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ORIGINAL ARTICLE

Chemoradiation with adjuvant hysterectomy for stage IB-2 cervical cancer: a 10-year experience

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Abstract To review outcomes of patients with stage IB-2 cervical carcinoma treated with chemoradiation therapy (CRT) followed by total abdominal hysterectomy (TAH), common iliac and para-aortic lymphadenectomy (PAL). A retrospective review of patients with stage IB-2 cervical cancer treated with CRT followed by TAH/PAL from 1999 to 2009 was performed. Brachytherapy was limited to 1,500–1,800 cGy. Sixty-nine patients were identified. The mean age was 46.7 years, tumor diameter 5.4 cm, and all patients had complete clinical response to CRT. The mean follow-up was 61.7 months. There were no central pelvic relapses and two pelvic sidewall failures (97% pelvic control). The mean time to progression was 31.6 months, and 5-year disease-specific survival was 81%. Three (4.3%) patients developed symptomatic vaginal stenosis. CRT plus adjuvant hysterectomy for stage IB-2 cervical cancer resulted in excellent pelvic control and 5-year survival. Vaginal stenosis was rare.

Keywords Chemoradiation · IB-2 cervical carcinoma · Adjuvant hysterectomy · Outcomes analyses · Survival

Background

In 2010, there were approximately 12,200 newly diagnosed cases of cervical cancer and 4,210 deaths in the USA [1]. The treatment of International Federation of Gynecology and Obstetrics stage IB-2 "bulky" cervical carcinoma continues to be debated. While survival for patients with IA and IB-1 tumors is generally reported greater than 90%, patients with stage IB-2 tumors have a worse prognosis with 5-year survivals ranging from 69% to 73% [2, 3] in case series collected prior to the use of cisplatin with primary or secondary radiation. More recently, Goksedef et al. reported 86% 3-year survival with chemoradiation therapy (CRT) [4]. Zivanovic et al. [5] found 55% IB-2 patients alive at 3 years with primary CRT and selected patients undergoing radical hysterectomy with secondary CRT had a 72% estimated 3-year survival.

There are four suggested therapies for stage IB-2 cervical carcinoma, three of which are included in the National Comprehensive Cancer Network (NCCN) Guidelines. Whole-pelvis radiation with cisplatin-based chemotherapy has category 1 evidence with uniform consensus. Radical hysterectomy with pelvic and para-aortic lymphadenectomy followed by tailored postoperative chemoradiation [6] has category 2B evidence with a nonuniform consensus and lower level evidence including clinical experience. A third NCCN treatment option is preoperative pelvic CRT followed by adjuvant hysterectomy and has category 3 evidence with major disagreement from panelists that the recommendation is appropriate [6]. A fourth described treatment paradigm is neoadjuvant chemotherapy followed by radical hysterectomy with or without tailored adjuvant radiation and is not recommended by the NCCN. None of these treatment regimens are uniformly considered superior, and there are no prospective randomized trials comparing the three NCCN guideline treatment options.

It has been observed that many patients with stage IB-2 cervical cancer suffer from vaginal stenosis following primary chemo/RT [7, 8]. While pelvic control is in general excellent with primary CRT [9], some patients suffer

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relapse and require pelvic exenteration. Furthermore, some patients develop secondary malignancy (uterine sarcoma) in the radiation field many years after radiation [10]. Primary radical hysterectomy for IB-2 lesions can be associated with considerable blood loss, may be technically difficult in morbidly obese patients, and still the majority will require adjuvant CRT for high-risk pathology [5]. Therefore, we hypothesized that chemo/RT with a reduced brachytherapy dose (in order to minimize vaginal toxicity) followed by simple hysterectomy may overcome these potential shortcomings. The purpose of this study was to retrospectively analyze clinical outcomes of patients with stage IB-2 cervical carcinoma treated with concurrent CRT followed by adjuvant extrafascial total abdominal hysterectomy (TAH), common iliac and para-aortic lymphadenectomy treated at a single institution.

Materials and methods

A retrospective review of records from 69 consecutive patients with stage IB-2 cervical carcinoma who underwent CRT followed by adjuvant hysterectomy from January 1999 to January 2009 was performed. All surgeries were performed at our institution; however, 24 (35%) patients received CRT at outside facilities. A standardized treatment protocol with dosing guidelines and allowances for dose reductions was provided to radiation oncologists and medical oncologists outside our facility; however, dosing was ultimately at the discretion of the treating physician. This retrospective review of patient records was conducted with our institutional review board approval.

All patients underwent contrasted computed axial tomography (CAT) scans of the abdomen and pelvis and were excluded from this treatment for evidence of extrapelvic disease by either physical exam or CAT scan, including para-aortic lymphadenopathy. Patients were administered cisplatin (25–40 mg/m^2 weekly) during radiation therapy with six weekly treatments, dosed to tolerance of the patient. An alternative regimen of cisplatin/5-FU (50 mg/m^2 day 1, 1,000 mg/m^2 daily × 4 days, i.e., days 1–4 and 27–30) was administered to some patients with cervical adenocarcinoma. The recommended whole pelvic radiation dose was 4,500 cGy utilizing 20 MeV X-ray in a four-field technique in 180 cGy/day fractions. The pelvic sidewall was optionally boosted utilizing anterioposterior/posterioanterior fields for an additional 540 cGy in three fractions. The total external beam dose was 4,500–5,040 cGy in 25–28 treatments and high-dose rate brachytherapy was prescribed at 1,500–1,800 cGy to point A, in three equal doses. The superior margin of the pelvic radiation field was to the mid-sacroiliac joint. Patients underwent extrafascial hysterectomy with common and para-aortic lymphadenectomy. The lymphadenectomy was performed from above the radiation field, but was not taken routinely to the inferior mesenteric artery, as this was not a therapeutic lymphadenectomy. Surgery was completed 6 to 8 weeks following completion of brachytherapy.

Preoperative, intraoperative, and postoperative, demographics and clinical variables were collected by reviewing the patients' hospital, office records, tumor registry entries, and the Social Security Death Index database (available at http://genealogy.rootsweb.com). Direct patient contact, telephone interviews with family, or the patient's primary care physician was used to collect patient updates. Data were collected in a standardized manner using prespecified definitions. This approach provided for standardized reporting of each patient's clinical status before and after the operation. A 100% follow-up was obtained in the present study.

Data are presented as frequency distributions and simple percentages. Patient survival was expressed by actuarial estimates according to the method of Kaplan and Meier using time zero as the start date of external beam radiation and the date of death or last follow-up as the end point (with variability expressed as the standard error of the mean). Patients alive at the last follow-up were included as right-censored values in the analysis. Data collected were analyzed using the Number Cruncher Statistical Systems, Kaysville, UT.

Findings

A total of 69 women underwent CRT followed by adjuvant hysterectomy, common iliac and para-aortic lymphadenectomy. The overall patient demographics and pathologic characteristics are shown in Table 1. The mean age of patients was 46.7±10.7 years (range 27–82). The mean follow-up time was 61.7 months (range 10.9–122.5). Clinical complete response determined by physical exam was documented in all patients prior to surgery.

All patients received external beam radiation. Six (9%) did not receive the recommended dose of external beam radiation; three patients received lower doses (3,980–4,140 cGy) and three were administered higher doses (5,400 cGy) than the protocol guidelines. Brachytherapy was omitted in four (6%) patients, three because of altered vaginal geometry (upper vaginal stenosis) and one for undocumented reasons. Twenty three (35%) of 65 patients receiving brachytherapy had doses outside the protocol guidelines. Fourteen patients received less brachytherapy dose (500–1,200 cGy), and nine received more doses (2,000–3,000 cGy). Cisplatin was administered weekly to all patients during pelvic radiation. Forty-nine (71%) patients received cisplatin 40 mg/m^2, 17 (25%) received

Table 1 Patient demographics and pretreatment pathologic characteristics

Variables	Mean±SD or absolute number	Range or percentage
Age (years)	46.8±10.7	27–82
Body mass index (kg/m^2)	29.5±6.0	18.2–44.8
Clinical tumor size (cm)	5.4±1.2	4.0–9.0
4–6 cm	57 (83%)	N/A
>6 cm	12 (17%)	6.5–9.0
Histology		
Squamous	55	80
Adenocarcinoma	11	16
Adenosquamous	3	4
Tumor grade		
1	4	5.8
2	24	34.8
3	19	27.5
Unknown[a]	22	31.9

[a]Biopsy reports were from several pathology departments outside our institution, and tumor grading was not always provided

SD standard deviation, *N/A* not applicable

25 mg/m^2, and 3 (4%) received cisplatin/5-FU. Nineteen (39%) patients received all 6 cycles of cisplatin at 40 mg/m^2 without dose reduction, and in the other 30 patients, chemotherapy was held for one or more weeks of therapy, or dose-reduced therapy to 25 mg/m^2. The most common reason for dose reduction or discontinuation was nausea and vomiting or fatigue. There were no dose reductions for patients who initiated therapy at 25 mg/m^2, and all received 6 cycles. Likewise, there were no reductions for patients receiving cisplatin/5-FU. There were no grade 3 or 4 hematologic toxicities related to CRT.

The mean operative time for TAH, common iliac and para-aortic lymphadenectomy was 62±15 min, and estimated blood loss (EBL) was 187±103 mL. Four (6%) patients received preoperative or intraoperative transfusions because of chronic anemia. There were no intraoperative or postoperative transfusions related to excessive blood loss. The mean LOS was 3.1 days (range 2–7). The Foley catheter was removed on the first or second postoperative day for all patients except for one patient who had a cystotomy and repair. Common iliac and para-aortic lymph node counts averaged 6.3±2.9 (range, 2–15). Despite all patients achieving a complete clinical response by exam, 35 (51%) had microscopic residual disease on pathologic exam of the cervix. Only two (3%) patients had positive cervical–vaginal surgical margins (Table 2).

Ten (14%) patients had complications potentially related to treatment, and four (6%) required surgical management (Table 3). There were no treatment-related deaths. There were no vesicovaginal or ureterovaginal fistulae. All patients requiring reoperation were greater than 12 months postadjuvant hysterectomy. There was one intraoperative cystotomy and repair that healed without further sequelae. All patients requiring surgery for treatment-related complications received radiation dosing per protocol. Only one of the four patients who required surgery for complications received additional CRT to the para-aortic nodes following adjuvant hysterectomy. Other major complications not requiring surgery are described in Table 3 and include only two (3%) cases of radiation-related vaginal stenosis.

Thirty-five (51%) patients had residual disease identified in hysterectomy or nodal specimens by hematoxylin and

Table 2 Surgical and clinicopathologic data

Factors	Mean±SD or absolute number	Range or percentage
Operative time (min)	62±15	37–112
EBL (mL)	187±103	50–600
Transfusions (perioperative)	4	6%
Length of stay (days)	3.13±1.03	2–7
Lymph node count (common iliac/aortic)	6.32±2.94	2–15
Residual disease	35	51%
Positive margins	2	3%
Adjuvant therapy[a]	20	29%

SD standard deviation

[a]See Table 4 for details

Table 3 Treatment-related complications

Specifics	Patients (n=10)
Perioperative complication	
Cystotomy with repair	1
Deep venous thrombosis	1
Complete small bowel obstruction[a]	1
Vaginal vault necrosis	1
Vaginal vault necrosis/grade 4 proctitis[a]	1
Rectovaginal fistula (radiation proctitis grade 4/pSBO)[a]	1
Enterocutaneous fistula, ureteral stenosis[a]	1
Ureteral stenosis requiring temporary stent	1
Vaginal stenosis	2

[a]Required surgical intervention

eosin staining. Microscopic residual disease was identified in the cervix in 29 (42%) patients (22 cervix only, 7 cervix plus lymph nodes). Four (6%) patients had nodal metastasis and no residual cervical disease. Twenty patients with residual disease received additional therapy, including five treated with CRT to para-aortic nodes (Table 4). Fourteen patients with residual disease received additional platinum therapies, and one patient was administered additional vaginal cuff radiation. Fifteen study patients had residual disease and did not receive additional therapy, 14 of whom had residual cervical disease only. For the 22 patients who had residual cervical cancer identified in the hysterectomy specimens, there were no relapses and no deaths related to cervical cancer. Conversely, 11 (16%) patients had positive common or para-aortic lymph nodes identified at hysterectomy, and 10 died from metastatic disease. Five of the 11 patients (45%) with nodal disease had bulky lymphadenopathy identified at surgery, and their mean survival was 15 months (range 11–26). Three of these five patients with bulky nodal disease received additional chemotherapy, one received CRT, and one refused additional therapy. The other six patients with microscopic nodal metastasis all received additional therapy; five patients had progressive disease despite therapy [mean time to progression (TTP)= 18.5 months, range 6–33], and their mean OS was 41 months (range 19–62). The remaining patient with microscopic nodal disease received 4 cycles of cisplatin with topotecan and was alive without disease at 90 months. Two (3%) patients had microscopically positive vaginal margins, and one received a brachytherapy boost of 1,500 cGy. This patient was without evidence of disease at 73.4 months. The other patient also had positive para-aortic nodes and was dead of disease at 36.8 months (included in data above), having received 1,440 cGy radiation to para-aortic nodes.

Thirty-four (49%) patients had no active carcinoma identified in the hysterectomy or nodal specimens. Twenty-nine of these patients (85%) were alive without evidence of disease, including one who relapsed in para-aortic lymph nodes, received subsequent CRT, and is currently without disease at 119 months. Two patients with no evidence of disease at surgery died from recurrent cervical cancer (one pelvic sidewall, one pulmonary) despite additional therapy. Two other patients died of breast

Table 4 Residual disease based on pathological findings

Residual disease	Total patients (n=35)	Alive patients (%)	Deceased patients (%)	Treatment: number of patients (% of patients treated)
Central (cervix/vaginal)	22	21 (95)	1 (5)[a]	Chemo=8/22 (36.4)
				Vaginal brachytherapy=1/22 (4.5)
Central and nodal	7	0 (0)	7 (100)	Chemo=3/7 (42.9)
				Chemo/radiation=3/7 (42.9)
Nodal	4	1 (25)	3 (75)	Chemo=2/4 (50)
				Chemo/radiation=2/4 (50)
Nonviable tumor[b]	2	1 (50)	1 (50)	Chemo=1/2 (50)

NED no evidence of disease

[a] Deceased of other causes, NED at time of death

[b] Pathology suggested necrosis; however, the treatment was at the discretion of physician

cancer, and both were free of cervical cancer at the time of death. One additional patient who relapsed in the liver at 110 months was alive on chemotherapy 118 months from initial CRT.

The mean TTP for the entire group was 31.6± 28.3 months. Kaplain–Meier estimated 5-year disease-specific survival (DSS) was 81% (Fig. 1a, b). The "pelvic control" rate was 97% with only two patients relapsing in lymph nodes of the pelvic sidewall. Specifically, no patients recurred with vaginal or parametrial disease; and no exenterative procedures were performed. Distant relapse was evident in 20% of patients (para-aortic, mediastinal, and supraclavicular lymph nodes, lung, liver, and brain). There were 13 deaths secondary to cervical cancer and three from unrelated causes (two breast cancer, one cardiovascular), and two (3%) patients remain alive with disease at the time of this analysis.

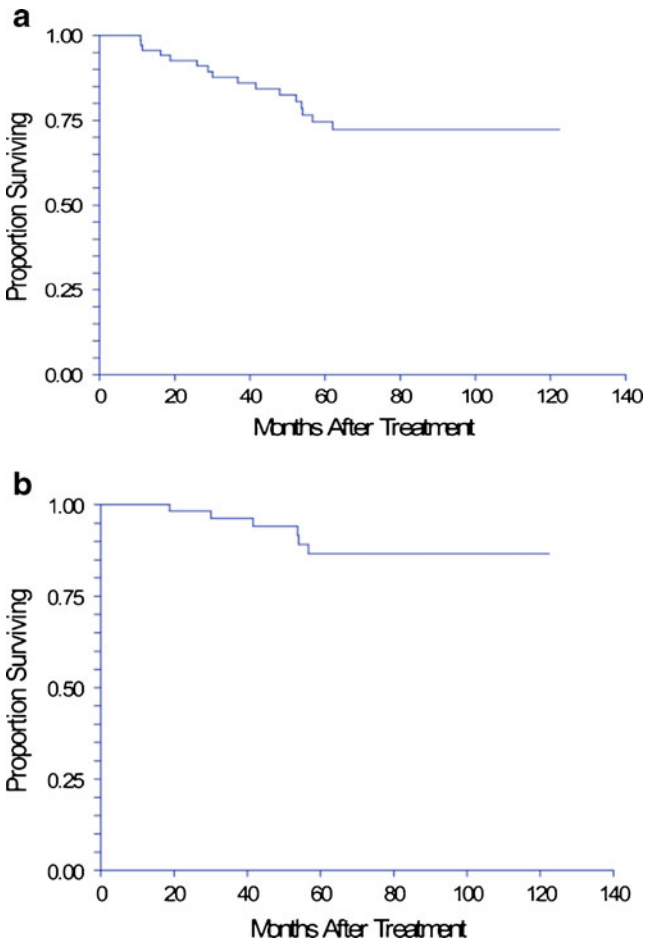

Fig. 1 **a** Actuarial 5-year overall survival ("all causes," includes three deaths from other causes in patients without evidence of active disease) curve for all 69 stage IB-2 cervical cancer patients as determined by Kaplan–Meier analysis. **b** Actuarial 5-year survival curve for 58 stage IB-2 cervical cancer patients (with negative nodes at surgery) as determined by Kaplan–Meier analysis

Discussion

Each of the NCCN guideline-supported treatment options for stage IB-2 cervical cancer has theoretical advantages and disadvantages that have not been fully compared in well-designed, prospective randomized clinical trials [6]. The GOG-71 study compared radiation therapy alone and radiation plus adjuvant hysterectomy for patients with stage IB-2 cervical cancer and reported no significant difference in overall survival between the two treatment arms [9]. However, subgroup analysis of patients with 4–6-cm lesions did benefit from adjuvant hysterectomy with unadjusted relative risk of progression at 0.58 and death 0.60, and conversely no improvement for patients with lesions greater than 6 cm [9].

In GOG-123, the effect of adding cisplatin to radiation therapy plus adjuvant hysterectomy was tested in a phase III trial. CRT using cisplatin followed by hysterectomy produced a statistically significant improvement in the OS and decreased pelvic recurrence rate compared to those treated with radiation and adjuvant hysterectomy [11]. There was no significant difference in the distant relapse rate, indicating that CRT likely had minimal affect on metastatic disease outside the radiation field. Two thirds of patients in GOG-123 had lesions ≥6 cm, and therefore, cisplatin apparently overcame some of the issues with lesion size noted in GOG-71 trial. The authors hypothesized that based on the results of the GOG-71 study, where adjuvant hysterectomy appeared to improve outcomes for patients with "small" IB-2 lesions (4–6 cm), adjuvant hysterectomy may have been of no benefit to patients in GOG-123 study. Thus, GOG-123 was designed to test the effects of cisplatin added to preoperative radiation for IB-2 lesions and perhaps the authors may have been in error suggesting that adjuvant hysterectomy was not therapeutically important without prospective randomized data [9]. Primary CRT versus radical hysterectomy was compared in the randomized GOG 201 trial; however, poor accrual lead to early termination of the trial, perhaps highlighting the polarized opinions of gynecologic and radiation oncologists regarding the best treatment of IB-2 cervical cancer.

Personal observations of our patients enrolled in the GOG-123 trial who often achieved complete clinical responses in the platinum arm and had acceptable surgical morbidity lead us to hypothesize that CRT followed by adjuvant hysterectomy was possibly the treatment of choice for stage IB-2 cervical carcinoma. Common and para-aortic lymphadenectomy was performed with hysterectomy in our protocol, recognizing the reported 10% incidence of occult para-aortic metastasis in patients with IB-2 cervix cancer [12]. Furthermore, brachytherapy dose was reduced from 30 to 15–18 Gy in order to limit radiation toxicities including vaginal stenosis. We hypothesized that the addition of cisplatin and

the use of adjuvant hysterectomy likely diminish the therapeutic index of maximal brachytherapy, given that many patients were observed to have a complete clinical response prior to brachytherapy. Our bias was to avoid primary radical hysterectomy for patients with IB-2 lesions because the majority required postoperative pelvic chemoradiation [13, 14]. Furthermore, we found simple hysterectomy within 8 weeks of CRT technically easier to perform in obese patients than type III radical hysterectomy. Consequently the majority of patients with IB-2 lesions at our institution were treated on this protocol, other than a very few who were not deemed surgical candidates for medical reasons such as acute deep vein thrombosis.

This study represents one of the few investigations of patients with IB-2 carcinoma of the cervix that reports more than 5 years of median follow-up. Estimated 5-year DSS was 81% for the entire study group and 89% for the subgroup found to have no disease or only microscopic residual cervical disease and negative lymph nodes at surgery. In contrast, 10 out of 11 patients (91%) with common iliac or para-aortic nodal disease died from progressive disease. The subgroup of patients with microscopic nodal disease probably benefited from further therapy as their mean survival was 41 months, whereas those with CAT negative, but grossly bulky adenopathy at surgery had a mean survival of only 15 months. Because fluorodeoxyglucose–positron emission tomography (FDG-PET) imaging is more sensitive than CAT scanning for detecting metastatic disease [15], pretreatment screening with PET may allow exclusion of patients with occult para-aortic disease who would be less likely to benefit from adjuvant hysterectomy.

There were no central pelvic relapses and no patient required exenterative surgery in this study. In a recent retrospective investigation of primary cisplatin-based CRT, Goksedef et al. [4] reported an 86% 3-year OS. Seven of the 10 patients with recurrent disease had central pelvic recurrence, and the median TTP was only 22 months. Nevertheless, the authors concluded that completion hysterectomy was not necessary because overall patient survival was similar to the GOG-123 CRT arm. While the estimated 3-year survival may appear similar to the current study, it is possible that some patients with central relapse may have required exenterative surgery to achieve this survival, and longer follow-up would be necessary to be confident of that opinion.

Other potential disadvantages for primary CRT include short- and long-term side effects of radiation including vaginal stenosis and sexual dysfunction related to full-dose brachytherapy. Vaginal stenosis can lead to long-term sexual dysfunction, pain on examination, and difficulty diagnosing central disease recurrence. Vaginal stenosis is underreported or not quantified in the majority of studies but has been reported as high as 88% [7]. Intracavitary implants were shown to be associated with decrease in vaginal length, decreased coital frequency and satisfaction, and increased dyspareunia [8]. A recent Cochrane review reported that there is no reliable evidence to show routine dilation during or after radiotherapy prevents late effects or improves quality of life and that treatment during radiation may be harmful [16].

The present study should be considered an exploratory analysis, and its limitations include those typically associated with observational, nonrandomized, retrospective studies. The relatively small sample size, lack of control group for comparison, and surgeon bias may have affected the findings by excluding poor surgical candidates. We could not accurately identify all patients with IB-2 lesions treated primarily with CRT or radical hysterectomy during the study period. CRT with simple hysterectomy was clearly our preferred management during the study period, and patients with severe comorbid illnesses were managed with primary CRT, undoubtedly enriching the outcomes in our study compared to what might be recognized in a multi-institutional phase III trial. We also recognize that there were several radiation dosages outside our guidelines, which is inherent in a retrospective analysis. Chemotherapy was given postprotocol to some patients with residual disease at the discretion of the treating physician. There were not enough patients in this study to determine whether this effected survival. Strengths of the study include the mean follow-up time greater than 5 years and complete follow-up for all patients. We currently exclude patients with extrapelvic metastasis using FDG-PET scans and perform hysterectomy with aortic node dissection using robotic-assisted laparoscopic surgery. A prospective randomized trial of CRT and limited brachytherapy with adjuvant simple hysterectomy, compared to both primary CRT and primary radical hysterectomy, followed by risk-based CRT will be necessary to fully evaluate the efficacies and toxicities of these three approaches for IB-2 lesions.

Based on the observations in this study, we hypothesize that overall 5-year survival would be similar for the three treatment regimens in a phase III trial. However, we also predict that significant differences in acute and long-term morbidities, especially with respect to vaginal stenosis, bladder dysfunction, and central failure requiring pelvic exenteration, might also be recognized.

Declaration of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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