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Survival outcomes of obese patients in type II endometrial cancer: Defining the prognostic impact of increasing BMI

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HIGHLIGHTS

- Obesity is highly prevalent in women with type II endometrial cancers
- BMI was not associated with endometrial cancer outcomes in type II endometrial cancers
- The role of obesity as a risk factor for type II EC should be further investigated

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ABSTRACT

Objective. To investigate the role of obesity as a risk factor for type II endometrial cancer (EC), as well as the prognostic significance of increasing body mass index (BMI) on survival.

Methods. A single institution retrospective analysis of 154 type II EC cases from 1987 to 2010 was conducted. Patients were categorized into cohorts by BMI (normal (<25), overweight (25–29.9), obese class I (30–34.9), and obese class II—III (≥35)). Descriptive, regression and ANOVA analyses were performed. Kaplan-Meier curves were compared with log rank tests.

Results. The BMI distribution was 22.8% normal BMI; 24% overweight; 17.5% class I; and 35.7% class II—III. The median follow up was 41 months. The median progression-free survival (PFS) was 45.4, 36.0, 35.3 and 42.0 months and overall survival (OS) was 54.7, 44.7, 44.8 and 49.7 months, among the respective groups. There was no association between BMI and PFS ($p = 0.71$), OS ($p = 0.72$), or time to recurrence ($p = 0.71$). There were no differences among the increasing BMI groups compared to normal weight women for the risk of death.

Conclusions. Our analysis did not reveal any differences in outcomes by BMI group. Our data reveals that obesity is highly prevalent in type II ECs, though obesity has not historically been described as a risk factor. While BMI as a single variable may not be prognostic for survival outcomes, the role of obesity as a risk factor for type II EC should be further investigated, given the increasing prevalence of obesity in type II ECs.

1. Introduction

Endometrial cancer (EC) has historically been dichotomized into two distinct classifications based primarily on histology [1,2]. Type I ECs include tumors of grade 1 or 2 endometrioid histology, comprise roughly 80% of EC diagnoses, and have a favorable prognosis. These tumors are often estrogen-responsive, and are often preceded by endometrial hyperplasia [3–5]. Conversely, type II ECs include grade 3 endometrioid tumors, as well as non-endometrioid histologies such as serous, clear cell and carcinosarcoma. Unlike type I cancers, type II cancers are considered high grade, are not typically associated with estrogen stimulation, are associated with poorer prognosis, and rarely have an identifiable precursor lesion [6–18]. Despite comprising only 20% of EC cases, they account for 40% of endometrial cancer related deaths [19]. Though the relationship between type I EC and obesity has been well established [20], the impact of obesity on women with type II EC is less clear [2,19,21]. Recent studies suggest that obesity may be an independent risk factor. Bjorge and colleagues reported that overweight and obese women were 1.26 and 1.94 times more likely to develop a type II tumor, respectively, compared to normal weight women over 25 years reviewed data in a population of over 1 million Norwegian women [22]. Similarly, McCullough et al. reported that a BMI of ≥30 mg/m^2 or higher was significantly associated with the development

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of a type II tumor (RR 2.87, 95% CI 1.59–5.16) [23]. Both of these studies included high grade endometrioid cancers in the type II category, along with serous and clear cell cancers, supporting the association between obesity and type II cancers. However, compared to type I ECs, type II EC patients are less likely to be obese, as described in a prospective study by Felix et al., in which BMI was inversely related to having a type II endometrial cancer (OR 0.45, 95% CI 0.29–0.70) compared to women with a type I cancer [2]. Despite the inverse relationship described, a large proportion of type II cases were seen in overweight or obese women (27.3 and 36.4%, respectively) [2].

While obesity has been extensively studied as both a risk factor and prognostic factor for endometrial cancer, its direct effect on oncologic outcomes, including progression-free survival (PFS) and overall survival (OS), specifically in type II EC has not been extensively examined. Conversely, studies have noted improved outcomes for obese women with type I tumors. Martra et al. reported on 766 women with endometrial cancer who were categorized as non-obese (body mass index, BMI < 30 kg/m^2) and obese (BMI ≥ 30 mg/m^2), the majority of whom had type I EC [24]. Among 681 women with endometrioid histology, the 4-year cancer-related survival in obese women was 10% higher than all cause deaths. This compares with 6% in non-obese women [24]. While an apparent survival advantage of obesity with type I tumors has been described, the effect of obesity on type II cancers has not been well described. As a result, we sought to specifically examine the relationship of obesity and oncologic outcomes in women with type II endometrial cancers.

2. Methods

Approval to conduct this study was obtained from the Institutional Review Board at The Ohio State University Wexner Medical Center. Patients were eligible for study inclusion if they had histologically confirmed type II endometrial cancer, which included the following histology types: serous carcinoma, clear cell carcinoma, carcinosarcoma, and poorly differentiated endometrioid (grade 3) carcinoma.

Patients with type II EC diagnosed on endometrial biopsy, dilation and curettage sample, or hysterectomy were identified from institutional tumor registry databases from 1987 to 2010. All included patients underwent primary surgical treatment including total hysterectomy, salpingo-oophorectomy, with pelvic lymphadenectomy ± para-aortic lymphadenectomy.

Clinical data abstracted included patient age, race, body mass index, gravity, parity, use of hormone replacement, and menopausal status. Operative reports were reviewed for surgical procedures performed and pathology reports reviewed for histology, grade and stage using the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system. Additional data regarding the adjuvant therapy and outcome including time to and site of recurrence, date and status at last contact, and PFS and OS (all cause) data were collected.

When the data were analyzed, patients were categorized by BMI at time of surgery, calculated as (kg/m^2), and further classified using the WHO classification system (normal (<25), overweight (25–29.9), obese class I (30–34.9), and obese class II—III (≥35)) [25]. Frequency distributions were calculated for each of the variables. Descriptive and regression analyses were performed to assess demographic and comparative data. ANOVA testing was performed to analyze differences between groups. Kaplan-Meier curves were compared with log rank tests.

3. Results

Of the 198 women with type II EC treated consecutively from 1987 to 2010 identified, 154 patients met all study inclusion criteria. The median age of the study cohort was 65 years (range 36–91) and the study cohort was predominately Caucasian (85.1%). Demographic and clinical data are shown in Table 1, stratified by BMI. The most common histology was carcinosarcoma (53.9%), followed by serous (32.5%), clear cell (11%), and high grade endometrioid (2.6%) (Table 1).

The median BMI was 30.5 (range 15.4–67), with the majority of patients having a BMI ≥ 25 (77.3%). There were 22.8% of women classified as normal weight, 24% were overweight, 17.5% were obese class I, and 35.7% were classified as obese class II—III.

The median follow up was 41 months for the study population. Adjuvant therapy included intravaginal brachytherapy, pelvic and extended field radiation, and chemotherapy. Recurrence was documented in 40 patients (26.1%), with a crude estimate of median time to recurrence of 27 months, however, there was no significant difference among the BMI groups ($p = 0.71$). The median PFS (Fig. 1) was 45.4, 36.0, 35.3 and 42.0 months and the median OS was 54.7, 44.7, 44.8 and 49.7 months (Fig. 2) among normal weight, overweight, obese class I and obese class II—III women, respectively. There was no association between BMI and survival outcomes, including PFS ($p = 0.71$), OS ($p = 0.72$), or time to recurrence ($p = 0.71$) on adjusted analyses.

There were no differences among the increasing BMI groups compared to normal weight women for the risk of death ((OR 1.06, 95% CI 0.42–2.65), (OR 1.54, 95% CI 0.56–4.24), (OR 1.17, 95% CI 0.53–2.61)) among the overweight, obese class I and obese class II—III women, respectively, and no differences for recurrence among the groups compared to normal weight women ((OR 0.58, 95% CI 0.20–1.67), (OR 0.73, 95% CI 0.24–2.25), (OR 0.72, 95% CI 0.30–1.74), respectively).

4. Discussion/conclusions

Obesity, an ever-increasing health problem and epidemic, has been established as a risk factor for endometrial cancer. While the majority of studies have focused on the association between obesity and type I ECs, recent evidence suggests that the type II cancers share more risk factors with type I ECs than initially believed [26]. While type II EC patients have been historically described as a leaner build, we noted in our cohort that the majority of women were at least overweight, with 53% being obese with a BMI of 30 or higher. These findings are similar to recent studies which reported that patients with type II EC were overweight or obese in 61–79% cases [26,27].

The causal relationship between type I EC and excess estrogen stimulation from peripheral fat conversion of androgens has been well described [28], however does not explain the increasing incidence of obese women with type II ECs. While obesity contributes to hyperplasia, which can develop into endometrioid carcinoma, high grade (FIGO 3) histologies only comprised of 2.6% of our type II cohort. Over 40% of patients had clear cell or serous cancer, with the large majority of those being overweight or obese, which begs the questions whether obesity related estrogen plays a role in the development of non-endometrioid type II ECs. This was investigated in a pooled analysis by the Epidemiology of Endometrial Cancer Consortium, which identified associations between estrogenic factors and increased risk of type II cancers (which included on serous and mixed histologies). The authors suggest that either estrogen-driven proliferation is also important for type II tumors or that associated mechanisms related to and associated with risk factors that promote estrogen-driven proliferation (such as obesity) drive these associations [26]. Other such factors associated with obesity may contribute to the tumorigenesis of type II cancers, such as diabetes/hyperinsulinemia, inflammation, altered hormonal milieu, as well as other related processes [21,27,29–31], all which may act in a synergistic fashion to stimulate tumor growth or recurrence. Such complicated interplays among related factors can make identifying individual risk factors a challenge. Alternatively, the increased prevalence of obese women with type II EC may simply be related to the increasing epidemic of obesity overall, which has undoubtedly increased the prevalence of obese patients in a multiple of disease states. However, how obesity impacts such disease processes remains uncertain. Ko and colleagues failed to find an association diabetes and BMI in the outcomes of type II or high grade endometrial cancers [27], however these