-WPRT patients had lower rate of chronic grade 1-3 gastrointestinal toxicity (11% vs 50%). The percentages of IM-WPRT patients with grade 1, 2, and 3 toxicities were 8%, 3%, and 0%, respectively. Corresponding percentages in the WPRT group were 30%, 17%, and 3%, respectively. They stated that longer follow-up with more patients is needed to ascertain the benefit of IM-WPRT. Moreover, a familiarity with appropriate field design, normal tissue dose constraints, and recognition of organ motion and deformation is crucial prior to initiating any IMRT program for this patient population.

Extended-Field Radiation Therapy

EFRT refers to irradiation of abdominal para-aortic/paracaval lymph node regions in addition to the pelvic CTV that encompasses the bilateral common iliac, external iliac, internal iliac, and presacral lymph node regions and the vaginal/paravaginal soft-tissue CTV.

Reports of clinical experiences as well as a limited number of randomized studies of EFRT have been published for different types of clinical situations. One group of patients has biopsy-confirmed metastases to the
para-aortic nodes regardless of the clinical stage [44,45]. Second group of patients with biopsy-confirmed pelvic nodes who have early-stage cervical carcinoma are undergoing surgical therapy and have elective EFRT. A third group of patients have advanced-stage cervical carcinoma with intact cervix that has high risk of occult pelvic and para-aortic metastases but without biopsy confirmation, or have imaging findings of lymph node metastases and are also considered for elective EFRT along with definitive external beam pelvic RT and brachytherapy [46,47].

In a GOG study of 95 patients who underwent extraperitoneal pelvic and para-aortic lymphadenectomy, Ballon et al [44] reported estimated 5-year survival rates without recurrence of 75% in patients with no lymph node metastases, 56% for those with pelvic node metastases, and 23% for those with para-aortic node metastases. Van et al [45] reported the results of the GOG study of EFRT with concurrent chemotherapy in patients with biopsy-confirmed para-aortic node metastases. The 3-year OS and PFS rates were 39% and 34%, respectively, for the entire group. OS rates were 50% for stage I patients, 39% for stage II patients and 38% for stage III/IVA patients. Late morbidity actuarial risk of 14% at 4 years primarily involved the rectum rather than small-bowel.

Rotman et al [47] reported the 10-year results of the RTOG® 79-20 randomized study of prophylactic EFRT of para-aortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas. The 10-year OS rate was 44% for the pelvic-only irradiation arm and 55% for the pelvic plus para-aortic irradiation arm (P=0.02). Haie et al [46] have reported the results of the EORTC randomized study of prophylactic para-aortic irradiation in the treatment of advanced cervical carcinoma. The 4-year no-evidence-of-disease survival rate was 41%. They concluded that routine para-aortic irradiation for all high-risk patients with cervical carcinoma is of limited value. Finally, it must be pointed out that the phase III trial showing a benefit of adjuvant chemoradiation over radiation alone included the use of EFRT for patients with positive common iliac nodes [18]. Yet patients with a moderate to high probability of involvement of para-aortic lymph nodes may benefit from EFRT even with an increase in digestive complications. High-risk cervical cancer patients undergoing adjuvant therapy would fit into this group. (See Variant 3 and Variant 4.)

Methods of Routine Surveillance and Post-treatment Toxicity

Adjuvant radiation or chemoradiation after radical hysterectomy for stage I/II cervical cancer has been well studied. Randomized trials have been conducted to determine prognosis, risk factors for recurrence, side effects, and treatment strategies. Less attention has been directed towards follow-up, including evaluation of long-term side effects, especially in sexual and ovarian function. The utility and comparative effectiveness of imaging in the postoperative setting for cervix cancer has not been established, and the comparative effectiveness of computed tomography (CT), MRI, and positron emission tomography (PET) remains undefined. Serial cross-sectional imaging is generally not used for post-therapy surveillance.

The GOG conducted a randomized trial in women who underwent radical hysterectomy and had at least two risk factors for recurrence consisting of >1/3 stromal invasion, capillary lymphatic space involvement, and large clinical tumor diameter. As has been described previously, patients were randomized to pelvic PORT or observation. Follow-up observation in this study consisted of physical examination, blood counts, blood chemistries, and chest radiographs every 3 months during the first 2 years of follow-up, and every 6 months during subsequent years. Intravenous pyelograms and renal sonograms or CT scans with contrast were to be done at 6 months and then yearly. No mention was made of Pap smears done for surveillance. Nine (7.0%) of the 128 patients who received RT experienced grade 3 or 4 adverse effects, compared to three (2.1%) of the 140 patients in the observation group. The most common grade 3 and 4 adverse effects were genitourinary, gastrointestinal, and hematologic toxicities. One woman in the RT group died from complications of an enteric fistula [17].

The Austrian GOG conducted a randomized trial in women who had undergone a radical hysterectomy and had pelvic lymph node metastases and/or vascular invasion. Patients were randomized to carboplatin and bleomycin chemotherapy, pelvic RT, or no further treatment. There was no detailed evaluation of long-term side effects available for review. However, the authors did report that 4% of patients in the chemotherapy arm developed mild thrombocytopenia and leucopenia. The incidence of complications in the patients who received radiation was 3%, but the type and severity of the complications were not presented. Surveillance consisted of physical examination, colposcopy/cytology, tumor markers, chest radiograph, intravenous urogram, and ultrasound/CT [16]. Another randomized trial regarding adjuvant chemoradiation after radical hysterectomy with at least one of the following findings: positive pelvic lymph nodes, positive margins, or microscopic involvement of the parametrium. Patients were randomized to pelvic radiation with or without concurrent cisplatin and 5-FU chemotherapy. There was considerably more grade 3 and 4 toxicity in the chemotherapy arm, mostly hematologic [18].

A few studies have examined long-term side effects in women who received treatment for cervical cancer. These studies include patients who received adjuvant radiation or chemoradiation following radical hysterectomy. One study reviewed women 5 years after treatment for cervical cancer. Post-treatment surveillance included imaging studies, cystoscopy, and proctosigmoidoscopy at 1 and 5 years after therapy. Most complications were gastrointestinal, urinary, or lower-extremity edema. Women who received RT, either alone or after radical hysterectomy, had significantly more gastrointestinal toxicity at 5 years after treatment than women who had surgery alone [48].
An observational study was done to evaluate micturition, defecation, and sexual function after radical hysterectomy/pelvic lymphadenectomy in women with early-stage cervical cancer. Age-matched controls were used. The patients had significantly more problems with sexual function, including less lubrication, a more narrowed and foreshortened vagina, decreased sensation, dyspareunia, and sexual dissatisfaction. Initially, patients had more bladder dysfunction, colorectal motility disorders, and lymphedema. Yet, after 2 years of follow-up these differences between patients and controls were no longer significantly different [49].

Regarding prevention of vaginal stenosis following surgery and adjuvant pelvic radiation, reports on the use of vaginal dilators have been anecdotal in the literature. However, one review paper did suggest that some type of vaginal dilation post-treatment could not only prevent vaginal stenosis but also could treat existing stenosis. Furthermore, the use of vaginal dilation was effective even if patients were sexually active. Finally, it was recommended that patients regularly use the dilator for 15-20 minutes for at least two times per week for their remaining lifetime [50].

Ovarian function after treatment for cervical cancer has been reviewed. One hundred and two premenopausal women who underwent surgery for early-stage cervical cancer with ovarian preservation were retrospectively analyzed for age at onset of menopause. Mean follow-up of the study cohort was 87.0 months. Radical hysterectomy without transposition of the ovaries did not affect the age of onset of menopause compared to historical controls. However, the addition of ovarian transposition or unilateral oophorectomy to hysterectomy did reduce the age of onset appreciably [51]. It is well known that low doses of pelvic RT can induce premature menopause. Unless the dose to the ovary(s) can be kept sufficiently low, the value of performing oophorectomy in premenopausal woman undergoing radical hysterectomy for early-stage cervical cancer remains uncertain. One potential improvement pertains to the use of IMRT to reduce the exposure to the ovaries during pelvic PORT. (See Variant 5.)

Summary
Information on radical hysterectomy and lymph node dissection surgical pathology can be used to divide cervical cancer patients into three groups that help to predict the risk of recurrence and the indications for adjuvant therapy. In addition there is a fourth group of patients who are discovered to have invasive cervical carcinoma following simple hysterectomy for benign indication and need further treatment.

I. Low risk. Patients with primary lesion <4 cm, minimal cervical stromal invasion, no LVI, no extracervical tumor extension, negative parametrial margins, and no lymph node metastases are considered adequately treated by surgical therapy and do not require adjuvant therapy.

II. Intermediate Risk. Patients with no extracervical tumor extension, negative parametrical margins, and no lymph node metastases, but who have certain combinations of LVI, depth of cervical stromal invasion, and primary lesion size are considered to have about 30% risk for recurrence.

III. High Risk. Patients with regional lymph node metastases, PMI, and/or positive parametrial/vaginal margins are considered to have substantial risk of recurrence. Five-year OS rates reported in the literature in this group of patients are 50%-60%.

Role of Adjuvant Radiation Therapy
The literature reveals category 1 data from two randomized phase III trials indicating that the conclusions are valid and strongly supported by the study design, analysis, and results regarding adjuvant postoperative radiation therapy. For the stage IB intermediate-risk cervical cancer patients, the GOG #92 study demonstrated a significant reduction in loco-regional recurrence with adjuvant pelvic irradiation compared to observation [17]. A more recent update on GOG #92 confirmed the reduction in recurrences (especially for adenocarcinoma or adenosquamous cell carcinoma); however, no OS benefit was detected [18]. The other trial, involving early-stage I and II high-risk cervical cancer patients (the SWOG/GOG/RTOG® intergroup study), found a positive survival benefit from the addition of platinum-base chemotherapy during pelvic PORT for early-stage I and II cervical cancer [18]. There is also category 2 evidence from the GOG [14,15] that the conclusions are likely valid. However, the study design of GOG #49, which was a review of the outcome of 645 prospectively enrolled patients with stage IB squamous cell carcinoma who underwent radical hysterectomy and pelvic lymphadectomy, does not permit certainty regarding the risk assessment model concerning pelvic relapse in at-risk patients.

Adjuvant Radiation Therapy Planning
Regarding the use of true pelvic fields, the cited studies provide category 2 evidence that the conclusions of the studies are likely valid, but study designs do not permit certainty. The studies had small number of patients, lacked dose volume assessments, and were retrospective. There were no concurrent control arms or formal prospective data collection that document post-treatment morbidity in detail. The use of formal and periodic imaging studies to assess local and pelvic control is not evident in these published reports.

Techniques for Delivering Adjuvant Radiation Therapy
The studies regarding operative techniques to reduce bowel toxicity during subsequent RT provide mixed category 2 and 4 evidence levels [26, 27]. These investigations suggesting that a decrease in the small-bowel volume in the pelvic radiation fields is achievable are valid, but evidence that it decreases small-bowel morbidity may not be valid. There is additional concern that it may increase overall morbidity as result of the operative procedure. The studies had small number of patients, lacked dose-volume assessments, and were more like pilot studies. There was no concurrent control arm or
formal prospective data collection to document post-treatment morbidity in detail. The use of formal and periodic imaging studies to assess local and pelvic control is not evident in these published reports. With respect to nonsurgical interventions, these referenced studies provide category 3 evidence that the conclusions are likely valid. However, the number of patients was small, and the study by Ghosh et al [29] did not have dose-volume assessments. Adli et al [30] is a dosimetric study and does not have clinical outcome data.

**Adjuvant Pelvic Radiation Therapy Planning Guidelines**

There are category 2 and 3 data concerning adjuvant pelvic radiation therapy that raise concern over the problems of geographical miss as well as difficulty of reducing the dose and volume of the normal organs with standard pelvic fields based on bony landmarks. The presented dosimetric studies of pelvic IMRT provide category 3 evidence that the conclusions of the study may be valid but need careful attention to IMRT planning requirements for CTV coverage and reduction of dose to the normal organs.

**Adjuvant Extended-Field Radiation Therapy Planning Guidelines**

There is category 2 evidence that the conclusions of these studies are likely valid and supported by study design, analysis, and results that show long-term DFS with some increase in treatment toxicity for a portion of patients with biopsy-proven para-aortic/common iliac node metastases. However, the study design does not permit certainty about the choice between elective chemo-EFRT compared to EFRT alone, as there are no prospective randomized trials of this comparison. However, it would be reasonable to extrapolate from other prospective randomized studies comparing pelvic radiation only with pelvic chemoradiation, that when EFRT is indicated, concurrent chemoradiation therapy might be beneficial.

**Methods of Routine Surveillance and Post-treatment Toxicity**

The literature does not depict the details of adequate surveillance testing or time intervals following adjuvant RT for early-stage cervical cancer. There is category 1 evidence that the conclusions of the studies are valid and strongly supported by the phase III study design, analysis, and results regarding the significant risk of severe toxicity from adjuvant therapy for early-stage cervical cancer, especially concerning hematologic toxicity from chemoradiation versus pelvic PORT alone [18]. There is category 3 evidence that the conclusions of the studies may be valid, but the evidence supporting the conclusions may not be reliable given the study design or analysis pertaining to the use conformal-type (3D or IMRT) treatment techniques to reduce exposure to the bowel, bladder, rectum, or bone marrow, particularly if EFRT is being employed. There is category 2 evidence that the conclusions of the study are likely valid, but the study design does not provide certainty about there being no statistically significant increase in late effects on bladder function, gastrointestinal motility, or sexual functions with adjuvant pelvic irradiation [49]. There does exist category 2 evidence indicating without certainty that the use of ovarian transposition does negatively impact ovarian function, which is only compounded by the addition of PORT [51].

**Supporting Document(s)**

- ACR Appropriateness Criteria® Overview
- Evidence Table

**References**


The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient’s clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient’s condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.
Clinical Condition: Early Stage Cervical Cancer

Variant 1: 40-year-old woman with a 2 cm cervical tumor undergoes radical hysterectomy and pelvic lymphadenectomy. Pathological review of the surgical specimens reveals the following: moderately differentiated squamous cell carcinoma of the cervix, middle third cervical stromal invasion, positive capillary-lymphatic space invasion, negative nodal metastases, and negative surgical margins.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant Treatment</td>
<td></td>
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</tr>
<tr>
<td>Pelvic external beam irradiation alone</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Concurrent pelvic irradiation and chemotherapy</td>
<td>5</td>
<td></td>
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<tr>
<td>Observation</td>
<td>2</td>
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<tr>
<td>Chemotherapy alone</td>
<td>1</td>
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</table>

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

Variant 2: 30-year-old woman with a 4 cm cervical tumor undergoes radical hysterectomy and pelvic lymphadenectomy. Pathological review of the surgical specimens reveals the following: poorly differentiated adenocarcinoma, positive right parametrial invasion, positive capillary-lymphatic space invasion, 3 positive pelvic nodes in the right external iliac region, and negative surgical margins.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Adjuvant Treatment</td>
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<td></td>
</tr>
<tr>
<td>Concurrent pelvic irradiation and chemotherapy</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Extended field (pelvic and para-aortic) irradiation with chemotherapy</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pelvic external beam irradiation alone</td>
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<tr>
<td>Observation</td>
<td>1</td>
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<tr>
<td>Chemotherapy alone</td>
<td>1</td>
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</tbody>
</table>

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate
Clinical Condition: Early Stage Cervical Cancer

Variant 3: 40-year-old woman with a 2 cm cervical tumor undergoes radical hysterectomy and retroperitoneal pelvic/para-aortic lymphadenectomy. Pathological review of the surgical specimens reveals the following: well differentiated squamous cell carcinoma, no parametrial invasion, positive capillary-lymphatic space invasion, outer third cervical stromal invasion, 0 out of 16 positive nodes, and negative surgical margins. Assume adjuvant radiation has been recommended.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiation Treatment Considerations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole pelvic fields</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>3D conformal RT</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Patient supine</td>
<td>8</td>
<td>Considered most likely position for reproducibility of setup.</td>
</tr>
<tr>
<td>Patient prone</td>
<td>7</td>
<td>May be advantageous if significant volume of small-bowel can be excluded.</td>
</tr>
<tr>
<td>Use belly board device</td>
<td>7</td>
<td>May be advantageous if significant volume of small-bowel can be excluded.</td>
</tr>
<tr>
<td>IMRT</td>
<td>7</td>
<td>Great care is required in delineation of CTV.</td>
</tr>
<tr>
<td>Four-field “box” technique</td>
<td>7</td>
<td>In venues lacking sufficient resources and equipment, may be best option for ensuring adequate target coverage.</td>
</tr>
<tr>
<td>True pelvic fields</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Use of implantable mesh or device</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Use of implantable tissue expanders</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Extended fields</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate*
Clinical Condition: Early Stage Cervical Cancer

Variant 4: 50-year-old woman with a 3 cm cervical tumor undergoes radical hysterectomy and retroperitoneal pelvic/para-aortic lymphadenectomy. Pathological review of the surgical specimens reveals the following: poorly differentiated squamous cell carcinoma with positive left parametrial invasion, positive capillary-lymphatic space invasion, outer third cervical stromal invasion, 4 out of 10 positive left pelvic nodes, 3 out of 6 positive bilateral para-aortic nodes, and negative surgical margins. Assume adjuvant chemoradiation has been recommended.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Radiation Treatment Considerations</td>
<td></td>
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<tr>
<td>Extended fields</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>3D conformal RT</td>
<td>8</td>
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<tr>
<td>Patient supine</td>
<td>8</td>
<td>Considered most likely position for reproducibility of setup.</td>
</tr>
<tr>
<td>IMRT</td>
<td>7</td>
<td>Great care is required in delineation of CTV.</td>
</tr>
<tr>
<td>Four-field “box” technique</td>
<td>7</td>
<td>In venues lacking sufficient resources and equipment, may be best option for ensuring adequate target coverage.</td>
</tr>
<tr>
<td>Patient prone</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Use belly board device</td>
<td>2</td>
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<tr>
<td>Use of implantable mesh or device</td>
<td>2</td>
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<tr>
<td>Use of implantable tissue expanders</td>
<td>2</td>
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<tr>
<td>True pelvic fields</td>
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<tr>
<td>Whole pelvic fields</td>
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</table>

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

Variant 5: 30-year-old woman with a 2.5 cm cervical mass undergoes radical hysterectomy and retroperitoneal pelvic/para-aortic lymphadenectomy along with oophoropexy. Pathological review of the surgical specimens reveals the following: moderately differentiated squamous cell carcinoma, no parametrial invasion, positive capillary-lymphatic space invasion, outer third cervical stromal invasion, 0 out of 16 positive nodes, and negative surgical margins. Assume adjuvant chemoradiation (pelvic external beam) has been completed.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Routine Follow-up Recommendations</td>
<td></td>
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<tr>
<td>Follow-up visits every 3-6 months with pelvic examination and PAP smears with gynecologic oncologist and/or radiation oncologist for at least 5 years</td>
<td>9</td>
<td></td>
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<tr>
<td>Sexual function evaluation every 3-6 months for at least 5 years</td>
<td>8</td>
<td></td>
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<tr>
<td>Discuss use of vaginal dilator every 3-6 months for 5 years</td>
<td>8</td>
<td></td>
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<tr>
<td>Follow-up imaging studies every 3-6 months such as PET/CT and/or MRI scans for at least 5 years</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Female hormonal laboratory studies every 3-6 months for at least 5 years</td>
<td>3</td>
<td></td>
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</tbody>
</table>

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