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

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Summary of Literature Review

Background on Surgical Management

Radical abdominal hysterectomy (RAH), along with pelvic lymphadenectomy (PL), has been the standard of care for the primary surgical management of patients with what the International Federation of Gynecology and Obstetrics (FIGO) deems early clinical stages I and II cervical carcinoma [1]. The first RAH 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 recognized today as the first true radical hysterectomy [2]. 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 [3]. Procedural modifications were later introduced by Okabayaski (isolation of the rectum and resection of the cardinal and uterosacral ligaments prior to the anterior dissection) and by Schauta (radical vaginal approach) [4,5]. Liu and Meigs [6] reinvigorated interest in primary surgical treatment of cervical cancer with reported 5-year survival rates >75% and no operative deaths among their 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 RAH was first described by Piver et al [7] and recently updated by Querleu and Morrow [8].

More recent advances in surgical techniques have allowed the implementation of less invasive procedures such as laparoscopic assisted radical vaginal hysterectomy as well as vaginal assisted laparoscopic radical hysterectomy [1]. There have been emerging data to suggest that vaginal radical trachelectomy is oncologically feasible while still maintaining fertility for 125 patients with FIGO stage IA2 and IB1 from a single institution's prospective database [9]. Another single institutional retrospective study showed that in patients having RAH with FIGO stages IA2 to IIB, radical parametrectomy or radical trachelectomy in conjunction with PL achieved excellent survival with only 22% of the patients requiring postoperative radiation therapy (PORT) [10]. However, the total number of pelvic nodes to be harvested at the time of RAH has not been clearly established [11]. Moreover, the use of sentinel lymph node biopsy, which uses Tc-99m-labeled phytate, has not only become common in cervical cancer patients undergoing RAH, but is also common in selected cervical cancer patients undergoing radical abdominal trachelectomy to preserve fertility [12].

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Role of Adjuvant Radiation Therapy

The optimal role of adjuvant radiation therapy (RT) for patients with stage I/II cervix cancer continues to evolve. The use of certain clinical/pathological appropriateness criteria for the implementation of adjuvant therapy in the management of early-stage carcinoma of the cervix has been previously published by an American College of Radiology panel of clinical experts [13]. This report is an update of this previous experience.

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 from May 1981 to February 1984 [14]. Of this group, 645 patients with squamous cell carcinoma underwent radical hysterectomy and retroperitoneal lymphadenectomy, with no patients having any gross disease outside the cervix and uterus; however, microscopic pelvic nodal involvement was permitted. A multivariate analysis found that clinical tumor size, tumor involvement of the capillary-lymphatic spaces, and depth of tumor invasion of the cervical stroma were independent predictors of disease-free interval [15]. In fact, a risk assessment model was created that divided these patients into 3 groups for which the use of adjuvant therapy could be considered: low-risk (relative risk [RR] = 7.5–40), intermediate-risk (IR) (RR = 41–120), and high-risk (HR) (RR >120). A GOG score of >120 was associated with a 41% recurrence rate [15]. These RR group criteria from this latter study were recently retrospectively applied to 126 patients with cervical carcinoma who underwent RAH and PL at a single institution. Those patients with a RR of <41 received no adjuvant therapy, patients in the Delgado et al IR group [15] had true pelvic PORT, while those in the Delgado et al HR cohort [15] had whole pelvic adjuvant RT. The 5-year disease-free survival (DFS) for all 126 patients was 98.2% with no reported grade 3 or 4 chronic toxicities [16].

A phase III randomized trial conducted by the GOG evaluated the effect of PORT in FIGO stage IB IR patients with pathologically negative pelvic nodal metastases (PNM). 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 IR factors for recurrence were stratified by lymphovascular space invasion (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*=.019). Clinical tumor diameter was determined to be the most significant risk factor for recurrence [17]. An updated review at more than 9 years since GOG #92 closure 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% versus 20.7%) and distant (2.9% versus 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 nonsquamous 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*=.009). However, there was no statistical difference in overall survival (OS) between the 2 groups (*P*=.074) [18]. In addition, a recent meta-analysis of 2 prospective trials that included GOG #92 found no statistical OS benefit concerning PORT versus no adjuvant therapy; however, a subset analysis found a definitely positive impact of PORT on the OS of patients with negative LVSI, positive DCSI, and tumor diameter >4 cm [19]. (See Variant 1.)

A sentinel phase III randomized intergroup trial conducted jointly by the Southwest Oncology Group (SWOG), SWOG protocol #8797, Radiation Therapy Oncology Group® (RTOG®) protocol #91-12, and the GOG protocol #109 evaluated the addition of concurrent chemotherapy to adjuvant pelvic PORT in HR patients with FIGO pathological stages IA2, IB, or IIA cervical cancers following radical hysterectomy and PL with certain HR pathological findings [20]. There were 127 evaluable patients with PNM, positive parametrial invasion (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/m^2 intravenous (IV) infusion and 5-fluorouracil (5-FU) at 4,000 mg/m^2 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*=.003) and OS (*P*=.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*=.03) and OS (*P*=.03) [20]. 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*=.009) as well as with at least 2 positive pelvic nodes (*P*=.006) [21]. Thus, this latter trial established the standard of care of adjuvant chemoradiation for patients with FIGO stages I and II cervical cancer with HR pathological factors, namely positive surgical margins, PNM, and PMI. This latter reviewed study [20,21] has recently been included in a meta-analysis that demonstrated that the addition of chemotherapy to PORT for the HR patient population with stage IA2, IB, and IIA cervix cancer significantly lowered the risk of death and disease progression more than those receiving only PORT [22]. Furthermore, there is an ongoing phase III randomized study being jointly conducted by the GOG and the RTOG (protocol #0724) that seeks to determine the impact of adjuvant chemotherapy (involving carboplatin and paclitaxel) added to postoperative CMT on DFS versus adjuvant CMT alone for patients with HR stages IA2, IB, or IIA cervical carcinoma. (See Variant 2.)

However, for patients with early-stage cervical cancer there are 3 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 in a phase III randomized trial (protocol #0263), which is evaluating the impact on recurrence-free survival of adjuvant PORT versus CMT, consisting of PORT and chemotherapy, following RAH with PL in IR patients with stages I and IIA cervical carcinoma.

Another retrospective study reviewed the experience of 25 patients with FIGO stages IB, IIA, and IIB cervical cancer with at least 2 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/m^2] and 5-FU [1500 mg/m^2] with either bleomycin [30 mg/m^2] for squamous cell carcinoma or epirubicin [35 mg/m^2] 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/m^2). After completion of adjuvant chemoradiation, patients received 5 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 [23]. Besides the number of positive nodes, a more recent retrospective study involving 256 patients with stage IB and II cervical cancer who had either PORT or adjuvant CMT found that patients having greater than 10% positive metastatic lymph node ratio had a worse outcome, which included OS [24].

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 PL were all given adjuvant chemotherapy alone. The drug regimen consisted of bleomycin (5 mg IV continuous infusion for 7 days), vincristine (0.7 mg/m^2 IV bolus on day 7), mitomycin C (7 mg/m^2 IV bolus on day 7), and CDDP (10 mg IV continuous infusion for 7 days). Patients received 3 cycles of chemotherapy every 4 weeks for positive DCSI and 5 cycles for the presence of the other factors. The estimated 5-year DFS rate 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 [25].

Although retrospective in nature, these latter 3 retrospective series [23-25] suggest further investigation of adjuvant therapy is indicated in a well-controlled prospectively randomized trial to include various subsets of cervical cancer patients. In addition, future studies should consider evaluating the role of adjuvant treatment for patients with early-stage I or II adenocarcinoma of the cervix independent of squamous cell carcinoma histology based on the results of a recent retrospective study of 520 patients with stages IA2 and IIB cervical cancer patients treated with and without PORT and/or CMT who had IR and HR features [26]. Finally, more investigations are needed to identify novel treatment strategies for patients undergoing adjuvant RT with or without chemotherapy for early-stage cervical cancer at risk for having poor DFS [27] and OS [28].

Postoperative Radiation Therapy Planning

Clinical target volume (CTV) considerations are different in planning adjuvant RT for IR patients with no extracervical disease extension but with pathologic risk factors in the cervix, and in planning adjuvant RT for HR patients with PNM, PMI, or positive parametrial margins 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 of 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, 3-D 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 2 previously mentioned randomized phase III trials that addressed adjuvant irradiation for IR/HR patients with cervical carcinoma [17,20]. Although these reports did not elaborate on the techniques of delivery of PORT, they did describe the use of a 4-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 [29]. Of the total 83 patients who were enrolled into RTOG 0418, 40 had pathologic stages T1a–T2b, N0–N1, M0 disease. Although the complete pelvic bone marrow was not contoured for this latter study, patients receiving IMRT (40 Gy) to more than 37% of the pelvic bone marrow were more likely to experience at least grade 2 hematological toxicity within 90 days of starting pelvic IMRT [30].

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 findings after simple hysterectomy 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.

One retrospective study [31] did examine 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 the 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% versus 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 polyglycan mesh sling. Others have used tissue expanders (TEs) or silicone breast implants. These have had minimal success and are associated with morbidity from the surgical procedure itself.

Geller et al [32] 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 vesicovaginal 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 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 requiring that the patient have a full bladder during the delivery of RT fractions.

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 [33] studied the use of BBD with the patient in prone position and with a 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 medical interventions required for gastrointestinal morbidity in 86% of the patients.

Adli et al [34] 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 [35] reviewed various RT 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 dose to organs at risk.

McAlpine et al [36] 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% of patients would receive inadequate coverage of one or both lateral boundaries of pelvic radiation.

3-D 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 [37,38] 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 [35] performed a dosimetric study to compare 4 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 [38] reported that IMRT decreased irradiated small-bowel volume at doses >30 Gy. They compared IMRT to standard 4-field WPRT. At a 45 Gy prescription dose, the small-bowel volume >30 Gy was reduced

from 34% to 17% (*P*=.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 4-field 3DCRT pelvic plan to a 7-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 4-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 malignances, with no patient developing grade 3 toxicity. Grade 2 acute gastrointestinal toxicity was less common in the IM-WPRT group (60% versus 91%, *P*=.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*=.001) [43].

Mundt et al [37] 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 a lower rate of chronic grade 1–3 gastrointestinal toxicity (11% versus 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.

Mature prospective studies demonstrating the impact of adjuvant pelvic IMRT on the outcome of at-risk patients with early-stage cervical cancer are not currently available. However, there is one recently reported retrospective study of 34 patients at a single institution having either IR or HR features of stage I/IIA cervical cancer. These investigators found that the study cohort, which underwent adjuvant CMT following RAH with PL, had a 5-year OS of 91.1% (confidence interval 81.3%, 100%) with <3% acute grade 3 gastrointestinal toxicity and no acute grade 3 or higher genitourinary toxicity [44]. Yet, more studies are needed to determine if pelvic IMRT can contribute to reducing the incidence of lower-extremity edema following RAH with PL that has been significantly associated with the use of PORT [45].

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 had biopsy-confirmed metastases to the para-aortic nodes regardless of the clinical stage [46,47]. A second group of patients had biopsy-confirmed pelvic nodes and early-stage cervical carcinoma and underwent surgical therapy and elective EFRT. A third group of patients had advanced-stage cervical carcinoma with intact cervix and a high risk of occult pelvic and para-aortic metastases but without biopsy confirmation, or they had imaging findings of lymph node metastases and were also considered for elective EFRT along with definitive external beam pelvic RT and brachytherapy [48,49].

In a GOG study of 95 patients who underwent extraperitoneal pelvic and para-aortic lymphadenectomy, Ballon et al [46] reported an estimated 5-year survival rate 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. Varia et al [47] 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 [49] 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=.02). Haie et al [48]

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 HR patients with cervical carcinoma is of limited value. Finally, it must be noted 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 [20]. 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. HR 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 toward 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), magnetic resonance imaging (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 2 of the following risk factors for recurrence: >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 3 (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].

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, mostly hematologic, in the chemotherapy arm [20].

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. Gastrointestinal or urinary concerns or lower-extremity edema made up most types of complications. 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 [50].

An observational study was done to evaluate micturition, defecation, and sexual function after radical hysterectomy/PL 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 [51].

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 after 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 2 times per week for their remaining lifetime [52].

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 [53]. 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 oophoropexy 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

- The standard of care for IR stage I and II cervical cancer after RAH is adjuvant PORT. Concurrent cisplatin chemotherapy is currently being tested in this group.
- The standard of care for HR stage I and II cervical cancer after RAH is adjuvant PORT with concurrent platinum-based chemotherapy. Extended adjuvant chemotherapy is currently being tested in this group.
- The use of IMRT versus conventionally delivered adjuvant pelvic external beam irradiation with or without chemotherapy for patients with stage I/II cervical cancer requires further phase III testing with appropriate follow-up study.
- More investigations are warranted to determine optimal and cost-effective surveillance testing for this patient population.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Role of Adjuvant Therapy in the Management of 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 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.**

Treatment	Rating	Comments
Adjuvant Treatment		
Pelvic external beam irradiation alone	8	
Concurrent pelvic irradiation and chemotherapy	5	
Observation	2	
Chemotherapy alone	1	
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 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.**

Treatment	Rating	Comments
Adjuvant Treatment		
Concurrent pelvic irradiation and chemotherapy	9	
Extended field (pelvic and para-aortic) irradiation with chemotherapy	5	
Pelvic external beam irradiation alone	2	
Observation	1	
Chemotherapy alone	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Role of Adjuvant Therapy in the Management of 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 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.**

Treatment	Rating	Comments
Radiation Treatment Considerations		
Whole pelvic fields	8	
3-D conformal RT	8	
Patient supine	8	This is considered the most likely position for reproducibility of setup.
Patient prone	7	This position may be advantageous if significant volume of small bowel can be excluded.
Use belly board device	7	This may be advantageous if significant volume of small bowel can be excluded.
IMRT	7	Great care in this treatment is required in delineation of CTV.
Four-field "box" technique	7	In venues lacking sufficient resources and equipment, this may be the best option for ensuring adequate target coverage.
True pelvic fields	5	
Use of implantable mesh or device	2	
Use of implantable tissue expanders	2	
Extended fields	1	
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 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.**

Treatment	Rating	Comments
Radiation Treatment Considerations		
Extended fields	9	
3-D conformal RT	8	
Patient supine	8	This is considered the most likely position for reproducibility of setup.
IMRT	7	Great care in this treatment is required in delineation of CTV.
Four-field "box" technique	7	In venues lacking sufficient resources and equipment, this may be the best option for ensuring adequate target coverage.
Patient prone	3	
Use belly board device	2	
Use of implantable mesh or device	2	
Use of implantable tissue expanders	2	
True pelvic fields	1	
Whole pelvic fields	1	
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 oophorpexy. Pathological review of the surgical specimens reveals 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.**

Treatment	Rating	Comments
Routine Follow-up Recommendations		
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	9	
Sexual function evaluation every 3–6 months for at least 5 years	8	
Discuss use of vaginal dilator every 3–6 months for 5 years	8	
Follow-up imaging studies every 3–6 months such as PET/CT and/or MRI scans for at least 5 years	3	
Female hormonal laboratory studies every 3–6 months for at least 5 years	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		