Original Article

Primary Management of Early Stage Cervical Cancer (IA1-IB) and Appropriate Selection of Adjuvant Therapy

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Abstract
Cervical cancer is the third most common gynecologic malignancy in the United States but the leading gynecologic cancer worldwide. Most patients will present with clinical early-stage disease (International Federation of Gynecology and Obstetrics [FIGO] stage IA1–IB). These patients are a clinically heterogeneous group, and primary treatment can be either surgery or radiotherapy. Standard surgery is either radical hysterectomy with lymphadenectomy (stage IA2–IB2) or simple hysterectomy for microinvasive disease (stage IA1). Interest has been increasing in using conservative fertility-sparing surgery through radical trachelectomy as an option for select patients with early-stage disease who want future fertility. Primary radiotherapy is delivered as a combination of external-beam teletherapy and brachytherapy. It is given with concurrent cisplatin-based chemotherapy, based on 5 large randomized controlled trials that showed significant improvement in overall survival with the addition of chemotherapy. Using either radical surgery or radiation therapy in stage IB disease yields 5-year survival rates of 87% to 92%. The addition of postoperative adjuvant radiation with concurrent chemotherapy is recommended in patients with high- or intermediate-risk disease after radical hysterectomy to reduce risk for recurrence and improve progression-free survival. In select patients with stage IB2 disease with bulky tumors undergoing primary chemoradiation, adjuvant hysterectomy may provide benefit after treatment. (*JNCCN* 2008;6:47–52)

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Experts predict that 11,150 women in the United States will be diagnosed with invasive cervical cancer and 3670 will die from this disease in 2007, making cervical cancer the third most common gynecologic malignancy.[1] With the implementation of universal screening policies using the Papanicolaou test (Pap smear), rates of cervical cancer have been steadily dropping in the United States since 1930. However, it remains a prominent global killer, with more than 490,000 women diagnosed and 275,000 deaths per year worldwide.[2]

Most patients in the United States present with early-stage disease (stage IA–IB). By convention, cervical cancer is clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines from 1998 (see FIGO/TNM staging in the NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer, page 27). Clinical staging presents a unique problem, because the clinical presentation of patients may not match the finding of surgical spread of disease (e.g., metastasis to lymph nodes discovered postoperatively). Therefore, patients with early-stage cervical cancer are a heterogeneous group for whom therapy should be tailored accordingly. This article discusses the various primary treatment options for early-stage cervical cancer (stage IA1–IB) and selection of adjuvant therapy after primary treatment.

Treatment of Microinvasive Disease (Stage IA)

Defining a subset of patients with early preclinical disease who have a favorable prognosis has been the source of much debate for the past 50 years.[3] Patients with microinvasive disease usually do not have grossly visible lesions and are diagnosed using cone biopsy. The most current FIGO staging guidelines define stage IA as microinvasive

cancer. Stage IA1 includes lesions with stromal invasion of not more than 3.0 mm and a width of 7.0 mm. Stage IA2 includes lesions with stromal invasion of 3.0 to 5.0 mm and lesion width of 7.0 mm or less. Any larger lesion would be classified as stage IB1. The presence of lymph vascular space involvement does not alter stage, although several reports indicate a poorer prognosis with this finding.

Treatment options offered for these patients are based on the relationship of depth of invasion and risk for nodal metastasis. Nodal metastasis in early-stage disease is the single most important predictor of survival. For patients who have tumors with 3 mm of invasion or less (stage IA1), the risk for nodal metastasis is very low, with published reports ranging from 0.5% to 1.2%. For lesions with invasion between 3 and 5 mm (stage IA2), risk for nodal metastasis is reported to be 5% to 7%.[4]

Therefore, patients with stage IA1 microinvasive disease can be treated with a simple extrafascial hysterectomy, without lymph node dissection, either abdominally or vaginally. Risk for recurrence is 1% and overall 5-year survival is 99%[5] with this therapy. Select patients with stage IA1 disease who desire future fertility and without evidence of lymphovascular space invasion (LVSI) may be offered cone biopsy as treatment. However, little long-term information is available on recurrence risk or survival with this method.[6]

Patients with stage IA2 have a higher risk for lymph node involvement and are therefore usually offered a modified radical hysterectomy (type II; Table 1). In this surgery, additional parametrial or paracervical tissue is removed along with the uterus and cervix, and pelvic lymphadenectomy is performed with or without para-aortic lymph node sampling. Risk for recurrence for IA2 tumors is 3% to 5%, and overall 5-year survival is 96%.[5]

The application of microinvasive guidelines was developed primarily for squamous cell histologies, which currently constitute approximately 85% of all cervical cancers (with adenocarcinoma rates rising). Experts disagree on whether the term *microinvasive* should apply to adenocarcinomas. However, several reports advocate a low-risk category for adenocarcinomas based on volume of invasive disease (< 600 mm^3) that may be candidates for more conservative therapy with low or negligible recurrence rates.[7,8]

Treatment of Stage IB Disease

Stage IB represents a clinically diverse spectrum of early-stage disease, with most patients having visible gross lesions, some with microscopic disease with depth of stromal invasion greater than 5 mm or width of invasive disease greater than 7 mm. Stage IB is further subdivided based on tumor size into stage IB1 (≤ 4 cm) and IB2 (> 4 cm). The 2 standard treatment options for these patients are primary radical surgery and radiotherapy with concurrent cisplatin-based chemotherapy. Generally, patients with stage IB disease have a 15% risk for pelvic nodal metastasis. Therefore, treatment includes either surgical removal of lymph nodes or radiation-directed therapy to include the pelvic lymph nodes.

Primary Surgery: Radical Hysterectomy

First described by Werthiem[9] in the early 1900s for surgical treatment of early cervical cancer, the radical hysterectomy (type III) is the surgical standard offered to patients with stage IB tumors. Analysis of patterns of cervical cancer spread shows that these tumors tend to spread from the cervix laterally to the adjacent parametrial tissue and through lymphatic channels. Therefore, radical hysterectomy removes the uterus and cervix along with paracervical tissues, or parametria, and part of the upper vagina. Pelvic lymphadenectomy and para-aortic lymphadenectomy are also performed (Table 1). In postmenopausal or perimenopausal women, removal of the fallopian tubes and ovaries (salpingo-oophorectomy) may also be performed. Recent reports suggest a cardioprotective effect of conserving ovaries even in postmenopausal women.[10] Therefore, a thorough discussion between the provider and patient regarding the risks and benefits of oophorectomy should occur preoperatively. Premenopausal women with squamous carcinomas and small tumors may have ovaries preserved. However, because of the higher rate of adnexal spread, women with adenocarcinomas, which constitute 15% of all histologic types, should be counseled on salpingo-oophorectomy. Rates of recurrence after radical hysterectomy for stage IB tumors is 20%, and overall survival is 87%.[5]

Minimally Invasive Surgery: Laparoscopic-Assisted Radical Hysterectomy

Demand for minimally invasive techniques in gynecologic oncology using laparoscopic or robotic-assisted technology is increasing. The proposed benefit is to

Table 1 Hysterectomy Types

Type	Hysterectomy	Description	Lymph Nodes
I	Extrafascial	Simple hysterectomy	No
II	Modified radical	Ligation of uterine artery medial to crossing over ureter; resection of medial half of cardinal ligaments and proximal uterosacral ligaments; upper third of vagina removed	Pelvic
III	Radical	Ligation of uterine artery at origin from hypogastric artery; resection of cardinal and uterosacral ligaments at attachments to sacrum and sidewall; resection of upper half of vagina	Pelvic and para-aortic
IV	Extended radical	Same as type III, with superior vesicle artery ligated; three-quarters of the vagina resected	Pelvic and para-aortic
V	Partial exenteration	Resection of portion of bladder and distal ureter with reimplantation	Pelvic and para-aortic

Modified from Piver SM, Rutledge F, Smith JP. Five classes of extended hysterectomy for women with cervical cancer. Obstet Gynecol 1974;44:265–272.

reduce surgical morbidity while providing similar outcome as a traditional open surgical approach. Since the early 1990s, multiple retrospective series have been published describing laparoscopic-assisted radical vaginal hysterectomy (LARVH) with pelvic lymph node dissection for early-stage cervical cancer.

In one of the larger series, results from 71 patients with stage IA/B who underwent LARVH were compared with 205 similar patients who underwent traditional open radical hysterectomy during the same 8 years. Significant findings between the groups were increased length of operative time (3.5 vs. 2.5 hours; $P < .001$) and increased intraoperative injury (13% vs. 4%; $P < .03$), but shorter hospital stay (1 vs. 5 days; $P < .001$) in the LARVH versus open radical hysterectomy groups. However, the 2-year recurrence-free survival rate was 94% in both groups.[11] Other published series have shown similar results.

A prospective randomized trial comparing the 2 methods is unlikely. Retrospective data suggest that LARVH with pelvic lymphadenectomy for patients with early cervical cancer is a safe and reasonable alternative in centers with experience and training in this technique.

Radiotherapy With Concurrent Cisplatin Chemotherapy

Stage IB tumors are also amenable to treatment with radiotherapy with good clinical outcomes. External beam whole pelvic radiation is delivered as a 4-field technique to the pelvis in daily fractions of 180 cGy, to a total of 50.4 Gy to point A. Concurrent radiation-sensitizing cisplatin chemotherapy is given, based on findings from 5 randomized controlled trials that showed a significant survival advantage when cisplatin-based chemotherapy was given concurrently with radiotherapy.[12–16] After external beam radiation, brachytherapy is administered by either low– or high–dose-rate, to a total of 80 to 85 Gy to point A.[17,18]

Surgery Versus Radiation

Outcomes are similar in patients with stage IA2 or IB2 disease treated with radical hysterectomy or primary radiotherapy, with overall survival with either method ranging from 87% to 92%.[19] Treatment modality is chosen after thoroughly discussing the morbidities associated with each treatment type with the patient.

The advantages of surgery[20] are proper surgical staging and removal of bulky lymph nodes, immediate therapy, ovarian conservation in younger women, and preservation of vaginal function. The disadvantages of primary surgery are surgical morbidity, including possible bladder dysfunction, need for blood transfusion, and need for postoperative radiotherapy. Generally, the morbidity of radical surgery followed by radiation therapy is great enough that clinicians should consider radiation with chemosensitization alone for patients with a high rate of need for subsequent radiation after surgery. Primary radiation therapy is commonly proposed to avoid surgical morbidity and mortality in patients who may be at higher risk for intraoperative complications. Conversely, radiation therapy can cause vaginal shortening, reduction in caliber and lubrication, and worse sexual functioning.[21] Other significant possible toxicities include ovarian failure,

chronic radiation cystitis/proctitis, fistula formation, and development of secondary malignancy.

Patients with stage IB2 tumors (> 4 cm) may be offered primary radical hysterectomy versus chemoradiation therapy up-front. In an Italian randomized trial of primary surgery versus radiation, 84% of patients with stage IB2 tumors treated surgically underwent postoperative adjuvant radiation therapy, with 28% of patients experiencing severe morbidity.[19] Therefore, some advocate providing primary chemoradiation up-front for all IB2 lesions to prevent the morbidities associated with radical surgery followed by radiation. However, it is prudent to individualize treatment and thoroughly discuss the options with patients.

Fertility-Sparing Surgery: Radical Trachelectomy

Because more women delay childbearing until later in life, interest has increased in preserving fertility in cervical cancer care. Recent reports indicate that up to 15% of all cervical cancers and 45% of all surgically treated early-stage cancer occur in women younger than 40 years who would be potential candidates for fertility-sparing surgery.[22] First described in 1994 by Dargent et al.,[23] radical vaginal trachelectomy with laparoscopic pelvic lymphadenectomy (LARVT, or *Dargent's procedure*) has gained popularity worldwide as a method of treating small invasive tumors (stage IA2–IB1). In addition, this procedure can be approached transabdominally.[24] The goal of the procedure is to remove all the parametrial tissue and vaginal margins with the cervix, as in a radical hysterectomy, in conjunction with a laparoscopic pelvic lymphadenectomy, plus/minus para-aortic lymph node sampling. This leaves the main body and fundus of the uterus intact for childbearing. Experts usually recommend placing a cerclage at the conclusion of the procedure.[23]

A contemporary review of data found more than 500 published cases of radical trachelectomy for early cervical cancer worldwide.[25] Recurrence rates are 5% and mortality is 3%. The highest rates of recurrence occurred in patients with tumors larger than 2 cm (17%) and the presence of LVSI (12%). Similar rates of ureteral injuries and bladder dysfunction were found compared with contemporary data for radical hysterectomy. Pregnancy rates ranged from 41% to 79%, and the term delivery rate was 38%. The authors concluded that radical trachelectomy with pelvic lymphadenectomy may be considered an option for patients with early-stage disease (stage IA2–IB1), with tumors smaller than 2 cm, who want to maintain fertility.

Adjuvant Therapy After Primary Treatment

Adjuvant Radiotherapy

The intent of primary surgery for early-stage cervical cancer is therapeutic and diagnostic. Approximately 15% of early-stage tumors will show evidence of spread to pelvic lymph nodes after radical surgery and lymphadenectomy. Surgical staging allows for evaluation and removal of bulky lymph nodes, which may induce a therapeutic effect. Retrospective analysis has revealed prognostic features that predict a higher risk for recurrence after radical hysterectomy: positive lymph nodes, positive parametria, and positive surgical margins.[26,27] Therefore, patients with these high-risk features should be treated with postoperative radiotherapy. Furthermore, in a randomized controlled trial (GOG 109), 268 patients with high-risk features (positive pelvic lymph nodes, parametria, or margins) after radical hysterectomy were randomized to pelvic radiation therapy with or without concurrent cisplatin chemotherapy. A significant reduction in relapse-free survival was noted in patients treated with concurrent cisplatin chemotherapy.[14]

Other pathologic features that pose an intermediate risk for recurrence have been identified. In GOG 92, 277 patients with stage IB, node-negative disease with intermediate-risk features (large tumor size >4 cm, deep stromal invasion to the outer third, or LVSI) after radical hysterectomy were randomized to undergo postoperative pelvic radiation therapy or no treatment. Patients who underwent adjuvant radiotherapy experienced significant improvement in relapse-free survival rates, with a 46% reduction in risk for recurrence, although the overall survival rates did not reach statistical significance.[28,29] Therefore, the recommendation for patients with 2 of 3 intermediate-risk pathologic features is postoperative radiation therapy. Although radiotherapy was given alone in GOG 92, most clinicians would argue for treating with concurrent cisplatin-based chemotherapy based on the multiple trials showing improvement in survival when it is given as radiosensitization.

Table 2 Primary Treatment Recommendations by FIGO Stage

FIGO Stage	Treatment
IA1	Extrafascial abdominal hysterectomy or vaginal hysterectomy
IA2	Modified radical hysterectomy, pelvic LND, +/– BSO
	OR
	WPXRT with concurrent cisplatin chemotherapy + brachytherapy
IB1	Radical hysterectomy, pelvic and para-aortic LND, +/– BSO
	OR
	Laparoscopic or robotic–assisted radical vaginal hysterectomy, pelvic and para-aortic LND, +/– BSO
	OR
	WPXRT with concurrent cisplatin chemotherapy + brachytherapy
IB2	Radical hysterectomy, pelvic and para-aortic LND, +/– BSO
	OR
	WPXRT with concurrent cisplatin chemotherapy + brachytherapy

Abbreviations: BSO, bilateral salpingo-oophorectomy; FIGO, International Federation of Gynecology and Obstetrics; LND, lymph node dissection; WPXRT, whole pelvic external radiotherapy.
Based on the NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. The latest versions of these and other guidelines are available at www.nccn.org/professionals/physician_gls/default.asp.

In summary, patients with high-risk features after radical hysterectomy (positive pelvic lymph nodes, positive parametria, and positive margins) should receive postoperative pelvic radiotherapy with concurrent cisplatin-based chemotherapy. Additionally, adjuvant pelvic radiation therapy should be given for patients with at least 2 of 3 intermediate-risk features (large tumor size > 4 cm, deep stromal invasion, or LVSI) with consideration of concurrent cisplatin-based chemotherapy.

Adjuvant Hysterectomy

In patients with bulky stage IB tumors treated with primary radiotherapy, evidence of residual disease is seen in up to 50% to 60% of extrafascial hysterectomy (EH) specimens.[30,31] Additionally, patients who undergo EH after primary radiotherapy have lower rates of pelvic recurrence, thereby providing a compelling argument for offering this procedure to these patients, although a survival benefit has not been seen. Generally, hysterectomy is performed at least 6 to 8 weeks after completion of radiation to reduce morbidity.

Conclusions

Early-stage cervical cancer (stage IA–IB) is a common gynecologic disease with a generally good prognosis and high overall survival. Primary treatment recommendations are summarized in Table 2. Select patients with stage IA1 microinvasive squamous cell tumors with less than 3 mm of stromal invasion may be offered simple hysterectomy or cone biopsy if they do not show LVSI. Patients with stage IA2 to IB2 lesions can be treated with primary radical hysterectomy or cisplatin-based chemoradiation therapy, and similar outcomes but differing morbidities can be expected. The minimally invasive laparoscopic-assisted radical vaginal hysterectomy seems to provide similar outcomes to traditional radical hysterectomy. The use of fertility-sparing procedures, such as radical trachelectomy for small tumors (stage IA2–IB1), is increasing in popularity, although data on long-term outcomes are not mature. Patients with high or intermediate risk for recurrence after primary surgery should be treated with postoperative chemoradiation therapy to reduce that risk.

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