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SCIENCE DIRECT

Gynecologic Oncology 97 (2005) 887–892

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Vaginal brachytherapy alone: An alternative to adjuvant whole pelvis radiation for early stage endometrial cancer

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Received 30 December 2004

Abstract

Objective. Postoperative management of early stage adenocarcinoma of the endometrium remains controversial. The use of pelvic radiation therapy as shown by the Gynecologic Oncology Group (GOG)-99 trial improves the event free interval at the cost of increased toxicity. We reviewed and compared our results treating early stage endometrial adenocarcinoma using hypofractionated high dose rate (HDR) vaginal brachytherapy (VB) alone with the results of the GOG-99.

Methods. From 1992 to 2002, 243 endometrial cancer patients were treated with TAH/BSO and selective lymph node dissection followed by adjuvant radiotherapy (RT). Of these, 50 FIGO stage I–II (occult) adenocarcinoma (no clear cell or serous papillary) of the endometrium were managed with HDR hypofractionated VB as monotherapy using Iridium-192 to a dose of 30 Gy in 6 fractions twice weekly prescribed to a depth of 5 mm and median length of 4 cm. The characteristics, toxicity rates, and outcomes of our patients were compared with the results of the GOG-99. The median follow up of our patients and the GOG-99 were 3.2 years and 5.8 years, respectively.

Results. Patient characteristics including age, stage, and grade were similar in our study and the GOG-99. The local recurrence rate in our study, the pelvic RT arm of the GOG-99, and the no RT arm of the GOG-99 were 4% ($n = 2$), 2% ($n = 3$), and 9% ($n = 18$), respectively. In our study, one patient failed in the vagina alone and a second patient failed in the vagina and pelvis. In the GOG-99, the vagina as a component of locoregional failure was also the most common failure site in the no RT arm 77.8% ($n = 14$) and in the RT arm 100% ($n = 3$). The 2-year cumulative recurrence rate in our study was 2%, which compares favorably with the GOG-99 pelvic RT arm (3%) and observation arm (12%). Four-year survival rates of the no RT arm of the GOG-99, the RT arm of the GOG-99, and our study with HDR VB were 86%, 92%, and 97%, respectively. Chronic grade 2 toxicity rates were reduced by the use of VB compared to pelvic RT, especially GI toxicity 0% vs. 34% (P value < 0.001), and GI obstruction 0% vs. 7% (P value = 0.08).

Conclusion. Stage I–II (occult) endometrial adenocarcinoma treated with postoperative HDR vaginal brachytherapy has similar overall survival, locoregional failure rates, and cumulative recurrence rates to standard fractionation external beam pelvic RT with the benefit of much lower toxicity rates and shorter overall treatment time.

Keywords: Endometrium; Endometrial adenocarcinoma; Radiotherapy; Brachytherapy

Introduction

Endometrial cancer is the most common gynecologic malignancy diagnosed in the United States. Over 75% of these cancers are staged International Federation of Gynecology and Obstetrics (FIGO) I–II with favorable prognostic factors [1]. Although it is generally agreed that postoperative radiation improves local control in early stage endometrial cancer patients, the use of adjuvant pelvic radiation vs. vaginal brachytherapy alone remains controversial. Three randomized trials have shown an improvement in local regional control in early stage endometrial cancer patients with the addition of pelvic radiation [2–4]. It

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0090-8258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2005.02.021

remains unclear if vaginal brachytherapy alone can substitute pelvic radiation with equivalent local control rates and decreased toxicity [5–11].

Recently, Keys et al. [4] (Gynecologic Oncology Group-99) reported on the results of a prospective randomized trial with surgically staged intermediate risk early stage endometrial carcinoma (FIGO stage IB–II occult) to address the utility of postoperative radiation therapy. Patients receiving adjuvant pelvic radiation therapy were found to have fewer pelvic and vaginal recurrences. Given the toxicity associated with whole pelvis radiation, it was recommended that such adjuvant radiation therapy be limited to patients with high intermediate risk category defined on risk factors such as age, grade, myometrial invasion, and lymphovascular space invasion (LVSI). These risk factors were previously delineated by Morrow et al. [12] in the GOG-33. In the GOG-99, 72% (13/18) of local failures in patients receiving no adjuvant pelvic radiation experienced recurrences in the vagina.

We hypothesized that patients with similar risk factors could be treated with vaginal brachytherapy alone with equivalent local control rates and decreased toxicity. We reviewed and compared our results treating postoperative early stage endometrial adenocarcinoma patients using hypofractionated high dose rate (HDR) vaginal brachytherapy alone with the results of the GOG-99 using whole pelvis radiation.

Materials and methods

After receiving approval from our institutional Human Investigations Committee, a retrospective review of endometrial cancer patients was conducted. From 1992 to 2002, 243 patients seen at William Beaumont Hospital (WBH) with newly diagnosed endometrial carcinoma underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and selective pelvic/para-aortic lymph node dissection followed by adjuvant RT. Fifty of these 243 patients, staged I–II, were treated with postoperative vaginal hypofractionated brachytherapy as monotherapy and were further selected for analysis. Two gynecologic oncologists performed the vast majority of the surgeries. Furthermore, all cases were reviewed at our institutional tumor board in detail. The selective surgical dissection was performed per the Gynecologic Procedure manual of the GOG guidelines. These are the same guidelines utilized in the GOG-99 publication. Vaginal brachytherapy alone was used only for stage I–II endometrial adenocarcinoma patients. Papillary serous or clear cell carcinoma was excluded. No tumors with deep wall invasion and grade 3 (Stage IC grade 3) were included. The remaining patients were treated with either pelvis treatment or whole abdomen and pelvis irradiation (WAPI). Whole pelvis treatments were generally reserved for patients who did not meet the inclusion criteria per our in-house WAPI protocol or lacked appropriate lymph node assessment. Indications for WAPI include papillary serous or clear cell histology, pathologic stage III with positive peritoneal cytology, or positive lymph nodes. In addition, Stage IC grade 3 adenocarcinoma patients also received WAPI. Surgery alone was reserved for superficial low-grade non-bulky tumors. There was no overlap in treatment recommendations.

Multiple patient variables including age, race, FIGO stage, grade, histology, LVSI, lymph node involvement, acute/chronic toxicity, and local/distant recurrence were selected for analysis and compared with the GOG-99 patient population. High-intermediate risk group patients were defined as: (1) tumor grade 2–3, LVSI, and >50% myometrial invasion; (2) patients ≥50 years of age with at least other two risk factors; or (3) patients ≥70 years of age with one risk factor [4,12].

The hypofractionated high dose rate vaginal vault brachytherapy was delivered as monotherapy postoperatively. Under sterile conditions, a Foley catheter was placed. The simulation treatment planning process initially included placement of an auto-suture radio-opaque clip at the vaginal apex. The largest possible diameter of the vaginal cylinder was selected for treatment to decrease the vaginal mucosa dose and improve depth dose. Dummy sources were placed in the vaginal applicator during simulation and subsequently prior to each treatment for appropriate placement under fluoroscopic guidance. The Nucletron treatment planning system was utilized for dosimetric calculations and treatment (Nucletron V.B., Netherlands). The patients then underwent treatment with hypofractionated HDR brachytherapy using Iridium-192 to a dose of 30 Gy in 6 fractions twice weekly. With the exception of one patient whose treatment length was 6 cm, the remaining 49 patients were treated to length of 4 cm. Dose was prescribed to a depth of 5 mm from the applicator surface. The 100% isodose line was optimized to cover the prescription points over the dome and length of the vaginal cylinder.

In contrast, the radiation therapy course of the GOG-99 was to a dose of 50.4 Gy given in 28 fractions of 1.8 Gy each. Radiation was initiated within 8 weeks after surgery via cobalt 60 teletherapy or linear accelerator with an energy of 4 MeV or greater. The minimum source to skin distance or target to skin distance was 80 cm. The treatment was delivered either through anterior and posterior treatment fields or with a four-field pelvic treatment technique. The ports covered the total pelvis including the upper half of the vagina, paracervical, parametrial, and uterosacral tissues, as well as the external iliac, hypogastric, common iliac, and obturator lymph nodes. The superior border was defined as a line drawn through the L4–L5 interspace, while the inferior border was at the mid-portion of the obturator foramen. The lateral borders were set at 1 cm beyond the lateral margins of the bony pelvic wall at the widest plane of the pelvis. Lateral field borders were the posterior border of the S3 vertebral body and the anterior border of the symphysis pubis. No pelvic organs or structures were to