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CLINICAL INVESTIGATION **Endometrium**

LONG-TERM RESULTS OF HIGH-DOSE-RATE BRACHYTHERAPY IN THE PRIMARY TREATMENT OF MEDICALLY INOPERABLE STAGE I–II ENDOMETRIAL CARCINOMA

TAMIM M. NIAZI, M.D.,* LUIS SOUHAMI, M.D.,* LORRAINE PORTELANCE, M.D.,* BORIS BAHORIC, M.D.,* LUCY GILBERT, M.D.,† AND GERALD STANIMIR, M.D.†

*Department of Oncology, Division of Radiation Oncology, and †Division of Gynecology Oncology, McGill University, Montreal, Quebec, Canada

Purpose: Total-abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) is the gold-standard therapy for patients with endometrial carcinoma. However, patients with high operative risks are usually treated with radiation therapy (RT) alone. The goal of this study was to update our experience of high-dose-rate brachytherapy (HDRB), with or without external-beam irradiation (EBRT), for such patients.

Methods and Materials: Between 1984 and 2003, 38 patients with Stage I and Stage II adenocarcinoma of the endometrium considered high operative risk received RT as the primary treatment. The median age was 74.1 years. Before 1996, the local extent of the disease was assessed by an examination under anesthesia (EUA) and by EUA and magnetic resonance imaging (MRI) thereafter. Eight patients (21%) were treated with combined HDRB and EBRT, and 30 patients (79%) were treated with with HDRB alone. The median HDRB dose was 23.9 Gy, typically delivered in 3 fractions in a weekly schedule. The median EBRT dose was 42 Gy.

Results: At a median follow-up of 57.5 months for patients at risk, 11 patients (29%) have failed: 6 patients (16%) locally, 4 patients (10.5%) distantly, and 1 patient (3%) locally and distantly. Local failure was established by biopsy, and 4 patients were salvaged by TAHBSO. Higher stage and higher grade were both associated with increased failure rate. The 15-year disease-specific survival (DSS) was 78% for all stages, 90% for Stage I, and 42% for Stage II ($p < 0.0001$). The 15-year DSS was 91% for Grade I and 67% for Grade II and III combined ($p = 0.0254$). Patients with Stage I disease established by MRI (11 patients) and who received a total HDRB dose of 30 Gy had a DSS rate of 100% at 10 years. Four patients experienced late toxicities: 1 Grade II and 3 Grade III or IV.

Conclusions: Medically inoperable Stage I endometrial carcinoma may be safely and effectively treated with HDRB as the primary therapy. In selected Stage I patients, our results are equivalent to that of surgery. We believe that the alternative option of HDRB as the primary therapy for selected Stage I endometrial carcinoma, even in patients with low operative risks, needs further evaluation.

Endometrial cancer, Inoperable endometrial cancer, Radiotherapy, High-dose-rate brachytherapy.

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy. Total-abdominal hysterectomy and bilateral salpingo-oophrectomy (TAHBSO) with lymphadenectomy remains the standard of care for these patients. Patients with poor prognostic factors are often treated with adjuvant external-beam radiation therapy (EBRT), intracavitary brachytherapy, or a combination of these two (1–6).

The median age for endometrial cancer is 65 years, and around 3% to 9% (7–9) of these patients present with concurrent medical comorbidities that preclude surgery as primary treatment. These patients are often treated with a combination of EBRT and brachytherapy or brachytherapy alone.

In this report, we update our long-term results of medically inoperable patients with Stage I and Stage II endometrial carcinoma treated with high-dose-rate brachytherapy (HDRB), with or without EBRT.

METHODS AND MATERIALS

Study patients

Between 1984 and 2003, 38 medically inoperable patients with a median age of 74.1 years (range, 50–97 years) and histologically proven adenocarcinoma of the endometrium were treated with primary irradiation at our institution. Cardiovascular diseases and morbid obesity accounted for most of the inoperable cases (Table 1). Postmenopausal bleeding, with a median duration of 4 months (range, 1–24 months), was the presenting symptom of all patients.

Reprint requests to: Luis Souhami, M.D., McGill University Health Centre, 1650 Cedar Avenue, Montreal, Quebec, H3G 1A4, Canada. Tel: (514) 934-8040; Fax: (514) 934-8220; E-mail: luis.souhami@muhc.mcgill.ca

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Table 1. Comorbid diseases precluding surgery (n = 38)

Disease	Number of patients (%)
Hypertension	19 (50)
Coronary artery disease	13 (34)
Obesity	12 (32)
Diabetes mellitus	10 (26)
Stroke	5 (13)
Hepatic failure	2 (5)
Severe COPD	2 (5)
Other malignancy	2 (5)

Abbreviation: COPD = chronic obstructive pulmonary disease.

The pretreatment evaluation consisted of a complete history and physical examination that included pelvic examination. All patients had complete blood count, biochemical profile, and chest X-ray. The diagnostic procedure was dilatation and curettage (D&C) in 32 patients and endometrial biopsy in 6 patients. Patients were staged according to the recommendations of the FIGO staging system. Before 1996, the clinical FIGO (10) staging system was used, and the extent of the disease was assessed by an examination under anesthesia (EUA) and, in 15 cases, by abdominal ultrasound. Magnetic resonance imaging (MRI) and EUA were used thereafter to assess the disease extension. Eleven patients were staged with MRI to assess the depth of invasion and size of the uterus. Table 2 shows patient characteristics.

Radiation therapy

High-dose-rate brachytherapy was the primary treatment in all the patients. Eight patients (21%) were treated with combined HDRB and EBRT and 30 patients (79%) were treated with HDRB alone. Six of the 8 patients treated with combined modality were Stage II, and 2 patients were Stage I.

High-dose-rate brachytherapy was delivered by a remote high-dose-rate afterloader. Details of treatment techniques have been previously published (11–14). Briefly, after a written consent, patients were treated in lithotomy position under spinal anesthesia. Patients with Stage I disease were treated by either a rigid tandem or a biconcave (butterfly) applicator. Stage II patients were treated with a tandem and two colpostats. The median HDRB dose was 23.9 Gy (range, 4.4 – 34 Gy). Before 1996, the dose was prescribed to a point 2 cm from the central axis at the midpoint of the central applicator (tandem or butterfly), and 27 patients were treated in this fashion. Treatments were typically delivered in 3 fractions, 1 week apart. Once MRI was introduced in the assessment of the disease extension (after 1996), treatments were customized and based upon the size and shape of the uterus and location and extension of the tumor, as seen on the MRI. Because of the changed source dwell time, treatments were optimized and the dose was prescribed to the surface of the uterus (Fig. 1). HDRB planning and prescription were similar when given with EBRT.

The median EBRT dose was 42 Gy (range, 40–46 Gy), delivered through a 4-field technique. The superior border was either L4/L5 or L5/S1 interspace. The inferior border was defined at the lower border of the ischeal tuberosity. The lateral borders were set at 1.5 to 2 cm beyond the lateral margins of the bony pelvic wall. Lateral field borders were the S2/S3 interspace posteriorly and the anterior border of the pubic symphysis anteriorly.

Follow-up

Follow-up consisted of history and physical examination that included complete pelvic examination and cervical cytology every 3 months for the first 3 years and every 6 months thereafter. After 1996, follow-up of patients also included MRI 3 months after the completion of the treatment and annually thereafter. Cessation of vaginal bleeding was considered indicative of response to treatment in those patients not assessed by MRI. Recurrent bleeding and/or positive cytology were considered local recurrence and were confirmed by D&C or endometrial biopsy. Symptom-specific or site-specific imaging was used to establish distant metastases.

Statistical analysis

The Kaplan-Meier method was used to calculate the survival rates (15). The log-rank test (16) was used to assess the difference between survival curves. If death was clearly the result of a cause other than endometrial cancer or treatment-related complications, the patient was censored at that time. Because the studied population was a cohort with serious intercurrent diseases, we felt disease-specific survival (DSS) to be more appropriate to report than overall survival rates.

RESULTS

At the time of this analysis (February 2005), the median follow-up time for patients at risk was 57.5 months (range, 10–218 months). The number of confirmed deaths was 22. Seven patients (32%) died of their disease, and 15 patients (68%) died of other causes (Table 3). A total of 8 patients were lost to follow-up. Their median follow-up from treatment to missing was 41 months. A total of 11 patients (29%) experienced failure. Six patients (16%) failed locally, 4 patients (10.5%) failed distantly and, 1 patient (3%) failed both locally and distantly. Four of the 6 local failures were subsequently salvaged by TAHBSO. Of these patients, 2 died of unrelated causes, at 71 and 79 months follow-up, and the other 2 are still alive at 55 and 218 months follow-up, respectively.

The 15-year DSS rate was 78% for all stages, 90% for Stage I disease, and 42% for Stage II disease ($p < 0.0001$) (Fig. 2). The 15-year DSS rate was 91% for Grade I and

Table 2. Patient demographics

Characteristic	Number of patients (%)
Age (years)	
Median	74.1
Range	50–97
Stage I	29 (76)
Stage II	9 (24)
Grade I	21 (55)
Grade II	11 (29)
Grade III	6 (16)
Radiation therapy	
HDRB alone	30 (79)
HDRB/EBRT	8 (21)

Abbreviations: EBRT = external-beam radiation therapy; HDRB = high-dose-rate brachytherapy.