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Neoadjuvant radiotherapy with or without chemotherapy followed by extrafascial hysterectomy for locally advanced endometrial cancer clinically extending to the cervix or parametria

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HIGHLIGHTS

- Clinical stage II or IIIB endometrial cancer, pre-operative chemoradiotherapy followed by extrafascial hysterectomy.
- High rates of clinical and pathologic response, low rates of toxicity.
- Impact of image-based HDR brachytherapy, chemotherapy, and PET/CT staging.

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ABSTRACT

Purpose. For locally-advanced uterine cancer clinically extending to the cervix, two treatment paradigms exist: surgical staging radical hysterectomy with tailored adjuvant therapy or neoadjuvant therapy followed by a less extensive simple hysterectomy. Currently, insufficient data exists to guide consensus guidelines and practical application of preoperative radiotherapy.

Materials and methods. Retrospective IRB approved cohort study from 1999 to 2014 of 36 endometrial cancer patients with clinical involvement of cervix ± parametria treated with neoadjuvant external beam radiotherapy (45–50.4 Gy in 25–28 fractions) and image-based HDR brachytherapy (5–5.5 Gy times 3–4 fractions) ± chemotherapy followed by extrafascial hysterectomy performed at a median of 6 weeks after radiotherapy.

Results. All patients had clinical cervical extension, 50% also had parametria extension, and 31% had nodal involvement. At the time of surgery 91% had no clinical cervical involvement, 58% had no pathologic cervical involvement, and all had margin negative resection. The pathologic complete response rate was 24%. Median follow-up from the time of surgery was 20 months (range: 0–153). The 3-year local control, regional control, distant control, disease free survival and overall survival rates were 96%, 89%, 84%, 73%, and 100%. The 3-year rate of grade 3 complications was 11%, with no grade 4+ toxicity.

Conclusions. Neoadjuvant radiation therapy ± chemotherapy followed by extrafascial hysterectomy appears to be a viable option for patients with endometrial cancer clinically extending to the cervix and parametria. The HDR brachytherapy schema of 5–5.5 Gy times 3–4 fractions, for a cumulative EQD_2 of 60–70 Gy, is well tolerated with high rates of clinical and pathological response.

Introduction

Locally advanced endometrial cancer with extension to the cervix is an uncommon presentation of uterine cancer estimated to represent <10–15% of all uterine cancers [1]. The majority of stage II endometrial cancers are occult stage II with microscopic cervical extension noted incidentally at the time of pathologic assessment. Patients with clinical evidence of disease extending to the cervix represent an even less common and challenging subset of uterine cancer patients for which there exist two dichotomous plans of care: (a) initial surgical staging including radical hysterectomy followed by adjuvant therapy tailored based on surgical pathology or (b) neoadjuvant therapy followed by less extensive extrafascial hysterectomy [2]. Radical hysterectomy (with salpingo-oophorectomy, pelvic washings, and lymph node

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sampling) is the preferred surgery for operable patients as it may be difficult to distinguish primary cervical adenocarcinoma from stage II endometrial cancer [3]. Retrospective data have suggested that radical hysterectomy improved local control and survival when compared to initial extrafascial hysterectomy [4,5]. However, radical hysterectomy carries with it a higher risk of surgical complications, especially in the endometrial cancer population often of advanced age with significant co-morbidities (obesity, diabetes mellitus, cardiovascular disease, among others.) [6]. Thus, pre-operative radiotherapy with or without chemotherapy has been used to downstage disease followed by a less extensive extrafascial hysterectomy.

Historically, prior to the 1988 change in FIGO staging to surgical staging, this approach of preoperative radiotherapy was standard, with institutional series documenting 5-year overall survival rates of 69–88% with a combination of external beam radiotherapy and low-dose-rate (LDR) brachytherapy to doses of 60–70 Gy prescribed to point A [7–10]. However, there exists limited data in the era of modern radiotherapy (including high-dose-rate (HDR) brachytherapy, 3D image-based planning, intensity modulated radiotherapy, and image-guided radiotherapy), chemotherapy, and surgical techniques (robotic and laparoscopic) to guide consensus recommendations and practical application [2]. Due to this lack of published data, the American Brachytherapy Society guidelines for HDR brachytherapy in endometrial cancer did not recommend a dose fractionation schema for neoadjuvant HDR brachytherapy for stage II endometrial cancer [11]. With patterns of care surveys showing up to 85% international utilization of HDR in gynecologic cancers, clearly additional data to guide the practical use of neoadjuvant HDR brachytherapy in endometrial cancer is needed [12]. Our approach has been to treat patients with locally advanced endometrial cancer with clinical extension to the cervix (with or without parametria extension) with neoadjuvant external beam radiotherapy (45–50.4 Gy in 25 to 28 fractions) and HDR Ir192 brachytherapy (5–5.5 Gy times 3–4 fractions) with or without concurrent and adjuvant chemotherapy. We previously presented the tolerability of our HDR fractionation schema of 5–5.5 Gy times 3–4 fractions in a smaller patient cohort [13]. Herein, we present a more robust, detailed analysis of clinical and pathologic response, radiotherapy related complications, and disease outcomes in an expanded cohort to better support the approach of neoadjuvant chemoradiotherapy followed by extrafascial hysterectomy in this uncommon, yet challenging subset of endometrial cancer patients. We hypothesize that the combination of advances in modern radiotherapy, advances in surgical technique, and increased integration of chemotherapy will improve outcomes without increasing complications relative to historical series.

Materials and methods

Following institutional review board approval, patients with clinical evidence of cervical (with or without parametrial) involvement treated with neoadjuvant radiotherapy with or without chemotherapy followed by extrafascial hysterectomy from 1999 to 2014 at Magee-Womens Hospital of the University of Pittsburgh Medical Center were retrospectively reviewed. Patients receiving prior pelvic radiotherapy and carcinosarcoma were excluded. Endometrial cancer was confirmed by biopsy with extent of disease defined clinically during exam under anesthesia (EUA). Additionally, staging evaluations either via a computed-tomography (CT) of the chest, abdomen, and pelvis (31%) or 18-Flurodeoxyglucose PET/CT (69%) were performed (usually post-EUA) to rule out distant metastases. Pelvic MRI with water-based vaginal gel and IV gadolinium was also performed in 86% of patients to define the extent of local disease and to guide subsequent image-guided brachytherapy planning [14].

Neoadjuvant radiotherapy consisted of a combination of external beam radiotherapy (56% IMRT) to a dose of 45–50.4 Gy in 25–28 fractions followed by HDR brachytherapy. IMRT planning was completed using CT or PET/CT-based simulation. The clinical target volumes included the entire gross tumor volume, cervix, uterus, ovaries, bilateral parametria, proximal ½ of vagina (except for those with vaginal extension when the entire vagina was included), and pelvic lymph nodes including bilateral obturator, upper pre-sacral, and external/internal/common iliac to the bifurcation of the common iliac vessel (with inguinal nodes included for patients with inguinal node or distal vagina involvement). For patients treated with IMRT, nodal clinical target volumes also included para-aortic lymph nodes prophylactically for patients with pelvic node positive and definitively for para-aortic node positive as previously described [15]. Common planning target volume (PTV) expansions were 1–2 cm for the primary and 7 mm for lymph nodes. Daily image guidance for localization was used for all patients treated since 2008. The constraints utilized for IMRT were the same constraints as previously described for the definitive treatment of cervical cancer [16,17]. For patients with node positive disease, IMRT included a simultaneous integrated boost to 55 Gy at 2.2 Gy per fraction to involved lymph nodes with 7–10 mm margin as previously described [17].

Remote afterloading Ir192 HDR brachytherapy was individually optimized to the clinical target volume (CTV) with 3D planning in the majority (78%) of the patients using Nucletron Plato version 14.3 or Oncentra version 4.0 (Nucletron, Veneendal, The Netherlands). HDR fractionation schemas were modulated based on response and extent of disease as follows: 5.5 Gy times 3 fractions ($n = 15$), 5 Gy times 4 fractions ($n = 10$), 5 Gy times 3 fractions ($n = 6$), 5.5 Gy times 4 fractions ($n = 3$), 5.5 Gy times 5 fractions ($n = 1$), and 4 Gy times 3 fractions ($n = 1$). For the 28 patients treated with image-based brachytherapy, 3D planning was completed using T2 weighted MR-based planning with each fraction for the majority (61%, $n = 17$). The remaining 11 patients (39%) underwent CT-based planning either due to a contraindication to MR imaging ($n = 3$), extensive disease requiring an interstitial application ($n = 2$), or a long uterine canal requiring an 8 cm or above tandem for which only a metal (non-MR compatible) applicator was available at our institution ($n = 6$). Brachytherapy applicator type was as follows: 78% ($n = 28$) ring and tandem, 17% ($n = 6$) tandem and cylinder, and 6% ($n = 2$) template based interstitial. Fifty percent were treated with a 6 cm tandem, while the remaining 50% were treated with an 8 cm or above tandem. The CTV for brachytherapy included the gross tumor volume plus the entire uterus and cervix. Total doses were summated and normalized to equivalent 2 Gy dose (EQD_{2Gy}) equivalents using an assumed α/β of 10 for tumor and 3 for normal tissue.

Sixty one percent received concurrent chemotherapy with weekly cisplatin (40 mg/m^2), 39% received adjuvant chemotherapy (86% carboplatin and paclitaxel, 7% gemcitabine and taxotere, and 7% bevacizumab), and 36% received both concurrent and adjuvant chemotherapy. Unless contraindication concurrent chemotherapy was favored in all contemporaneously treated patients, while adjuvant chemotherapy was recommended for patients with pretreatment clinical or imaging stage III disease (node positive on imaging or parametria involvement) or Type II pathology. Patients underwent a repeat exam under anesthesia in the final weeks of external beam radiotherapy at the time of Smit sleeve placement, and re-staging imaging (usually via CT) to rule out distant progression prior to surgery. Surgery was performed at a median of 6 weeks after completion of radiation as follows: abdominal ($n = 28$), total laparoscopic ($n = 3$), or robotic-assisted ($n = 2$) extrafascial hysterectomy and salpingo-oophorectomy. Nodal dissection was done for 10 patients who had suspicious intraoperative node or post-chemoradiotherapy imaging suggested residual nodal disease [5 pelvic only, 2 para-aortic only, 3 pelvic plus para-aortic with the median number of nodes dissected being 3 (range: 2–21)].

Toxicity was physician recorded as per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Vaginal recurrence was confirmed by biopsy. For patients suffering distant or nodal progression, histologic confirmation was not required to define failure if imaging findings were unequivocal to prompt a change in