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The impact of perioperative β blocker use on patient outcomes after primary cytoreductive surgery in high-grade epithelial ovarian carcinoma

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HIGHLIGHTS

- Stress is associated with poor prognosis in patients with solid tumors.
- β blocker can lower down the physiologic stress response.
- Use of perioperative β blocker after primary cytoreductive surgery for ovarian cancer associated with better overall survival

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ABSTRACT

Objective. To quantify the impact of perioperative β blocker use on survival after primary cytoreductive surgery for epithelial ovarian cancer.

Methods. We conducted a multi-center retrospective study of all women who underwent primary cytoreductive surgery for ovarian cancer (2000 − 2010). One institution had routinely used perioperative β blockers for patients "at risk" for coronary events. The other institution did not routinely use perioperative β blockers. Demographic, operative, and follow up data were collected. Cox proportional hazards models were used to assess the effect of β blockers on progression-free interval (PFI) as well as overall survival (OS).

Results. Out of 185 eligible patients, 70 received β blockers and 115 underwent cytoreductive surgery without perioperative β blockers. Both groups were similar in demographics. A history of hypertension was present more often in the β blocker group compared to the group that did not receive β blockers (22% and 6%, $p = 0.002$). PFI in β blocker group was greater at 18.2 vs. 15.8 months ($p = 0.66$). The OS in the β blocker group was significantly higher at 44.2 vs. 39.3 months ($p = 0.01$). In multivariate analysis, perioperative β blocker use was associated with significant improvement in OS (HR 0.68 (0.46–0.99); $p = 0.046$).

Conclusion. Our study showed an association between perioperative β blocker use and longer overall survival in patients undergoing primary ovarian cancer cytoreductive surgery. A prospective randomized clinical trial in this population would further validate these results.

1. Introduction

It is estimated that over 21,000 new cases of ovarian cancer are diagnosed in the United States every year. With annual estimated deaths of 14,180, the 5-year survival is estimated at 45% [1].

Optimal surgical cytoreduction and receipt of adjuvant platinum-based chemotherapy, along with stage, grade and age of the patient,

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are the most important determinants of prognosis [2]. Despite conventional treatments, 5-year survival remains around 45%, and cure rates remain around 15–20% [1]. The majority (75–80%) of patients recur with two years after treatment. Two years after initiation of treatment, 15–40% of patients will have cancer recurrence with an estimated average progression-free survival (PFS) from 20.8–28 months [3]. Despite the development of new therapeutic agents, it is clear that a more comprehensive approach, including addressing patient factors, is greatly needed.

Recent preclinical data indicate that surgical stress promotes tumor growth and angiogenesis in well-characterized orthotopic ovarian cancer mouse models, but the effects of surgical stress were completely abrogated with perioperative β adrenergic receptor blockade [4]. Stress response is a complex process that includes psychosocial and environmental factors and activation of the adrenergicreceptor pathway, resulting in enhanced tumor growth and metastasis [5,6]. A meta-analysis of various cancers, which included ovarian cancer, showed that use of β blockers improved overall and disease-free survival [7].

Similar findings have been demonstrated in ovarian cancer. A retrospective study of epithelial ovarian cancer patients found that postoperative β blocker use was associated with longer overall survival [8]. More recently, a large multi-institutional study that included 1425 cases of epithelial ovarian cancer showed a longer median OS for patients on β blockers compared to than those who were not on them [9]. However, the authors also have shown that nonselective β blockers (α and β blocker e.g. Propranolol) use are associate with longer survival compared selective β blockers. This study included patients with any documented β blocker (selective β_1 blocker e.g. Atenolol) use during chemotherapy. Despite these promising studies, a combined analysis of 2 prospective multicenter trials found no effect of β blockers on survival [10].

Because of the conflicting reports on the effect of β blockers in ovarian cancer patients and basic science suggesting the mitigating effects of β blockers on surgical stress, we chose to focus specifically on the perioperative use of the β blockers. We hypothesized that the perioperative use of selective β blockers will be associated with improved ovarian cancer patient outcomes. The primary outcomes in this study were progression-free interval and overall survival.

2. Methods

Institutional Review Board (IRB) approval was obtained at both the University of Minnesota and the University of Wisconsin. A retrospective analysis of patient records between 2000 and 2010 was performed. The University of Minnesota routinely used prophylactic perioperative β blockers, while the University of Wisconsin did not.

At the University of Minnesota, prophylactic perioperative β blockers were used with the goal of lowering the risk of postoperative coronary artery diseases. This protocol was used in "at risk" patients, who were defined as those patients undergoing primary cytoreductive surgery for ovarian cancer with either (1) history of myocardial infarction (MI) and not on beta-blockers; or (2) those with any two of the following: age >65 years, obesity (BMI > 30 kg/m^2), or a diagnosis of either diabetes mellitus or hypertension. In the Minnesota protocol, patients received IV β blockers before and during anesthesia (2.5–7.5 mg IV metoprolol every 6 h) and then transitioned to an oral regimen of either 12.5 mg or 25 mg twice daily during their hospitalization. Patients were then discharged from the hospital on this regimen for 7 days. Deviations from this protocol included patients who received only IV or oral metoprolol, received metoprolol in the hospital but did not take it at home, received metoprolol for several days and then were switched to their home medications such as lisinopril and hydrochlorothiazide, or were admitted to the ICU and metoprolol was stopped.

In this study, all consecutive patients from both institutions were included if they were scheduled for an exploratory laparotomy for primary cytoreductive surgery for epithelial ovarian cancer and would have qualified for meeting the definition of labeled "at risk" at both institution as defined above.

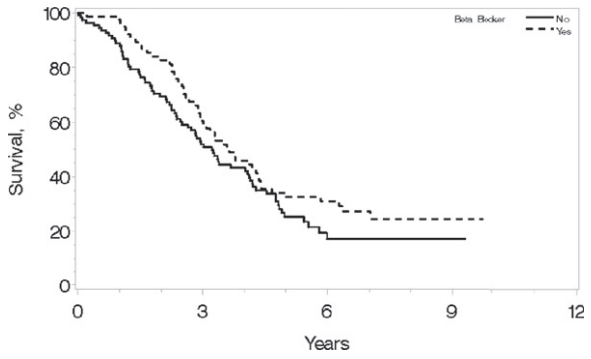
In both institutions, patients were excluded if they: had a diagnosis of non-epithelial ovarian cancer, had an aborted primary cytoreductive surgery, were already on β blockers, had any deviation from the protocol (either using an incorrect dose or shorter duration of β blockers) had missing data, or had no longitudinal follow-up.

Potential subjects were identified through billing records and institutional tumor registries. Patient demographic information was collected, including age at time of surgery, race, ethnicity, preoperative antihypertensive regimen, preoperative β blocker use, mode of β blocker administration, body mass index (BMI), date of diagnosis,

Table 1
Demographic data.

Patients' characteristics		No β blockers (N = 115)	On β blockers (N = 70)	p-Value[1]
Demographics	Age in years (SD)	66.2 (63.9–68.4)	63.8 (61.3–66.4)	0.19
	BMI in kg/m^2(SD)	32.0 (30.7, 33.1)	29.7 (27.6, 31.8)	0.06
	Race (Caucasian)	107/115 (93.0%)	58/62 (93.2%)	0.9
	Ethnicity (not Hispanic)	105/105 (100%)	57/58 (99.4%)	0.17
Medical comorbidities	Immunodeficiency	4/115 (3.5%)	1/69 (1.5%)	0.41
	COPD	9/115 (7.8%)	5/69 (7.3%)	0.88
	Hypertension	7/115 (6%)	15/69 (23%)	0.002[2]
	Diabetes mellitus	29/115 (25.2%)	10/69 (14.4%)	0.085
Stage	Stages I–II	29/115 (25.2%)	19/70 (27.1%)	0.77
	Stages III–IV	86/115 (74.8%)	51/70 (72.7%)	
Histology	Papillary serious	93/115 (81%)	58/70 (83%)	0.31
	Clear cell	9/115 (8%)	6/70 (9%)	
	Endometrioid	5/115 (4.2%)	2/70 (3%)	
	Mucinous	7/115 (6%)	3/70 (4%)	
	Others	1/115 (0.8%)	1/70 (2%)	
Pathology	Grade 1	11/115 (9.6%)	2/69 (2.9%)	0.08
	Grade 2–3	104/115 (90.4%)	67/69 (97.1%)	
Debulking status	Debulking (<1 cm)	96/115 (83.5%)	54/70 (77.1%)	0.28
Adjuvant chemotherapy	No chemotherapy	6/115 (5%)	3/70 (4%)	0.87
	IV Platinum based	88/115 (76%)	58/70 (82%)	0.6
	IV-IP Platinum based	21/115 (18%)	9/70 (13%)	0.22
Follow up (median in months)	All patients: 91 (range: 52–123)	98 (67–123)	82 (52–111)	0.42

[1] p-Values obtained by *t*-test for continuous variables and chi-square test for categorical variables.
[2] Statistically significant at the alpha = 0.05 level.

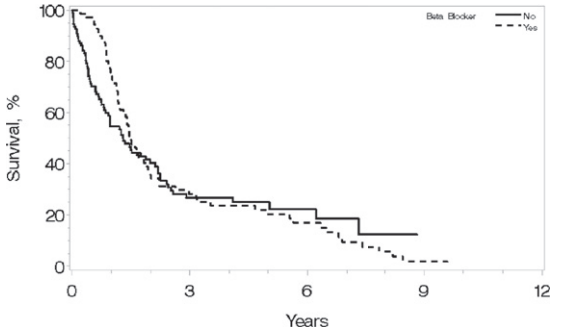


	Recurrence	Median PFS (months)	P-value
β blockers	65/70	18.2 (15-24)	0.66
No β blockers	72/115	15.8 (10-26)	

Fig. 1. Progression Free Survival (PFS), Kaplan-Meier curve depicting progression-free survival of those patients on β blockers.

comorbidities (diabetes mellitus, COPD, hypertension, and on immunosuppressive therapy), type of surgery, extent of cytoreductive surgery, cancer stage, histology, and grade. We collected data on patients' chemotherapy regimens, the number of chemotherapy cycles, and use of maintenance therapy. We also collected dates of recurrence, dates of death, causes of death, and disease status at last point of contact. Recurrence was defined by either radiologic, histologic, and/or biochemical marker evidence (CA 125). Progression-free interval (PFI) was defined as the time from the primary surgery until the time of recurrence. Overall survival (OS) was defined as the time from primary surgery to the date of death. Death was categorized as either cancer-related death or non-cancer related.

Univariate logistic regression analysis was used to examine the association between individual independent variables and both overall survival and progression-free interval. Multivariate Cox logistic regression analyses were conducted to explore the association between survival and the use of β blockers after controlling for the following potential confounding factors: age, stage, grade, cytoreduction status, BMI, and presence or absence of diabetes. A Kaplan-Meier survival analysis was performed to examine the influence of β blocker use on disease progression and overall survival.



	Death	Median OS (months)	P value
β blockers	48/70	44.2 (36-53)	0.09
No β blockers	75/115	39.3 (30-50)	

Fig. 2. Kaplan-Meier curve depicting overall survival for patients on β blockers.

Table 2
Multivariate analyses for progression-free survival using Cox proportional hazards model.

Variable	HR of death (95% CI)	p-Value
Age (for every 10 year increase)	1.14 (0.96–1.34)	0.116
Stage (III–IV vs. I–II)	3.90 (2.25–6.70)	<0.001
Grade (2–3 vs. 1)	2.13 (0.75–6.40)	0.178
Debulking (optimal <1 cm vs. >1 cm)	0.79 (0.50–0.93)	0.030
Perioperative β blockers (use vs. no use)	0.75 (0.54–1.10)	0.166

3. Results

We identified a total of 271 patients in both institutions. 86 patients met the exclusion criteria. Data from a total of 185 patients were analyzed: 70 received β blockers and 115 did not. The median longitudinal follow-up time for both groups combined was 91 months (52–123 months). There were no statistically significant differences between the demographics of the two study groups (Table 1). Hypertension was seen more in the β blocker group compared to the non-β blocker group (22% vs 6%, $p = 0.002$). Comparing the β blocker and non-β blocker groups, there were no differences in advanced stage at diagnosis (74% vs 72%, $p = 0.77$), distribution of histology, or percent of high-grade cancers (90% vs 97%, $p = 0.08$). Optimal surgical cytoreduction constituted 77% of those not on β blockers and 83% of those given β blockers ($p = 0.28$). The distribution of IV and IV-IP chemotherapy is similar in both groups.

The median progression-free interval (PFI) of patients on β blockers was 18.2 months (range: 14.9–23.6) compared to those not receiving β blockers, which was 15.8 months (range: 10.3–25.8, $p = 0.6$, Fig. 1). The median overall survival (OS) of patients on β blockers was 44.2 months (range: 36.1–53.4), compared to 39.2 (range: 30–50) for those who were not on β blockers $p = 0.01$) (Fig. 2).

After controlling for the confounding variables by multivariate Cox proportional hazards model, the use of β blockers was not associated with an increased PFI (HR 0.75 (0.54–1.11); $p = 0.16$). However, the overall survival continued to be significantly higher for those using perioperative β blockers (HR 0.68 (0.46–0.99); $p = 0.046$). Other factors independently associated with longer PFS and OS were early stage disease and optimal operative cytoreduction (Tables 2, 3).

4. Discussion

In this retrospective, multi-center analysis, we demonstrate an association between improved overall survival and perioperative β blocker use in patients undergoing primary cytoreductive surgery for high grade ovarian carcinoma.

Biologically, cancer progression itself includes six essential alterations in cell physiology that dictate malignant cell growth: self-sufficiency in growth signals, insensitivity to anti-growth signals, evasion of apoptosis, limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis [11,12]. These processes have been linked to neuroendocrine systems, and specifically the beta-adrenergic signaling pathway [12].

In ovarian cancer cell experiments, stress levels of norepinephrine and epinephrine acting on the beta 2 adrenoreceptors have been

Table 3
Multivariate analyses for overall survival using Cox proportional hazards model.

Variable	HR of death (95% CI)	p-Value
Age (for every 10 year increase)	1.20 (1.02–1.40)	0.025
Stage (III–IV vs. I–II)	2.00 (1.10–3.50)	0.011
Grade (3 vs. 1–2)	3.39 (0.74–14.9)	0.105
Debulking (optimal <1 cm vs. >1 cm)	0.78 (0.50–1.20)	0.296
Perioperative β blockers (use vs. no use)	0.68 (0.46–0.99)	0.046

Table 4
Summary of the published studies including the current one.

Study	Year	Study	Arms	N	PFI	OS	Notes
Diaz et al. [8]	2012	Retrospective study Primary cytoreductive	β blocker No β blocker	23 225	27 m 17 m p = 0.05	56 m 48 m p = 0.02	-Survival benefit for β blocker = 0.54 (p = 0.03) -None specific type of β blocker -Long term β blocker use
Heitz et al. [10]	2013	Nested case control study Recurrent platinum sensitive ovarian cancer	β blocker No β blocker	38 343	7.79 m 7.62 m p = 0.95	– –	-None specific type of β blocker -Long term β blocker use
Watkins et al. [9]	2015	Retrospective study Multi-institutional Primary cytoreduction and NAT	β blocker No β blocker	269 1156		47.8 m 42 m p = 0.036	-None specific type of β blocker -Long term β blocker use
Al-Niaimi et al. (current)	2016	Retrospective study Multi-institutional Primary cytoreductive	β blocker No β blocker	70 115	18.2 m 15.8 m p = 0.6	44.2 m 39.3 m p = 0.01	-Specific β blocker -Perioperative time only up to 6 weeks only.

shown to increase invasion and angiogenesis, and are also linked with cancer progression [5,13].

Although some of the gynecologic oncology literature supports the use of β blockers to improve surgical outcomes, in the non-gynecologic cancer literature, the concept of using adrenergic blockade to improve cancer outcomes has been challenged recently. Hicks et al. analyzed >1500 colorectal cancer patients, and found no association between post-diagnosis β blocker use and colorectal cancer-specific mortality [14]. In the breast cancer literature, Cardwell et al. published a large population-based cohort of breast cancer patients in the UK and found no association between post-diagnosis βblocker usage and breast cancer progression [15]. Similarly, in the prostate cancer literature, the evidence to support perioperative β-blockers has been lacking [16]. Numbere et al. conducted the largest non-gynecologic cancer study in 2015, a case control study of >18,000 patients with various cancers. They found no evidence to suggest that adrenergic blockade prevented common cancers. To the contrary, they found a slightly increased risk for colorectal and breast cancers in patients who had taken a β blocker [17].

In ovarian cancer, the literature in general reflects a different outcome (Table 4 is a summary of all the published studies including the current one). In a 2012 retrospective study of epithelial ovarian cancer patients, Diaz et al. showed that post-operative β blocker use was associated with longer overall survival (56 months vs 48 months, p = 0.02) and progression-free survival (27 months vs 17 months, p = 0.05) [8]. However, in 2013, Heitz et al. found no effect of β blockers on the survival of patients with ovarian cancer in a combined analysis of 2 prospective multicenter trials by the AGO Study Group [10]. Recently Watkins et al. published a study of 1425 epithelial ovarian cancer patients at 4 institutions, which showed that patients who used a β blocker during chemotherapy had a longer median OS than those who did not use them (47.8 months vs. 42 months; p = 0.036) [9]. Interestingly, they found that patients using nonselective β blockers (Propranolol) have longer OS compared to selective β blockers (94.9 months vs. 42 months; p < 0.001). However, there was no difference in t OS between selective β blocker users and nonusers (38 months vs. 42 months; p = 0.196). The above study included only patients who were taking β blockers as part of treatment for hypertension and not a temporary prophylactic perioperative measures, as was our study's protocol.

One of the strengths of our study is the use of a specific protocol of β blockers in the perioperative setting in patients previously not on these medications. The effect of this intentional addition of these agents has not been previously studied. Additionally, this protocol at the University of Minnesota was implemented and used for a specific "at risk" patient population who would otherwise not routinely be treated with β blockers. This protocol was used for a specific period of time after surgery and eliminated the heterogeneity of the protocol's duration of β blocker use, a limitation also seen in many previously reported studies.

This study is not without weaknesses. This is a retrospective study, and this might increase the risk of data inaccuracies, collection mistakes, and biases. Specifically, this study is at risk of selection bias. The comparison groups are drawn from two populations of patients at 2 distinct institutions. To mitigate this potential problem, we double-checked the data independently. Another weakness is the lack of information on patient behavior after discharge from the hospital. We have no way of assessing patient compliance with the β blocker regimen after discharge. Additionally, the number of patients in the β blocker group was only 70, which might have limited us in controlling for other factors in our multivariate analysis. As a matter of fact, our study did not intend to do subgroup analysis of the advanced staged ovarian cancer. A multivariate analysis was performed on both PFS and OS, both of which we took into account the advanced stage of the cancer. The multivariate analysis, controlling for the stage, showed that β blocker significantly impacting the OS. Furthermore, performing subgroup analysis might be hard taking the small number of patient that will need to be analyzed.

There are multiple potential future implications for the concept of using β blockers to improve the survival of patients with ovarian cancer. A randomized clinical trial will be the gold standard to correctly and accurately quantify the effect of β blocker use on survival. The concept of β blocker use might indicate the importance of the physiologic implications of "toning down" the sympathetic nervous system and the stress response in general. To continue on this line of inquiry, potential future studies could examine whether mindfulness, psychological therapies, or spiritual practices to promote calmness might induce such a physiological effect.

In conclusion, we uncovered a potential correlation between receipt of perioperative β blockers and improved overall survival, but not progression-free survival, for patients undergoing primary cytoreductive surgery for epithelial ovarian cancer. A prospective randomized clinical trial in this population is warranted to further validate these results.

Conflict of interest

The authors have no conflict of interest. Dr. Dickson was supported in part by the NIH T-32 training grant 5T32-CA132715. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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