Gynecologic Oncology Reports 25 (2018) 30–34

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Case series

Endometrial cancer in an increasingly obese population: Exploring alternative options when surgery may not cut it

Jeanine N. Staples[a,*], Lisa Rauh[a], M. Sean Peach[b], William D. Baker[c], Susan C. Modesitt[a]

[a] Division of Gynecology Oncology, Department of Obstetrics and Gynecology, University of Virginia, Charlottesville, VA, United States
[b] Department of Radiation Oncology, University of Virginia, Charlottesville, VA, United States
[c] Novant Health Oncology Specialists, Winston-Salem, NC, United States

ARTICLE INFO

Keywords:
Obesity
Endometrial cancer
Hormonal therapy
Medically inoperable
NSQIP

ABSTRACT

Objectives: The study objectives were to describe outcomes of obese patients with early endometrial cancer following primary non-surgical treatment, assess predictors of response, and estimate the increased surgical risk for these women.

Methods: Retrospective chart review identified women with early stage endometrial cancer at a single institution with BMI ≥ 30 kg/m^2 who did not undergo surgery as primary treatment modality due to obesity and medical co-morbidities. Clinicopathologic factors were abstracted, characteristics of responders vs. non-responders compared and the National Surgical Quality Improvement Program (NSQIP) surgical risk calculator utilized to quantify surgical risks.

Results: Fifty-one patients were identified, with a mean BMI of 49.0 kg/m^2. The NSQIP calculator predicted a significantly higher complication rate for our cohort compared to the expected average risk for hysterectomy (18.8% vs 7.2%, $p < .0001$). The majority of patients were treated with radiation alone (49%), followed by hormone therapy (45.1%). Response rates were 38.1% for women treated with hormones and 63.6% in the radiation group ($p = .063$). No significant differences were identified between responders and non-responders with regard to NSQIP scores, BMI, co-morbidities or age. Among those with persistent or progressive disease, 87.5% responded to secondary treatment. Only one death was from cancer progression. Two individuals died following treatment complications (one surgical, one chemotherapy); the remaining twelve deaths were due to pre-existing co-morbidities.

Conclusions: Hormone and radiation therapy are both viable options for obese patients deemed to have too significant risk of surgical complications. Pursuing surgical intervention in this population may do more harm than good.

1. Introduction

Endometrial cancer is the most common gynecologic cancer in the United States (Siegel et al., 2017). Since 2002, rates have increased approximately 2.5% annually, including a 10% increase from 2006 to 2012 (Constantine et al., 2017). Over 61,000 new cases were expected in 2017, with nearly 11,000 expected deaths (Siegel et al., 2017). Excess adiposity is a well-established risk factor for endometrial cancer and the rising obesity epidemic in the United States is likely a large contributor to these recent trends (Reeves et al., 2011). It is estimated that around 70% of adults aged 20 and over are overweight or obese (Ljungvall and Zimmerman, 2012). Furthermore, between 2009 and 2034, the number of people with diabetes is expected to increase from 23.7 million to 44.1 million (Huang et al., 2009). In addition to increasing one's lifetime risk for endometrial cancer, obesity and diabetes predispose patients to a number of other medical co-morbidities and potential surgical complications.

Surgical intervention, including hysterectomy with bilateral salpingo-oophorectomy and possible lymph node evaluation, is the standard treatment for early stage endometrial cancer; however, obesity and associated co-morbidities place these patients at high risk for surgical complications. As such, up to 10% of patients may be deemed medically inoperable due to excessive surgical risk (Niazi et al., 2005; Podzielinski et al., 2012; Acharya et al., 2016). If current trends persist, the number of patients deemed medically inoperable due to obesity will continue to rise as well. As such, exploring alternative treatment

* Corresponding author at: University of Virginia Medical Center, Division of Gynecology Oncology, Department of Obstetrics and Gynecology, P.O. Box 800712, Charlottesville, VA 22908, United States.
E-mail address: js6qf@hscmail.mcc.virginia.edu (J.N. Staples).

https://doi.org/10.1016/j.gore.2018.04.009
Received 18 February 2018; Received in revised form 19 April 2018; Accepted 21 April 2018
Available online 24 April 2018

options for this patient population is crucial, and radiation and hormonal therapy have often been utilized for non-surgical candidates. Several studies have investigated outcomes after radiation therapy alone in early endometrial cancer and it remains a viable option for local disease control in patients who cannot undergo surgery following an endometrial cancer diagnosis (SGO Clinical Practice Endometrial Cancer Working Group et al., 2014; Potish et al., 1985a; Varia et al., 1987a; Shenfield et al., 2009a).

Hormonal therapy may be another treatment alternative for this particular group of patients. Hormonal treatment for endometrial cancer can include aromatase inhibitors, luteinizing hormone-releasing hormone agonists, selective estrogen receptor modulators, or progestins. Aromatase inhibitors and luteinizing hormone-releasing hormone agonists both act by reducing serum levels of circulating estrogen. Selective estrogen receptor modulators work by preventing any circulating estrogen from stimulating further growth of any cancer cells. Progestins are synthetic progestogens that have effects similar to those of progesterone, and are the most commonly used hormonal treatment for endometrial cancer. The histologic effect of progesterone has been validated in a number of studies of serial biopsies obtained from patients in whom surgery or irradiation was contraindicated (Kohorn, 2012; Mentrikoski et al., 2012; Saegusa and Okayasu, 1998; Wheeler et al., 2007). Given the increasing numbers of patients with obesity, understanding outcomes of radiation and hormone therapy in early endometrial cancer as well as potential surgical risks will be of paramount importance for the ability to adequately counsel these patients on treatment options. The study objectives were to describe the outcomes of obese patients with early endometrial cancer following primary non-surgical treatment, to assess predictors of response, and to estimate the increased surgical risk for these women.

2. Methods

Prior to study commencement, approval was obtained from the institutional review board (IRB) at the University of Virginia. Retrospective chart review was performed using the Clinical Data Repository and the University of Virginia Tumor Registry and identified women with clinical stage I and II endometrial cancer, with a body mass index (BMI) $\geq 30\ kg/m^2$ who did not undergo surgery as primary treatment modality from January 1, 2000 to December 31, 2016. Inclusion criteria included age of at least 18 years of age, early stage endometrial cancer diagnosis with histologic confirmation, primary treatment modality with either chemotherapy, hormonal or radiation therapy, BMI $\geq 30\ kg/m^2$ documented at time of diagnosis, at least one year of documented follow-up care after diagnosis at UVA. All histologic subtypes were included. Exclusion criteria included evidence of stage III or IV disease based on clinical evaluation (imaging or biopsy), BMI $< 30\ kg/m^2$ at time of diagnosis, surgery as primary treatment modality, decision to omit surgical intervention for fertility-sparing or other reasons not related to obesity or significant co-morbidities, and lack of documented follow-up after initial diagnosis.

Data were abstracted by review of all clinical documentation in the electronic medical records, including those documents sent and scanned in through outside referring physicians. Gynecologic pathologists reviewed all pathology. Data abstracted included age at diagnosis, race, insurance status, BMI at time of diagnosis, obstetric history, co-morbidities, clinical stage at diagnosis, grade, histology, initial and subsequent treatment modalities, including response and complications, recurrences, date of death or last follow-up, pathology reports of all excisional procedures (including biopsies or curettage), all imaging reports, all radiotherapy treatments reports and operative reports. Major co-morbidities included in analysis were diabetes, hypertension, coronary artery disease, congestive heart failure, hyperlipidemia, venous thromboembolism, liver disease, chronic kidney disease, asthma and chronic obstructive pulmonary disease (COPD). Of note, asthma and COPD were considered together as a single co-morbidity. Furthermore, co-morbidities other than those listed above, only contributed to individuals' total number of co-morbidities if they were deemed by the authors to be significant.

Patients were followed until death, loss to follow-up, or time of data abstraction in August 2017. Disease status at each follow-up time point was determined by clinical exam, imaging, or endometrial sampling. Status at time of follow-up was characterized as complete response, partial response, stable disease, or progressive disease. Complete response was defined as no clinical evidence of disease on exam or imaging, or benign endometrium without atypia on subsequent endometrial sampling following treatment. Partial response was defined as clinically or radiographically improved exam in the setting of persistent disease, improvement in grade, or diagnosis of atypical hyperplasia following treatment for carcinoma. No response was defined as no change in clinical examination or imaging, or persistence of the initial tissue diagnosis on subsequent tissue sample. Progression was defined as any progressive grade or increasing disease burden following initial treatment. These definitions reflect methods previously reported by others who have examined endometrial response rates to primary hormonal treatment among patients in whom surgery is not an option (Baker et al., 2017; Hubbs et al., 2013). Individuals with complete response or partial response were categorized as having “Response” and individuals with stable or progressive disease were categorized as having “No Response.” Time to response was defined as the time of initial biopsy to first negative clinical exam, negative imaging or negative biopsy.

Complications and mortality from surgery were estimated for each patient at the time of initial diagnosis by using the American College of Surgeons National Surgical Quality Improvement Program's (NSQIP) Surgical Risk Calculator. The NSQIP Calculator is a decision-support tool based on reliable multi-institutional clinical data, which can be used to estimate the risks of most operations. For each individual in our cohort, their personal and health history was logged into the Risk Calculator with laparoscopic hysterectomy and bilateral salpingo-oophorectomy as the planned theoretical procedure. Their chance of an unfavorable outcome, including a major complication, any complication, or death, was calculated based on their unique information. These calculated estimates of unfavorable outcomes were then compared to that of age-matched healthy controls. The same was done for open hysterectomy and bilateral salpingo-oophorectomy. Calculations for complete surgical staging were not considered.

Response rates, including stratification of complete response, partial response, stable disease and progressive disease were examined among the primary radiation and hormonal therapy groups. Demographic and clinical characteristics were compared between the primary radiation group and the hormonal therapy group. Demographic and clinical characteristics of responders and non-responders were compared as well. Statistical analysis was performed using IBM SPSS Statistics (version 24.0, Armonk, NY), and student's *t*-test and chi-squared tests were employed as indicated.

3. Results

Data abstraction identified 130 patients with endometrial cancer and BMI $\geq 30\ kg/m^2$ who did not receive surgery as primary treatment modality. Forty-nine patients were excluded because of advanced disease. Thirteen patients were excluded for other medical or personal reasons precluding them from immediate planned surgery (five declined offered surgery, three excluded due to recent myocardial infarction (MI) or pulmonary embolism (PE) who required a course of anti-coagulant prior to surgery, one who had planned radiation to shrink primary tumor prior to surgery, two due to severe liver disease, one Jehovah's witness with severe anemia had surgery after optimization and one was delayed for coordination with general surgery for a concomitant procedure). Six patients were excluded because of desire to maintain fertility and 11 excluded due to loss to follow-up shortly