



Impact of obesity on secondary cytoreductive surgery and overall survival in women with recurrent ovarian cancer



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HIGHLIGHTS

- Examined epithelial ovarian cancer (EOC) patients undergoing secondary debulking
- Body mass index (BMI) correlated with survival at time of secondary cytoreduction
- Higher BMI associated with shorter overall survival in recurrent EOC
- Higher preoperative BMI not associated with suboptimal secondary tumor debulking
- BMI a prognostic factor for EOC patients undergoing secondary cytoreduction

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ABSTRACT

Objectives. Obesity may negatively influence tumor biology in women with epithelial ovarian cancers. To date, only body mass indices (BMI) determined at the time of diagnosis have correlated with clinical outcome. We hypothesized that obesity negatively affects survival throughout the disease course, and sought to determine the prognostic role of BMI at the time of secondary cytoreductive surgery (SCS) for recurrent ovarian cancer.

Methods. We performed a review of patients undergoing SCS for recurrent epithelial ovarian or peritoneal cancer between 1997 and 2012. We retrospectively reviewed data which were analyzed using Fisher's exact test, Kaplan–Meier survival, and Cox regression analysis. BMI was defined according to the National Institutes of Health's categorizations.

Results. We identified 104 patients; 2 were underweight, 46 were of ideal body weight, 32 were overweight, and 24 were obese. Overall, 90 patients underwent optimal resection and BMI did not correlate with ability to perform optimal SCS ($p = 0.25$). When examining BMI strata (underweight, ideal, overweight, and obese), we observed a statistical trend between increasing BMI and poor outcome; median survival was undetermined (greater than 50 months), 46 months, 38 months, and 34 months, respectively ($p = 0.04$). In a multivariate analysis, BMI was an independent predictor of survival ($p = 0.02$).

Conclusions. In this cohort of women undergoing SCS for recurrent ovarian cancer, BMI significantly and independently correlated with overall survival. This observation suggests an effect of excess weight on tumor biology and/or response to treatment that is prevalent throughout the disease course.

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1. Introduction

Epithelial ovarian cancer remains a highly aggressive and fatal disease. This year alone it is expected that there will be 21,980 new cases of ovarian cancer diagnosed in the United States. Furthermore, 14,270 women will die from ovarian cancer, making it the fifth most

fatal type of cancer death across all ages [1]. Of women diagnosed with ovarian cancer, greater than 70% of patients present with advanced stage disease and the five-year overall survival is approximately 30% [2]. The cornerstone of primary treatment for advanced stage disease involves both surgery and chemotherapy. Despite these interventions, recurrence is common with more than 60% of advanced stage patients developing recurrent disease [3]. Considering the dire natural history of ovarian cancer, the identification of prognostic factors – especially modifiable ones – is paramount. Age, stage of disease, histologic type, and residual tumor at the time of primary surgery are all established as prognostic factors with advanced ovarian carcinoma; however,

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these factors are non-modifiable [4–6]. Disease-free interval and complete secondary cytoreduction at time of recurrence are associated with increased median post-recurrence survival; these factors are, again, relatively unmodifiable [3].

Increasing obesity has been shown as an independent risk factor for an increase in all-cause mortality [7]. Furthermore, obesity is a well-established risk factor for many hormone-related cancers, including: breast, endometrial, colon, and prostate cancer [8]. The prognostic effect of obesity on epithelial ovarian cancer potentially has great implications considering the rising prevalence of obesity [9]. A recent meta-analysis was performed examining 10 studies on obesity and its prognostic effect on epithelial ovarian cancer. Due to the large amount of inter-study heterogeneity, no firm conclusion could be made [10]. Additionally, the studies examined body mass index in the upfront setting or prior to diagnosis without examining the possible effects of obesity throughout the disease course.

In this study, we hypothesize that obesity continues to play a role throughout the natural history of epithelial ovarian cancer and may adversely affect prognosis. Specifically, our objectives were to examine body mass index at the time of secondary cytoreduction and to determine any potential clinico-pathologic prognostic relationships.

2. Methods

A prospective database of all patients diagnosed with gynecologic malignancies is maintained by the Gynecologic Oncology service at Cedars-Sinai Medical Center. After submitting our study protocol to the Institutional Review Board and receiving approval, we identified 104 women with epithelial ovarian cancer who underwent secondary cytoreductive surgery (SCS) between January 1997 and February 2013 for their first recurrence of disease. Patients with tumors of low malignant potential were excluded from this study, while those with a history of invasive epithelial, fallopian tube, or primary peritoneal carcinoma who underwent secondary tumor debulking were included. In general, patients were considered candidates for secondary tumor debulking if they had a disease free interval greater than six months, Gynecologic Oncology Group performance status less than two, and three sites or less of suspected disease recurrence. One of six gynecologic oncologists performed all secondary tumor debulking with the intent of optimal tumor cytoreduction. Following first line chemotherapy, no patient underwent chemotherapy prior to SCS. After secondary debulking, patients received 4–6 cycles of carboplatin, carboplatin with liposomal doxorubicin, carboplatin with paclitaxel, or cisplatin. Optimal resection at SCS was considered if there was no microscopic residual disease. Data was abstracted regarding age at time of SCS, disease free interval from time of initial treatment, height, and weight. Co-morbidities were also examined, including diabetes, hypertension, coronary artery disease, and venous thromboembolism (including deep vein thrombosis and pulmonary embolism).

BMI categories were defined by the National Institutes of Health's: underweight (BMI < 18.5 kg/m²), ideal body weight (BMI 18.5 to 25 kg/m²), overweight (25 ≤ BMI ≤ 30 kg/m²), and obese (> 30 kg/m²) [11].

Fisher's exact test was used to examine difference in clinical factors between patients of various BMI categories. Cox proportional hazard models were used to assess the significance of BMI as a prognostic factor for patient survival. Survival probabilities were analyzed with Kaplan–

Table 1
Patient characteristics by body mass index.

Body mass index (BMI)	Number of patients (n = 101)
Underweight (BMI < 18.5)	2 (2%)
Ideal body weight (18.5 < BMI < 25)	44 (44%)
Overweight (25 < BMI < 30)	32 (32%)
Obese (BMI > 30)	23 (23%)

Table 2
Co-morbidities within each cohort.

	Diabetes	Hypertension	Coronary artery disease	Venous thromboembolism
Underweight	0	0	0	0
Ideal body weight	1	5	0	0
Overweight	1	4	0	0
Obese	0	7	0	0

Meier curves. Overall survival was defined as time from SCS until date of death. A p-value < 0.05 was considered to be statistically significant.

3. Results

We identified 104 women meeting study criteria within the database of gynecologic malignancies. Of those 104, 2 (2%) were underweight, 46 (44%) were ideal body weight, 32 (31%) were overweight, and 24 (23%) were obese (see Table 1). The mean age of the cohort was 56 years old (range 33 to 78). Co-morbidities were distributed across the BMI strata without statistical differences. Of the 2 patients who were underweight, no co-morbidities were noted. Of the 46 patients with ideal body weight, 1 had diabetes and 5 had hypertension. Of the 32 overweight patients, 1 had diabetes and 4 had hypertension. Of the 24 patients who were obese, 7 had hypertension. There were no patients that had coronary artery disease nor venous thromboembolism (see Table 2).

Of all the patients in the study, 90 women underwent optimal resection to no macroscopic residual disease. In order to determine whether BMI influenced the ability to fully resect disease, we divided the cohort into two groups: those with BMI greater than ideal body weight (BMI ≥ 25 kg/m²) and those with BMI < 25 kg/m². Of women with BMI < 25 kg/m², 44 were able to undergo optimal cytoreduction while 4 were not. Of those with BMI ≥ 25 kg/m², 46 women were able to undergo cytoreduction while 10 women were not. Comparison of these two cohorts suggests that BMI did not correlate with the ability to undergo optimal secondary cytoreductive surgery (p = 0.25).

We next performed Kaplan–Meier analysis to examine the effect of obesity on survival. After stratifying by BMI, we observed women with increasing BMI to have decreased overall survival (RR = 1.52, p = 0.04). Women who were underweight had a median survival more than that was undetermined (greater than 50 months) followed by ideal body weight (46 months), compared to overweight (38 months) and obese women (33 months, p = 0.03) (see Fig. 1).

In order to determine whether BMI retained significance as an independent prognostic factor, Cox regression analysis was performed on this cohort. After controlling for age, stage of disease, and co-morbidities, BMI continued to be an independent prognostic factor for survival with a relative risk of 1.52 (1.06–2.19, p = 0.04), along with

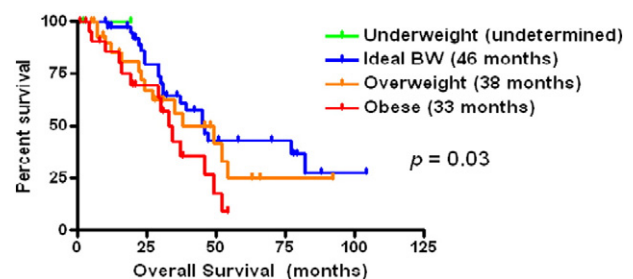


Fig. 1. Increasing BMI correlates with shorter overall survival. Patients with increasing BMI at the time of secondary cytoreductive surgery had decrease in overall survival compared. Underweight women had a median survival greater than 50 months, women with ideal body weight had median survival of 46 months, those women who were overweight had a median survival of 38 months, and women who were obese had a median survival of 33 months.

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