

## Scientific Article

# Definitive Radiation Therapy for Medically Inoperable Endometrial Carcinoma



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## Abstract

**Purpose:** Upfront radiation therapy consisting of brachytherapy with or without external beam radiation therapy is considered standard of care for patients with endometrial carcinoma who are unable to undergo surgical intervention. This study evaluated the cancer-free survival (CFS), cancer-specific survival (CSS), and overall survival (OS) of patients with endometrial carcinoma managed with definitive-intent radiation therapy.

**Methods and Materials:** This was a single-institution retrospective analysis of medically inoperable patients with biopsy-proven endometrial carcinoma managed with up-front, definitive radiation therapy at UMass Memorial Medical Center between May 2010 and October 2021. A total of 55 cases were included for analysis. Patients were stratified as having low-risk endometrial carcinoma (LREC; uterine-confined grade 1-2 endometrioid adenocarcinoma) or high-risk endometrial carcinoma (HREC; stage III/IV and/or grade 3 endometrioid carcinoma, or any stage serous or clear cell carcinoma or carcinosarcoma). The CFS, CSS, OS, and grade  $\geq 3$  toxic effects were reported for patients with LREC and HREC.

**Results:** The median age was 66 years (range, 42-86 years), and the median follow-up was 44 months (range, 4-135 months). Twelve patients (22%) were diagnosed with HREC. Six patients (11%) were treated with high-dose-rate brachytherapy alone and 49 patients (89%) were treated with high-dose-rate brachytherapy and external beam radiation therapy. Twelve patients (22%) were treated with radiation and chemotherapy. The 2-year CFS was 82% for patients with LREC and 80% for patients with HREC (log rank  $P = .0654$ ). The 2-year CSS was 100% for both LREC and HREC patients. The 2-year OS was 92% for LREC and 80% for HREC (log  $P = .0064$ ). There were no acute grade  $\geq 3$  toxic effects. There were 3 late grade  $\geq 3$  toxic effects owing to endometrial bleeding and gastrointestinal adverse effects.

**Conclusions:** For medically inoperable patients with endometrial carcinoma, up-front radiation therapy provided excellent CFS, CSS, and OS. The CSS and OS were higher in patients with LREC than in those with HREC. Toxic effects were limited in both cohorts.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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## Introduction

The rate of uterine corpus cancers is rising, making it the most common gynecologic cancer in the US and second most common in the world.<sup>1,2</sup> The most common uterine corpus cancer is endometrial carcinoma, comprising approximately 90% of cases. The prevalence of

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endometrial carcinoma is increasing, primarily owing to escalating obesity rates, changes in reproductive habits, and nonprogesterone contraceptive use.<sup>3-6</sup> Thus, investigating treatment options that consider these changes is crucial for the optimal care of these patients.

Diagnosis involves histologic review of endometrial tissue, typically after biopsy, curettage, or hysterectomy. Subsequently, surgical staging involving total hysterectomy, lymph node dissection, and bilateral salpingo-oophorectomy is typically conducted. Low-risk tumors, which are usually limited to the endometrium and are low-grade, are typically treated with surgery and postoperative surveillance.<sup>7</sup> Patients with high-risk tumors, including those with metastatic spread and/or serous or clear cell adenocarcinoma subtype, typically receive radiation therapy and chemotherapy. Depending on cancer subtype, radiation therapy may consist of whole pelvic radiation or vaginal brachytherapy. Usually, chemotherapy regimens for endometrial carcinoma consist of carboplatin plus paclitaxel.<sup>8-10</sup>

Although up-front surgical staging is considered standard of care in the treatment of endometrial carcinoma, not all patients are deemed medically operable. Approximately 10% of patients are poor surgical candidates owing to obesity, advanced age, chronic medical conditions, and other factors. Endometrial carcinoma disproportionately afflicts patients with these demographics.<sup>3,4</sup> The proportion of patients in this subset can be expected to grow as the population ages and obesity rates increase. Hormonal therapy, such as megestrol acetate, is a viable option for these patients.<sup>11</sup> Another promising alternative for these patients is receiving up-front radiation therapy with or without chemotherapy, depending on staging and pathologic features.<sup>12-15</sup> However, to our knowledge, the effectiveness of this approach has not been compared in any randomized clinical trials. Furthermore, the data on up-front radiation therapy for high-risk endometrial carcinomas is limited. This study aimed to investigate the clinical outcomes of patients receiving definitive radiation therapy for medically inoperable endometrial carcinoma.

## Methods

### Inclusion criteria

This was a single-institution retrospective review of patients treated with definitive-intent radiation therapy for pathologically confirmed endometrial carcinoma at UMass Memorial Medical Center between May 2010 and October 2021. Only patients with inoperable endometrial carcinoma treated with definitive intent were included in this analysis. Eligibility for definitive radiation therapy was determined by experienced radiation oncologists at UMass Memorial Medical Center who considered tumor

characteristics, degree of invasion and metastasis, patient functional status, use of chemotherapy and hormonal therapy, and medical comorbidities. Evidence of distant metastasis or palliative treatment subsequent to progression of disease after definitive treatment did not exclude patients from our analysis. Only patients deemed medically inoperable were included in this analysis. Given that diagnosis was made on biopsy specimens, pathologic adverse features such as lymphovascular invasion were not routinely reported. Patients treated with hormonal therapies, including levonorgestrel-releasing intrauterine devices, and megestrol acetate were also included in our analysis. This study was approved by the institutional review board for UMass Memorial Medical Center.

### Treatment technique

Treatment plans were planned and reviewed by staff from UMass Memorial Medical Center. Treatment was consistent with American Brachytherapy Society guidelines.<sup>16</sup> In select cases when preradiation magnetic resonance imaging (MRI) was available, patients with low-risk endometrial carcinoma (LREC) that was low-grade and had no lymph node involvement and absent or minimal myometrial invasion as determined by MRI were treated with high-dose-rate (HDR) brachytherapy alone. For all other LREC cases without MRI, HDR brachytherapy with external beam radiation therapy (EBRT) was used. For all patients with high-risk endometrial carcinoma (HREC), HDR brachytherapy with EBRT was used.

In brief, treatment for the majority of patients included an initial course of EBRT directed to the pelvis, followed by HDR brachytherapy using either tandem and ovoid or tandem and cylinder applicators. For the pelvic EBRT component of the treatment, patients underwent computed tomography (CT) simulation, and the clinical target volume (CTV) would include the entire uterus with or without the cervix and at-risk nodal sites (obturator, internal iliac, external iliac, and common iliac with or without paracervical and presacral), consistent with the American Brachytherapy Society guidelines.<sup>16</sup> The EBRT plans were generated in Varian Eclipse using 6 to 18 MV (3-dimensional conformal radiation therapy) or 6 MV (intensity-modulated radiation therapy) photons. Treatment was delivered on Varian 2100, Trilogy, or TrueBeam linear accelerators. Image guidance was specified as MV, kV, and/or conebeam CT before daily treatment. For HDR brachytherapy, patients underwent placement of a tandem and ovoid or tandem and cylinder applicator under real-time ultrasound guidance. Heyman capsules were used in select cases at the discretion of the treating radiation oncologist. Brachytherapy treatment planning was CT-based using Varian BrachyVision. The prescription for CT-based planning was generally determined with the goal of covering the high-risk CTV, defined as

the entire uterus, cervix, and upper 1 to 2 cm of the vagina,<sup>16</sup> using dose to 90% of the high-risk CTV as a metric for target coverage. The decision to add an EBRT boost was based on assessment of tumor characteristics (eg, size, stage, or grade) and patient functional status. An EBRT boost to the primary CTV was used when there was suboptimal dose from HDR brachytherapy and additional dose was either not technically feasible (eg, owing to anatomic constraints respecting normal organ tolerances to the bowel, rectum, and/or bladder) or if the patient refused additional HDR brachytherapy.

Medical operability and the use of chemotherapy and/or hormonal therapy was determined by multidisciplinary review with radiation oncologists and gynecologic oncologists. Reasons for inoperability and additional interventions included body mass index (BMI), advanced age, and/or other comorbidities. In total, 12 patients received chemotherapy in addition to radiation therapy. Staging, including assessment of the depth of invasion, was obtained by CT and/or MRI imaging, whereas grade was determined by endometrial biopsy. Ten patients received platinum-based (cisplatin or carboplatin with paclitaxel) chemotherapy, 1 patient received doxorubicin, and another received carboplatin with gemcitabine. Seven of these patients had HREC. All patients with stage III or IV cancers were treated with chemotherapy.

### Statistical analysis

Patient demographics, tumor characteristics, and outcomes were described from documentation gathered through chart review. Kaplan-Meier plots were used to compare survival and relapse outcomes in the LREC and HREC subgroups. The log-rank test was used to compare significance. A 2-tailed student *t* test was used to test significance of BMI box-and-whisker plots. The Fisher exact test was used to test significance of the association between chemotherapy status and outcome. The time course was measured from the start of radiation therapy to the date of last follow-up. Recurrence was defined as either local (endometrial, vaginal, or pelvic lymph nodes) or distant (outside of the pelvic region). Grade  $\geq 3$  toxic effects were defined according to Common Terminology Criteria for Adverse Events, version 5. Statistical analyses were conducted and graphs were designed using Graph-Pad Prism, version 5.

## Results

### Baseline characteristics

Table 1 lists the baseline characteristics of patients in this study. A total of 55 patients were included in the

**Table 1** Baseline characteristics of patients

Patient characteristics	Patients, No. (%) (N = 55)*
Age at treatment, median (range), y	66 (42-86)
Median follow-up, median (range), mo	44 (4-135)
Body mass index, median (range)	45.8 (25-70)
25-35	11 (21)
36-45	15 (28)
46-55	16 (30)
56-65	8 (15)
65-70	3 (6)
Ethnicity	
African American	2 (4)
Caucasian	47 (85)
Hispanic	5 (9)
Unknown	1 (2)
Stage	
I	20 (36)
IA	12 (22)
IB	9 (16)
II	9 (16)
IIIA	1 (2)
IIIB	1 (2)
IIIC	2 (4)
IV	1 (2)
Grade	
1	31 (56)
2	16 (29)
3	8 (15)
Histology	
Carcinosarcoma	4 (7)
Clear cell carcinoma	1 (2)
Endometrioid adenocarcinoma	50 (91)
Chemotherapy use	12 (22)
Megace use	11 (20)
Mirena intrauterine device use	19 (35)
Tamoxifen	2 (4)

\* Data are presented as the number (percentage) of patients unless otherwise indicated.

study, with a median age at time of therapy of 66 years (range, 42-86 years). The median follow-up was 44 months (range, 4-135 months). The median BMI was 45.8 (range, 25.2-70). The majority of patients were Caucasian (85%), followed by Hispanic (9%) and African American (4%). Forty-one cancers were stage I (74%), 9 were stage II

**Table 2** Baseline characteristics of cancers

Grade	Stage							
	I (NOS)	IA	IB	II	IIIA	IIIB	IIIC	IV
Grade								
	10	11	6	3	0	0	1	0
	5	1	3	4	1	1	1	0
	5	0	0	2	0	0	0	1
NOS	No. (%) (N = 55)							
LREC (nonbolded)	43 (78)							
HREC (bolded)	12 (22)							
Therapy	Fisher <i>P</i>			LREC, No. (%)			HREC, No. (%)	
Chemotherapy (total)	.0019			5 (12)			7 (58)	
Chemotherapy (definitive)	.1103			3 (7)			3 (25)	
Megace	.4223			10 (23)			1 (8)	
Mirena intrauterine device	.0407			18 (42)			1 (8)	
Tamoxifen	.3919			1 (2)			1 (8)	
Comorbidities	<i>t</i> test <i>P</i>							
Age at treatment, median, y	.1376			64			71	
BMI, median	.7701			47.7			42.1	

Abbreviation: BMI = body mass index; HREC = high-risk endometrial cancer; LREC = low-risk endometrial cancer; NOS = not otherwise specified.

(16%), 4 were stage III (8%), and 1 was stage IV (2%). Thirty-one were grade 1 (56%), 16 were grade 2 (29%), and 8 were grade 3 (15%). Fifty patients (91%) were diagnosed with endometrial adenocarcinoma, 4 patients (7%) with carcinosarcoma, and 1 patient (2%) with clear cell carcinoma. Twelve patients (22%) received chemotherapy—half received chemotherapy as part of definitive treatment and the other half only after progression of disease.

Table 2 shows the distribution of grade and stage for these patients. High-risk endometrial carcinoma was defined as cancer that was grade 3 endometrioid carcinoma, had high-risk histology (serous or clear cell carcinoma or carcinosarcoma), and/or was stage III or IV. Twelve patients (22%) had HREC, and the remaining 43 patients (78%) had LREC. Of patients with stage III endometrial cancer, 1 had internal and external iliac node involvement (IIIC1), 1 had retroperitoneal lymph node involvement (IIIC2), 1 had tumor extension along the anterior vagina (IIIB), and 1 had extensive uterine involvement (IIIA). The patient with stage IVB (M1) endometrial carcinoma had pulmonary metastases. There was no significant difference between BMI (2-tailed *t* test  $P = .7701$ ) and age at treatment ( $P = .1376$ ) in patients with LREC and HREC.

Six patients (11%) were treated with HDR brachytherapy alone, and 49 patients (89%) were treated with

HDR brachytherapy with EBRT. Additional information on radiation technique, fractionation schemes, and median doses on patients treated with brachytherapy alone and brachytherapy with EBRT can be found in Table 3.

All patients received definitive radiation therapy, and 12 patients received chemotherapy (22%). Of these patients, 5 received carboplatin and paclitaxel as part of definitive treatment—3 in the adjuvant setting, 1 in the neoadjuvant setting, and 1 using a “sandwich” approach. Four patients received carboplatin and paclitaxel at the time of progression of disease. The remaining 3 patients received paclitaxel alone. One received cisplatin concurrently with radiation therapy with definitive intent. The other 2 patients received chemotherapy after progression of disease—1 received carboplatin and gemcitabine instead owing to an anaphylactic reaction with paclitaxel and the other received doxorubicin owing to poor tolerance to carboplatin and paclitaxel. Patients with HREC were more likely to be treated with chemotherapy; 7 of the 12 patients treated with chemotherapy had HREC (Fisher exact test  $P = .0019$ ). However, there was no difference in likelihood when planned for definitive intent (Fisher exact test  $P = .1103$ ). A total of 32 patients received hormonal therapy in addition to radiation therapy—11

**Table 3 Radiation technique and median doses**

	Patients, No. (%) <sup>*</sup>
HDR brachytherapy only protocol (n = 6)	
Tandem and ovoids	2 (33)
Tandem and ovoids with capsules	4 (67)
HDR fractionation scheme	
14.0 Gy/2 fx	1 (17)
19 Gy/3 fx	1 (17)
35 Gy/4 fx	2 (33)
36.5 Gy/5 fx	1 (17)
17 Gy/3 fx + 15 Gy/3 fx	1 (17)
HDR dose, median (range), Gy	
Median CTV D <sub>90</sub> EQD <sub>2</sub>	53.26 (24.6-92.88)
Median bladder D <sub>2cc</sub> EQD <sub>2</sub>	51 (36.1-66.22)
Median rectum D <sub>2cc</sub> EQD <sub>2</sub>	24.9 (6.9-61)
Median sigmoid bowel D <sub>2cc</sub> EQD <sub>2</sub>	49 (11.3-66.12)
Median vaginal wall D <sub>2cc</sub> EQD <sub>2</sub>	44.3 (44.7-69.73)
HDR brachytherapy with EBRT protocol (n = 49)	
Endometrial applicator	7 (14)
Tandem and cylinder	5 (10)
Tandem and ovoids	18 (37)
Tandem and ovoids with capsules	19 (39)
HDR fractionation scheme	
5 Gy/1 fx	1 (2)
6.3 Gy/3 fx	3 (5)
8.5 Gy/1 fx	1 (2)
12 Gy/3 fx	2 (4)
15 Gy/3 fx	2 (4)
18.9 Gy/3 fx	8 (15)
19.5 Gy/3 fx	1 (2)
20 Gy/3 fx	1 (2)
21 Gy/3 fx	12 (22)
22 Gy/3 fx	1 (2)
22.5 Gy/3 fx	1 (2)
24 Gy/3 fx	2 (4)
28.5 Gy/5 fx	1 (2)
28.5 Gy/6 fx	1 (2)
30 Gy/5 fx	1 (2)
30 Gy/6 fx	6 (11)

(continued on next page)

**Table 3 (Continued)**

	Patients, No. (%) <sup>*</sup>
36 Gy/6 fx	1 (2)
7 Gy/1 fx + 13.2 Gy/3 fx	1 (2)
9 Gy/3 fx + 15 Gy/3 fx	1 (2)
17 Gy/3 fx + 15 Gy/3 fx	1 (2)
19.3 Gy/3 fx + 6.5 Gy/1 fx	1 (2)
EBRT fractionation scheme	
37.5 Gy/15 fx	1 (2)
44 Gy/22 fx	1 (2)
45 Gy/25 fx	36 (73)
50.4 Gy/28 fx	2 (4)
45 Gy/25 fx + 22.5 Gy/3 fx	1 (2)
45 Gy/25 fx + 5.4 Gy/3 fx <sup>†</sup>	2 (4)
45 Gy/25 fx + 12 Gy/2 fx	1 (2)
45 Gy/25 fx + 16 Gy/8 fx <sup>†</sup>	1 (2)
45 Gy/25 fx + 12 Gy/6 fx	1 (2)
45 Gy/25 fx + 15 Gy/3 fx	1 (2)
45 Gy/25 fx + 20 Gy/8 fx	1 (2)
45 Gy/25 fx + 25 Gy/5 fx	1 (2)
HDR with EBRT, cumulative dose, median (range), Gy	
Median CTV D <sub>90</sub> EQD <sub>2</sub>	77.2 (50.1-175.28)
Median bladder D <sub>2cc</sub> EQD <sub>2</sub>	80.1 (59.5-153.54)
Median rectum D <sub>2cc</sub> EQD <sub>2</sub>	67.75 (48.3-140.75)
Median sigmoid bowel D <sub>2cc</sub> EQD <sub>2</sub>	71.05 (51.4-138.59)
Median vaginal wall D <sub>2cc</sub> EQD <sub>2</sub>	104.7 (54-173.46)

*Abbreviations:* CTV = clinical target volume; D<sub>2cc</sub> = dose to maximally exposed 2 cm<sup>3</sup>; D<sub>90</sub> = dose to 90%; EBRT = external beam radiation therapy; EQD<sub>2</sub> = equivalent dose in 2 gray fractions; Fx = fraction; Gy = Gray; HDR = high-dose rate.

<sup>\*</sup> Data are presented as the number (percentage) of patients unless otherwise indicated.

<sup>†</sup> With the exception of these 3 cases, all EBRT boosts were applied directly to the tumor CTV, thus directly contributing to the cumulative primary CTV EQD<sub>2</sub> dose. Among these cases, the boost in 1 case (45 Gy/25 fx + 5.4 Gy/3 fx) contributed partially to the tumor CTV, whereas in the other 2 cases (45 Gy/25 fx + 5.4Gy/3 fx and 45 Gy/25 fx + 16 Gy/8 fx), the boosts did not contribute to the tumor CTV.

patients (20%) were treated with Megace, 19 (35%) with Mirena intrauterine devices, and 2 (4%) with tamoxifen. Mirena intrauterine devices use was more likely in patients with LREC ( $P = .0407$ ); 18 patients with LREC and only 1 with HREC received this therapy in addition to radiation. Use of Megace ( $P = .4223$ ) and tamoxifen ( $P = .3919$ ) did not differ among patients with HREC and LREC.

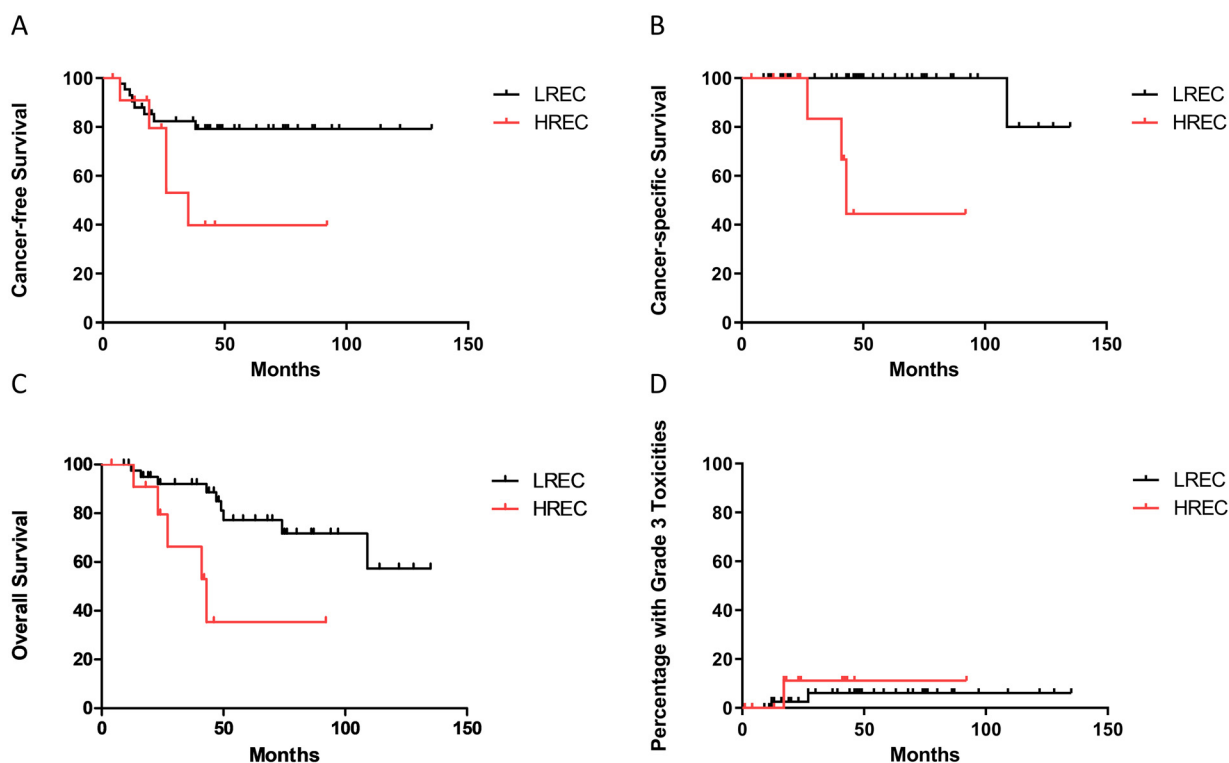
## Cancer-free survival

The 2-year cancer-free survival (CFS), or proportion of patients with no recurrence or progression of disease, was 82% for patients with LREC and 80% for patients with HREC (Fig. 1A). One patient with stage IB, grade 2 LREC developed local recurrence with vaginal bleeding 11 months after treatment. The patient died 1 month later from a cardiac event before receiving therapy. In total, 8 patients with LREC had recurrence during a range of 7 to 48 months after starting radiation therapy. Four of these cases (50%) were grade 1, whereas the remaining 4 cases (50%) were grade 2. Five patients with HREC had recurrence at 8, 12, 19, 27, or 30 months after starting radiation therapy. Among these cases, 3 (60%) were grade 3, 1 (20%) was grade 2, and 1 (20%) was grade 1. Of these grade 3 tumors, all had carcinosarcoma histology, as opposed to the grade 1 or 2 tumors, which had endometrioid histology. There was a trend toward an increased recurrence rate among patients with HREC (42%)

compared with patients with LREC (19%), although this was not statistically significant (log rank  $P = .0654$ ).

## Cancer-specific survival

The 2-year cancer-specific survival (CSS) was 100% in both the LREC and HREC groups (Fig. 1B). The overall CSS in patients with LREC was found to be statistically higher than in those with HREC (log rank  $P < .0001$ ). One LREC patient with local recurrence died from complications from vaginal bleeding 109 months after treatment. Three patients with HREC died from complications related to endometrial cancer. One died owing to respiratory failure related to heavy vaginal bleeding. A second died 27 months after initiating radiation therapy owing to severe acidosis and respiratory failure secondary to diffuse peritoneal carcinomatosis. The third patient with HREC died from hypotension and sepsis related to metastatic



**Figure 1** A, Cancer-free survival stratified by routine follow-up and screening in patients with low-risk endometrial carcinoma (LREC) ( $n = 43$ ) and high-risk endometrial carcinoma (HREC) ( $n = 12$ ). There was no significant difference in cancer-free survival (log rank  $P = .0654$ ). B, Cancer-specific survival stratified by routine follow-up and screening. The cancer-specific survival of patients with LREC was significantly higher compared to those treated for HREC (log rank  $P = .0009$ ). C, Overall survival stratified by routine follow-up and screening. Patients treated for LREC had a significantly increased overall survival time compared with those with HREC (log rank  $P = .0064$ ). D, Percentage of patients with grade 3 toxic effects following radiation therapy as defined by the Common Terminology Criteria for Adverse Events, version 5, stratified by routine follow-up and screening. There was no significant difference between patients with LREC compared with patients with HREC (log rank  $P = .5196$ ). Survival in A–C is reported as a percentage. Abbreviations: HREC = high-risk endometrial carcinoma; LREC = low-risk endometrial carcinoma.

spread. All remaining deaths were owed to causes unrelated to endometrial carcinoma.

### Overall survival

The 2-year overall survival OS in patients with LREC and HREC was 92% and 80%, respectively (Fig. 1C) (log  $P = .0064$ ). The most common cause of death was congestive heart failure exacerbation, with 2 patients in the LREC and 1 patient in the HREC group dying from this cause. The next most common cause was cardiac arrest (2 patients in the LREC group). The remaining patients died from complications from a perforated duodenal ulcer (HREC), abdominal hernia repair (LREC), septic shock (LREC), and worsening dementia that resulted in transfer to hospice care and withdrawal of medications (LREC).

### Toxic effects and tumor control

After treatment, the most common reported adverse effects were incontinence, bleeding, and weakness. One patient developed radiation cystitis, 2 developed radiation proctitis, and another developed a groin abscess that was successfully treated by antibiotic therapy (Table 4). No acute grade  $\geq 3$  toxic effects (occurring within 14 days of treatment) were reported. There were 3 late grade  $\geq 3$  toxic effects (Fig. 1D). One patient was hospitalized for severe diarrhea 17 months after starting radiation therapy. Another patient developed sepsis owing to suspected endometrial and/or bowel perforation. A third patient was hospitalized for radiation enteritis 27 months after treatment. No significant difference in the risk of grade  $\geq 3$  toxic effects was found between patients with LREC and HREC (log  $P = .6587$ ).

In total, 13 patients developed recurrence of endometrial carcinoma after treatment. The median time from end of radiation therapy to diagnosis of recurrence was 17 months (range, 8-48 months). Recurrences were mostly local, although 5 patients had metastatic recurrence (Table 4). Among patients with recurrent disease, 5 were originally diagnosed with HREC. Five patients received palliative therapy after recurrence. Nine of the 13 patients (69%) with recurrences eventually died.

### Predictive factors

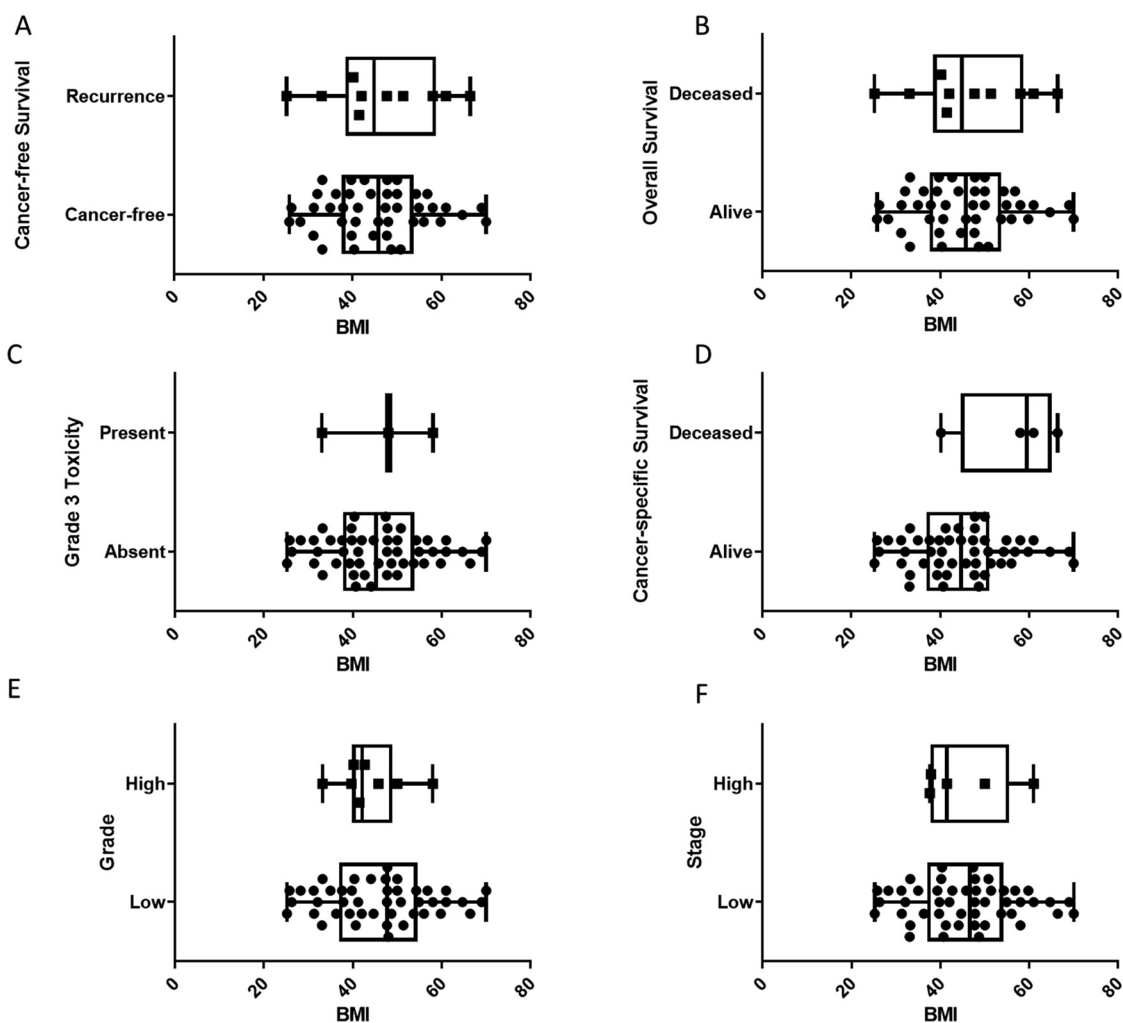
There was no correlation between patient BMI at the start of radiation therapy and CFS ( $P = .7598$ ), OS ( $P = .7598$ ), frequency of grade 3 toxic effects ( $P = .9114$ ), tumor grade ( $P = .6368$ ), and tumor stage ( $P = .9917$ ). However, there was a significant negative correlation between BMI and CSS ( $P = .0470$ ) (Fig. 2). Use of chemotherapy did not correlate with improved CFS ( $P = .1079$ ),

**Table 4 Common adverse effects and recurrence after radiation therapy**

	Patients, No. (%)
Adverse effects* (within 5 years of follow-up)	
Total patients, No.	55
Vagina or uterine bleeding	6 (11)
Rectal bleeding	3 (5)
Incontinence	8 (15)
Nausea or vomiting	2 (4)
Diarrhea	3 (5)
Constipation	2 (4)
Dysuria	2 (4)
Abdominal pain	1 (2)
Pelvic pain	1 (2)
Back pain	3 (5)
Weakness	4 (7)
Anorexia	1 (2)
Neuropathy	1 (2)
Radiation cystitis	1 (2)
Radiation proctitis	2 (4)
Groin abscess	1 (2)
Recurrence	
Total patients with recurrence, No.	13
Time until recurrence, median (range), mo	17 (8-48)
Patients with HREC	5 (38)
Patients deceased	9 (69)
Received palliative radiation	5 (38)
Region of recurrence	
Local only	8 (62)
Peritoneum, liver, or mesenteric nodules	1 (8)
Umbilicus, omentum, and inguinal and iliac lymph nodes	1 (8)
Neck and supraclavicular fossa	1 (8)
Retroperitoneum	1 (8)
Brain	1 (8)
Abbreviation: HREC = high-risk endometrial carcinoma.	
* All grade 1 or 2 toxic effects, with the exception of 3 cases.	

OS ( $P = .1285$ ), and frequency of grade 3 toxic effects ( $P > .9999$ ). However, there was a negative correlation with CSS ( $P = .0292$ ) (Table 5). There were no reported grade  $\geq 3$  events from chemotherapy.

We investigated a number of additional factors that could potentially influence the rate of disease-related recurrence and survival. Increasing patient age



**Figure 2** Box and whisker plots of body mass index (BMI) versus A, cancer-free survival; B, overall survival; C, development of grade 3 toxic effects; D, cancer-specific survival; E, grade; and F, stage ( $n = 53$ ). Low-grade was defined as grades 1 or 2, and high-grade was defined as grade 3. Low stage was defined as stage I or II, and high stage was defined as stage III or IV. Two-tailed  $t$ -test  $P$  values are as follows: BMI versus cancer-free survival,  $P = .7598$ ; BMI versus overall survival,  $P = .7598$ ; BMI versus grade 3 toxic effects,  $P = .9114$ ; BMI versus cancer-specific survival,  $P = 0.0470$ ; BMI versus grade,  $P = .6368$ ; and BMI versus stage,  $P = .9917$ . At the time of treatment, BMI was not obtainable for 2 patients. *Abbreviations:* BMI = body mass index.

( $P = .5088$ ), grade 3 tumor status ( $P = .388$ ), and addition of EBRT to HDR ( $P = .5879$ ) were not associated with significant changes to CFS. Similarly, age ( $P = .2739$ ) and grade 3 tumor status ( $P = .0967$ ) were not associated with significant differences in CSS. The addition of EBRT to HDR brachytherapy trended toward improvement in CSS and was almost statistically significant ( $P = .0546$ ). In our study, having non-endometrioid histology was associated with inferior CFS ( $P = .0006$ ) and CSS ( $P = .023$ ). Furthermore, a low CTV equivalent dose in 2 gray fractions to the tumor was associated with inferior CFS ( $P = .0167$ ) and CSS ( $P = .0432$ ). Patients with a high-risk disease stage (stage III or IV) at diagnosis had similar CFS ( $P = .0635$ ) and CSS ( $P = .3247$ ) as patients with a low-risk stage (stage I or II). However, when stratified between stage I

and all other stages, patients with disease that was stage II or above had inferior CFS ( $P = .0242$ ), although CSS remained similar ( $P = .2342$ ).

## Discussion

Given the positive correlation between advanced age and/or obesity and rates of endometrial carcinoma, it is inevitable that a certain percentage of patients will be poor candidates for definitive surgical resection. This is especially true given the aging population and rising rates of obesity. The use of up-front radiation therapy is thus likely to increase and may become standard of care for many patients.



**Table 5 Comparison of chemotherapy status of patients and outcomes**

	Patients, No. (N = 55)		P value
	Without recurrence	With recurrence	
Chemotherapy status vs cancer-free survival			
No chemotherapy	36	7	.1079
Chemotherapy	7	5	
Chemotherapy status vs overall survival	Alive patients	Deceased patients	
No chemotherapy	35	8	.1285
Chemotherapy	7	5	
Chemotherapy status vs presence of grade 3 toxic effects	No grade 3 toxic effects	Grade 3 toxic effects present	
No chemotherapy	40	3	.9999
Chemotherapy	12	0	
Chemotherapy status vs cancer-specific survival	Alive patients	Deceased patients	
No chemotherapy	42	1	.0292
Chemotherapy	9	3	

Although our treatment plans were consistent with the American Brachytherapy Society guidelines, there are several key aspects worth noting. A CT-based approach was used for all of our brachytherapy planning; when available, preradiation diagnostic MRI was used to guide tumor delineation. We also used single tandem applicators, because Y-tandem applicators were not used at our institution at the time the patients in our study were treated. In cases with lateralized disease, we used Heyman capsules in addition to tandem and ovoid applicators to increase dose coverage of the target. Nevertheless, use of these applicators may have limited coverage, and future treatments could use Y-tandem or multitandem applicators to improve dosimetry.<sup>16</sup> A wide range of doses were used in this study, with HDR doses ranging from 5 Gy/1 fx to 36 Gy/6 fx and EBRT doses ranging from 37.5 Gy/15 fx to 45 Gy/25 fx with or without boost to smaller EBRT field(s) (Table 3). These ranges are consistent with those reported in other studies<sup>17</sup> and support the need to personalize treatment plans for these patients.

Previous studies have compared the effectiveness of radiation therapy in treating endometrial carcinoma. A systematic review from Dutta et al<sup>14</sup> found that in patients with LREC, pelvic control in stage I carcinoma was 80% to 100% and in stage II carcinoma was 61% to 89%. Their review found that external beam radiation therapy, brachytherapy, and external beam radiation therapy combined with brachytherapy all had increased OS compared with no local therapy. These findings are supported by several other independent studies that found high OS in low-risk endometrial cancer being treated with up-front radiation therapy.<sup>13,15,18-21</sup>

There are fewer studies comparing the benefits of up-front radiation therapy between patients with medically inoperable LREC and HREC.<sup>19,22</sup> In the current study, we demonstrated that CFS, CSS, and OS in LREC was excellent. Of the deaths reported, most were owed to causes

unrelated to endometrial carcinoma. This is expected given the vulnerability of the medically inoperable population and consistent with previous studies focusing on radiation therapy for patients with LREC. The percentage of grade 3 or higher toxic effects in this group was generally low, also consistent with other studies.<sup>13,15,18-21</sup> Patients with HREC appeared to have lower CFS than the patients with LREC, although this was not statistically significant. This trend of higher recurrence in HREC is not entirely surprising, because more aggressive and/or established disease is more difficult to treat. If this trend is accurate, it may suggest that pelvic radiation therapy does not prevent recurrence in HREC as well as in LREC. Longer follow-up may reveal a statistical difference in recurrence risk between patients with HREC and LREC. We also found patients with HREC had significantly lower CSS and OS rates compared with patients with LREC. These interpretations differed slightly compared with previous studies,<sup>22</sup> although these findings could be explained by differences in patient populations, treatment modalities, and statistical power in small cohorts. Similar to the LREC group, deaths were mostly owed to causes not related to cancer. Further studies will be required to compare the outcomes of up-front radiation therapy for LREC and HREC. It is also interesting to note that most failures in our study were local, in contrast to a previous study<sup>23</sup> in which mostly distant recurrences were observed. It is possible that the wide range of doses used in our study could have contributed to differences in tumor recurrence and survival outcomes, because changes in CTV equivalent dose in 2 gray fractions correlated with changes in CFS and CSS. Future studies should investigate how differences in patient and tumor characteristics and treatment modalities could potentially influence recurrence patterns.

Toxic effects in both patient groups were generally well controlled. There were no acute grade  $\geq 3$  toxic effects.

For the 3 patients who experienced late grade 3 toxic effects attributed to radiation therapy, 1 patient is still being followed, whereas the other 2 died from complications unrelated to the toxic effects. These results are consistent with reported toxicity outcomes in previous studies.<sup>12-15,18-22,24</sup> It should be noted, however, that the number of toxic effects may be underreported, because many patients could have died before the development of late toxic effects.

Consistent with previously reported literature,<sup>25</sup> non-endometrioid histology was associated with worse CFS and CSS. However, it is interesting that while the presence of grade 3 tumors trended toward an inferior prognosis in our study, we did not find a statistically significant difference in CFS or CSS in patients with grade 3 disease. Although this could suggest that histology may be of more prognostic value in endometrial carcinoma, interpretation of this finding is limited by low statistical power in our reported cohort ( $n = 8$  patients with grade 3 disease). Analysis of additional patients with grade 3 disease may help clarify our findings.

Among all cancers, endometrial cancer has the strongest association with obesity, with 57% of all cases attributable to obesity.<sup>26</sup> Given this relationship, it is interesting that increasing BMI seemed to correlate with decreasing CSS. It is possible that elevated BMI contributes to inferior CSS simply due to stimulated growth of endometrial cancer cells in patients with more marked obesity.<sup>3-6</sup> Chemotherapy status was also negatively correlated with CSS. Chemotherapy treatment is typically reserved for endometrial cancers with worse prognosis (eg, HREC), which could explain the lower CSS. Although speculative, this could also explain why patients with HREC also had lower OS than patients with LREC, because chemotherapy could expose patients to adverse effects that reduce OS time. Of note, because only 6 patients received chemotherapy as part of their definitive treatment, it is not possible for us to draw a meaningful conclusion between chemotherapy use and CSS from our study alone given the limited cohort size. Mirena was used more frequently in patients with LREC, which could also have contributed to this outcome, because better control of bleeding could benefit OS. Further studies will be needed to determine the nature of these associations.

The strengths of this study include the relatively large population sample size and long follow-up times. However, this study has a number of limitations. Although the population size is comparable to that of previous studies, there were only 12 patients with HREC for comparison. The majority of patients were Caucasian, with relatively few African American and Hispanic patients. Notably, prognosis is inferior among Black women, who are diagnosed with endometrial cancer with high-risk histologic features and late stage at a disproportionate rate.<sup>26</sup> Additional study is required to shed light on the root cause of this disparity and how this might inform radiation

therapy-specific management of these patients. There was also a selection bias for older patients with more comorbidities, although this is expected given that the goal of this study was to investigate outcomes in medically inoperable patients who tend to have these characteristics. These limitations, however, are not unique to our study.<sup>12-15,18-22,24</sup> Although our results are largely consistent with outcomes reported for similar patient cohorts in the literature,<sup>12-14,18-22</sup> this was a single-institution retrospective study, and thus, differing patient demographics may reduce the generalizability of the findings.

Our study adds to the breadth of existing data showing favorable outcomes for medically inoperable patients with endometrial carcinoma being treated with up-front radiation therapy. Both patients with LREC and those with HREC had favorable CSS and OS with relatively few toxic effects. Taken together, these data suggest that for these patients, radiation therapy can serve as an excellent alternative when surgery is not an option.

## Conclusions

Our results suggest that up-front radiation therapy for medically inoperable patients with endometrial carcinoma provides favorable outcomes both in patients with LREC and patients with HREC. Patients with LREC experienced higher CSS and OS than did those with HREC. Complications from radiation therapy were rare. Increasing BMI and use of concurrent chemotherapy were found to negatively correlate with CSS. Although treating patients with medically inoperable endometrial carcinoma remains a challenge, the use of radiation therapy serves as a safe and effective approach.

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## Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.adro.2022.101003](https://doi.org/10.1016/j.adro.2022.101003).

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