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ORIGINAL ARTICLE

CME

Long-term Results for Postoperative Radiotherapy Following Radical Hysterectomy for Stage IB Cervix Cancer

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ABSTRACT

Objective: *To evaluate the long-term outcomes of patients with stage IB cervix cancer who were selected for primary surgery because they were thought to be at low risk for needing postoperative radiotherapy following radical hysterectomy.*

Methods: *Review of the outcome of 25 patients with clinical stage IB cervix cancer who were treated with radical hysterectomy and postoperative radiotherapy at the Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, Florida, USA, between 1975 and 2001.*

Results: *The median follow-up was 13 years. The 10-year rates of pelvic control, cause-specific survival, and overall survival were 88%, 75%, and 68%, respectively. The grade 3 to 4 complication rate was 8%. Twenty five percent of patients died of cervix cancer.*

Conclusion: *The long-term prognosis following radical hysterectomy and radiotherapy for stage IB cervix cancer was discouraging, even when patients were selected for primary surgery specifically because they were unlikely to have indications for postoperative radiotherapy.*

Key Words: *Hysterectomy; Radiotherapy; Uterine cervical neoplasms*

INTRODUCTION

There are 2 problems with most published series of radical hysterectomy and postoperative radiotherapy for cervix cancer: short follow-up and inclusion of patients with a high burden of residual disease.[1-4] These series may underestimate the rate of tumour recurrence and complications, and may not be applicable to patients with favourable stage IB tumours.

At the University of Florida College of Medicine, Gainesville, Florida, USA, the philosophy for the past 30 years has been that, if a patient with cervix cancer needs postoperative radiotherapy, they should have been treated with primary radiotherapy. This means that it is rare that a patient has indications for postoperative radiotherapy following radical hysterectomy. The purpose of this study was to evaluate the long-term outcome of patients with stage IB cervix cancer who were selected for primary surgery because they were thought to be at low risk for needing postoperative radiotherapy following radical hysterectomy.

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METHODS

This study included every patient with postoperative radiotherapy following radical hysterectomy and bilateral pelvic node dissection for clinical stage IB cervix cancer who was treated between 1975 and 2001 at the University of Florida College of Medicine. All patients were followed for a minimum of 2 years from the date of surgery. The median age at the time of surgery was 42 years (range, 21 to 69 years). No patient had gross residual disease. Table 1 shows the patients' characteristics.

The indications for postoperative radiotherapy following radical hysterectomy are positive margins, close margins (<5 mm), multiple positive nodes, a single node with extracapsular tumour extension, or more than 1 of the following risk factors: lymphovascular space invasion (LVSI), deep stromal invasion (>50% myometrial invasion), or tumour size ≥4 cm. Table 2 shows

Table 1. Patients' characteristics.

Characteristic	Number of patients (n = 25)
Age (years)	
Mean	42
Range	21-69
Race	
Caucasian	21
Black	3
Hispanic	1
Histology	
Squamous cell carcinoma	21
Adenocarcinoma	4
Clinical tumour size (cm)	
<4	6
>4	12
Unknown	7
Margin status	
Positive	1
Close (<5 mm)	11
Negative	11
Unknown	2
Parametrial invasion	
Yes	9
No	13
Unknown	3
Lymphovascular space invasion	
Yes	18
No	2
Unknown	5
Deep stromal invasion	
Yes	20
No	1
Unknown	4
Number of lymph nodes recovered	
Mean	27
Range	12-71
10-20	8
21-30	8
>30	8
Unknown number removed	1
Lymph nodes positive	
Yes	18
No	7
Number of lymph nodes (n = 18)	
Median	3
Range	1-8
Nodal extracapsular extension (n = 18)	
Yes	0
No	5
Unknown	13

the indications for postoperative radiotherapy following radical hysterectomy and bilateral pelvic node dissection in this patient population.

Radiation Technique

All patients received external beam radiotherapy to a median dose of 50 Gy (range, 41.4 to 60.0 Gy) at 1.8 to 2.0 Gy per fraction. A 4-field box technique with 18 MV photons was used for all patients. The superior field border was at the L1 to L2 interspace when the para-aortic nodes were irradiated. The usual indication for covering the para-aortic nodes was histologically positive nodes above the level of the common iliac vessels. On the anterior and posterior fields, the width of the para-aortic field was typically 8 cm. On the lateral fields, the anterior border of the para-aortic field was approximately 2 cm anterior to the vertebral bodies and the posterior border split the vertebral bodies.

Table 2. Indications for postoperative radiotherapy following radical hysterectomy and pelvic node dissection.

Indication	Number of patients
Margin <5 mm	12
Multiple positive lymph nodes	11
Deep stromal invasion and size >4 cm	1
Deep stromal invasion, lymphovascular space invasion, and single positive lymph node	1

The superior field border in patients who did not receive para-aortic node irradiation was typically at the L5-S1 interspace. On the anterior and posterior pelvic field, the lateral field borders were 1.0 to 1.5 cm lateral to the pelvic rim with a lateral dimension of 14 to 16 cm. The inferior border of the pelvic field was 3 cm inferior to the vaginal cuff, marked by a soft vaginal cylinder. The superior-inferior dimension of the pelvic field was usually 14 to 16 cm. On the lateral pelvic fields, the anterior border was 1 cm anterior to the pubic symphysis. The posterior border covered the presacral space. The anterior-posterior dimension of the lateral pelvic fields was 10 to 12 cm.

Eighty percent of patients received a brachytherapy boost; 56% (14/25) received low-dose–rate (LDR) brachytherapy for 72 hours with 2 vaginal ovoids and 24% (6/25) received a high-dose–rate (HDR) boost. The isotopes used in the intracavitary portion of the implants were radium-226 (^{226}Ra) or cesium-137 (^{137}Cs). For the patients treated with LDR brachytherapy, the dose was prescribed using the milligram-hour (mgh) system for a total of 2500 to 3000 mgh per 72-hour application. For the patients treated with HDR, the dose was prescribed to a depth of 5 mm. The median doses for LDR and HDR boosts were 47.7 and 12.5 Gy, respectively.

One patient received chemotherapy in the form of cisplatin as a weekly infusion during radiotherapy at a planned dose of 40 mg/m^2.

Complications

Complications were graded 1 to 4 based on the Common Terminology Criteria for Adverse Events version 3.[5] Only the most severe complication was graded for each patient.

Statistical Analysis

All statistical computations were performed with Statistical Analysis Systems and JMP software (SAS Institute, Cary, USA). The Kaplan-Meier product-limit method provided estimates of pelvic control, cause-specific survival, distant metastasis-free survival, and overall survival. Cause-specific survival events were defined as death from cancer or from a treatment complication. The only event in the overall survival calculations was death from any cause. Recurrences in the cervix, bladder, rectum, pelvic nodes, vagina, or parametrium were classified as pelvic failures. The authors were not confident specifying the subsite of recurrence within the pelvis in many cases. Recurrences in para-aortic lymph nodes, bone, lung, liver, brain, or supraclavicular lymph nodes were classified as distant failures. Patients with both pelvic and distant recurrences were coded as pelvic failures. The patients coded as distant failures did not have pelvic recurrences.

RESULTS

The study included 25 patients with clinical stage IB cervix cancer who were treated with radical hysterectomy and postoperative radiotherapy at the Department of Radiation Oncology between 1975 and 2001. The minimum follow-up for patients who did not die from disease was 2 years. The median follow-up was 13 years (range, 0.8 to 30.7 years).

Table 3. Actuarial results for tumour control and survival endpoints.*†‡

	Time (years) [%]		
	2	5	10
Pelvic control	92	87	87
Distant metastasis-free survival	96	86	86
Cause-specific survival	92	84	75
Overall survival	92	80	68

* All patients coded as distant failures had imaging with no evidence of pelvic disease.
† No patients with recurrent disease were salvaged and they all died within 10 years of their initial diagnosis.
‡ No patients died from treatment complications.

The crude pelvic failure rate was 12% (3/25) and the crude distant failure rate was 12% (3/25). Two of the 3 pelvic failures (67%) occurred within 2 years of completing radiotherapy and 100% occurred within 6 years. It was not possible to determine whether the number of lymph nodes removed predicted outcome because only 3 patients had a pelvic recurrence. The number of nodes positive/dissected in these 3 patients were 2/16, 0/28, and 4/23. All distant metastases occurred within 5 years of initial treatment. Salvage therapy was not successful for any patient who developed recurrent tumour. Table 3 shows the actuarial results for tumour control and survival endpoints.

Complications

Eight percent of patients (2/25) experienced a grade 3 to 4 complication. Radiation proctitis requiring intravenous fluids and blood transfusions occurred in 1 patient. Haemorrhagic cystitis requiring bilateral nephrostomy tubes occurred in 1 patient who eventually died from local recurrence of cervical cancer. Grade 2 complications, such as cystitis, dyspareunia, and proctitis, were probably under-reported. However, 2 grade 2 complications significantly impacted patients' quality of life; 1 patient had lower extremity oedema requiring daily wrapping and weekly physiotherapy, and 1 patient had multiple small bowel obstruction that required short-term hospital admission. Table 4 summarises the complications.

DISCUSSION

This study is an important contribution to the literature because of the long-term follow-up for every patient who was treated at the Department of Radiation Oncology during the study period. The study population was more homogeneous than many other study groups in that only patients with clinical stage IB disease prior to surgery were included.

The 5-year tumour control and survival results are slightly better than those reported in other major series.

Table 4. Complications (n = 4*).

Grade†	Complication
2‡	One patient had small bowel obstruction requiring hospital admission and intravenous fluids but no surgical intervention One patient had severe lower extremity oedema requiring daily wraps and weekly physiotherapy
3§	One patient had radiation proctitis requiring intravenous fluid and blood transfusions
4§	One patient had haemorrhagic cystitis requiring bilateral nephrostomy tubes

* One patient had a hip replacement that was not coded as a complication.
† Only the highest grade complication was coded for each patient.
‡ Grade 1 and 2 toxicities were probably under-reported.
§ Two of 25 patients (8%) experienced grade 3 to 4 complications, including 1 of the 19 patients with disease control. Three of the 19 patients (16%) with disease control had complications that severely impacted their quality of life.

The most prominent study of postoperative radiotherapy for early-stage cervix cancer was published in 2000 by Peters et al.[2] The 5-year relapse-free and overall survival rates for patients treated with surgery and postoperative radiotherapy were both approximately 65%. In this study, the 5-year cause-specific survival was 84% and the overall survival was 80%. The difference may be that this study was limited to stage IB tumours. Peters et al's study does not report 10-year results. However, the data from this study demonstrate that short follow-up produces actuarial calculations that overestimate the efficacy of therapy.

It is difficult to compare the complication rates in this study with those in other studies because other studies mix temporary acute side effects with permanent complications. These data suggest that, with long-term follow-up, a substantial portion of patients will develop serious complications in the years following postoperative radiotherapy in this setting. Specifically, 16% of patients who remained continuously free of disease experienced a complication that substantially compromised their quality of life.

A report of patients with stage IB to IIB cervix cancer who were treated with primary radiotherapy has recently been submitted (TJ Galloway, unpublished data, 2008). The tumour control and complication rates were similar to the results for the 25 patients in this series who were treated with radical hysterectomy and postoperative radiotherapy. Specifically, at 5 years, the pelvic control rate was 80% with primary radiotherapy versus 87% with postoperative radiotherapy, and the grade 3 to 4 complication rate was 8% for both treatment groups. These results support the view that radiotherapy alone or with concurrent chemotherapy is as effective as adding radiotherapy following radical hysterectomy.

It is not always possible to accurately predict surgical findings following radical hysterectomy and pelvic lymph node dissection for cervix cancer. The indications for postoperative radiotherapy at the Department of Radiation Oncology are a positive margin, margin <5 mm, <10 nodes recovered, multiple positive nodes, or a node with extracapsular extension. Also, patients who exhibit at least 2 of the following factors receive postoperative radiotherapy: parametrial invasion with a margin >5 mm, a single positive lymph node without extracapsular extension, tumour size >4 cm, or LVSI.

At the University of Florida College of Medicine, patients receive pelvic radiotherapy (superior field border at L4 to L5) to a dose of 39.6 to 45.0 Gy at 1.8 Gy per fraction with a 4-field technique or intensity-modulated radiotherapy. All patients receive brachytherapy to the vaginal cuff. The brachytherapy dose is 15 or 25 Gy at 5 Gy per fraction delivered at 5 mm from the surface of the vaginal cylinder by an HDR afterloader. The indication for a brachytherapy dose of 25 Gy is a positive surgical margin. The indications for concurrent cisplatin chemotherapy (40 mg/m^2 intravenously weekly for 5 cycles) are either multiple positive nodes or a positive margin.

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