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SCIENCE DIRECT

Gynecologic Oncology 98 (2005) 299 – 303

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Papillary serous carcinoma—A less radio-sensitive subtype of endometrial cancer

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Received 11 February 2005
Available online 16 June 2005

Abstract

Objective. To explore factors that determine the response of endometrial cancer to radiation therapy. Such factors may influence treatment outcome and yield predictive information about individual patients and their tumors.

Methods. A retrospective study of the complete pathologic response (pCR) rates in the hysterectomy specimens of patients, who had undergone pre-operative radiotherapy for ≥ Stage II biopsy-proven endometrial carcinoma, was performed. 62 patient records were reviewed with respect to patient characteristics, tumor stage, histological grade and subtype, radiation technique and dose, and presence or absence of pCR in the post-operative hysterectomy specimen.

Results. 24 of 62 specimens exhibited a pCR. The only significant factor with respect to pCR was presence of uterine papillary serous carcinoma (UPSC). None of the seven cases of UPSC displayed a pCR ($P = 0.036$ Fischer's exact test), despite not differing from the non-UPSC cases in any other tumor, treatment, or patient factors. No factors were found that separated non-UPSC cases with a pCR from those without.

Conclusions. These data suggest an intrinsic radioresistance within UPSC, which may have implications for future treatment strategies. UPSC has documented genetic aberrations that may account for this, although its true radiosensitivity has yet to be quantitated directly. Future studies should focus on the molecular basis of its response to radiation. The reasons for the heterogeneous response of non-UPSC has yet to be elucidated and should also be investigated.

Keywords: Carcinoma; Uterine; Papillary serous; Radiation; Pathologic response

Introduction

Endometrial carcinoma is the commonest gynecological malignancy, with over 40,000 new cases in the U.S. in 2003 [www.cancer.org]. Radiotherapy (RT) is employed in a large proportion of cases. Considerable effort has been expended in elucidating prognosticators that might improve the selection of patients who need adjuvant therapy [1,2]. However, there is a paucity of information regarding predictors of endometrial cancer response to RT, particularly in the clinical setting. Some subtypes, such as uterine papillary serous carcinoma (UPSC), exhibit high locoregional relapse rates, despite often receiving intensive RT [3]. Our experience shows high rates of local control of intermediate risk endometrial adenocarcinoma treated with adjuvant radiotherapy and high rates of salvage of low risk endometrial cancer relapsing at the vaginal vault [4]. The differences in pelvic control rates between subtypes of endometrial cancer might reflect differences in tumor aggressiveness but may also arise in part because of differences in response to radiation therapy.

Intrinsic radio-sensitivity has been shown to predict for radio-curability and patient outcome in certain malignancies [5,6]. In a rare study to address this issue, complete pathologic response (pCR) in the hysterectomy specimen was shown to correlate with increased 5-year survival in a set

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0090-8258/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2005.04.009

of patients receiving pre-operative radiotherapy for endometrial cancer [7]. pCR therefore may have clinical relevance and may be related – at least in part – to intrinsic radiosensitivity. The goal of individualizing adjuvant therapy – that is accurately selecting patients in need of adjuvant therapy and selecting patients who will respond to adjuvant therapy – is particularly relevant for RT in endometrial cancer, where patients are often older and adjuvant radiotherapy moderately toxic. The response of endometrial cancer to radiation therefore merits investigation.

Since radiation is used primarily in an adjuvant setting in endometrial cancer, it is difficult to assess actual tumor response. In our institution, we have an established policy of giving pre-operative RT to endometrial cancer patients with cervical involvement. This clinical situation yields a cohort of uniformly treated patients with pre-treatment biopsies and post-irradiation tissue available for analysis. In this study, we aim to determine any clinical or pathologic predictors of radiation response in this select group of endometrial cancer patients. This tissue could subsequently undergo further testing if analysis of the data yielded a suitable biological hypothesis for testing.

Methods and materials

The British Columbia Cancer Agency (BCCA) is a provincial multi-center provider of cancer treatment, with a referral base of 4.2 million people. Approximately 300 cases of endometrial cancer are referred annually. Community gynecologists are recommended to do fractional dilatation and curettage (D&C) in work up of endometrial cancer and then refer patients with stage II disease for consideration of pre-operative radiotherapy. Such patients are evaluated by a site-specialized radiation oncologist and a gynecologist. Patients with gross cervical involvement as determined by examination (MRI had only become commonly available recently) were felt to be at risk of a positive radial margin at hysterectomy and were recommended to have pre-operative radiotherapy. The remaining patients, without gross cervical involvement, regardless of fractional D&C findings, are referred back to their community gynecologist for TAH and BSO.

We reviewed all cases of biopsy-proven carcinoma of the corpus uteri, with FIGO stage II or greater, treated with pre-operative radiotherapy followed by clearing hysterectomy. Sixty-two patients treated between August 1991 and February 2003 met these criteria. The median patient age was 64 years (range 41–84). Distribution of pathologic subtypes was as follows: fifty endometrioid carcinomas; four clear cell carcinomas; seven papillary serous carcinomas; one carcinoma NOS. In preliminary analyses, the behavior of the clear cell, endometrioid, and carcinoma NOS was indistinguishable, and therefore these have been subsequently grouped together for analysis as non-UPSC tumors. Clear differences in p53 expression provide a biological rationale for separating UPSC from clear-cell carcinoma (CCC), as does literature suggesting differences in clinical outcome [9–11]. Clinical stages were distributed as follows: forty-nine II; seven IIIA; three IIIB; three IIIC. Histological grades were as follows: seventeen grade I; nineteen grade two; twenty-six grade three.

All patients were assigned a pre-treatment clinical stage (FIGO 1988 classification) based on clinical findings and any other imaging or investigational studies available. Some patients were upstaged by subsequent surgical and/or pathological findings. 52 of 62 cases had their pre-treatment pathology centrally reviewed at the BC Cancer Agency by pathologists with an interest in gynecologic malignancy. Sectioning was guided by residual gross pathology, if present on initial inspection and opening of the specimen. In cases without visible lesions, sections were according to protocol, which yielded 12 cervical, 2 parametrial, 2 tubes and ovaries, and 10 uterine sections for microscopic inspection.

All patients were treated according to BCCA protocol with pre-operative radiotherapy comprising external beam radiation and brachytherapy. Typically, the minimal field borders were as follows: L5/S1 superiorly; below the obturator foramina inferiorly; and 1.5–2 cm beyond the bony true pelvis laterally. Fields were extended as necessary to include all sites of gross disease extension. 47 of 62 patients were treated with anterior and posterior fields while the remainder was treated with a 4-field technique. Shielding was added to minimize dose to the small bowel, bony pelvis, femora, and the rectum. The external beam prescription was 45 Gy in 25 daily fractions with 10–25 MV photons. Brachytherapy comprised two tandem-and-ovoid implants 1 week apart, using Nucleotron's selectron system, delivering 13.5 Gy to point A at 100 cGy per hour. The median prescribed external beam dose was 45 Gy (range 45–54 Gy), delivered in 1.8 Gy fractions. The median point A brachytherapy dose was 27 Gy (range 13.6–27.6 Gy). The median total duration of radiotherapy was 44 days, and the median interval from completion of radiotherapy to surgery was 52 days.

All patients underwent extrafascial hysterectomy with bilateral salpingo-oophorectomy. Three underwent lymph node sampling or dissection. All surgical specimens were pathologically reviewed. We defined a complete pathologic response (pCR) as one in which the specimen contained no residual viable carcinoma cells.

Our primary endpoint was the proportion of complete pathologic responses. Exploratory analysis was planned to determine how this was influenced by patient, tumor, and treatment factors—specifically age, pre-treatment stage, histological subtype, tumor grade, duration of radiation treatment, and interval from completion of radiotherapy to surgery. However, the small sample size precluded meaningful interpretation of this. Our secondary endpoint was the proportion of pCRs in the endometrium and in the cervix, and to see if radiation technique was a factor.