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Significance of Diabetes on Morbidity and Mortality Following Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy

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Abstract

Background and Objectives—Patients with diabetes suffering from peritoneal surface disease represent a challenge to treat due to the effects of both processes on multiple organ systems. We sought to define the impact of diabetes on outcomes following cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS/HIPEC).

Methods—A retrospective analysis of a prospective database of 1065 CRS/HIPEC procedures was conducted. Patient demographics, comorbidities, and tumor characteristics were reviewed.

Results—CRS/HIPEC was performed in 91 diabetic and 844 non-diabetic patients with peritoneal surface disease from 1991 to 2013. Diabetics and non-diabetics spent 6.8 and 3.1 ($P = 0.009$) days in the ICU, respectively. Diabetics were more likely to suffer major complications ($P < 0.001$) including infectious ($P < 0.001$) and thrombotic ($P = 0.05$) complications, arrhythmias ($P = 0.007$), renal insufficiency ($P = 0.002$) and respiratory failure ($P = 0.002$) than non-diabetics. Mortality was significantly worse for diabetic patients at 30-days (8.8% vs. 2.7%, $P = 0.007$) and at 90-days (13.2% vs. 5.2%, $P = 0.008$). Even after adjusting for other significant predictors of morbidity, diabetes predicted more major complications and increased mortality following CRS/HIPEC.

Conclusions—Diabetes predicts major complications and specific complication patterns associated with increased ICU stay and worse mortality in patients undergoing CRS/HIPEC. Diabetic patients deemed to be appropriate candidates for CRS/HIPEC should be treated with caution.

Keywords

diabetes; HIPEC; cytoreduction; carcinomatosis; morbidity and mortality

INTRODUCTION

Diabetes negatively impacts the outcomes of surgical patients in terms of infectious complications and readmission across a variety of disciplines including general, bariatric, vascular, thoracic, and orthopedic surgery [1–4]. Diabetic patients undergoing cancer operations are no exception [5,6].

While cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) can yield meaningful survival benefits in patients with peritoneal surface disease (PSD), morbidity and mortality outcomes in diabetic patients have not been described. In general CRS/HIPEC can result in morbidity and mortality as high as 42% and 4%, respectively [7]. While high volume centers have observed improved rates of complete cytoreduction, decreased class IV and V complications, and increased overall survival (OS) rates with more experience, much of this success has been attributed to improvements in selecting patients [7]. Therefore, we sought to determine the impact diabetes has on morbidity and mortality in patients undergoing CRS/HIPEC. The secondary aim was to identify if diabetes affects survival in patients that have been treated with CRS/HIPEC for PSD from low-grade appendiceal (LGA) primary lesions or colon cancer.

MATERIALS AND METHODS

A retrospective review of a prospectively maintained database of 1065 CRS/HIPEC procedures performed from 1991 to 2013 was conducted. Institutional review board approval was obtained. Diagnosis of diabetes was one of the prospectively maintained data points, and all patients who presented for evaluation for CRS/HIPEC with a diagnosis of diabetes were included in the study. In order to prevent duplication of patient characteristics in multivariate analyses, only the first CRS/HIPEC procedure was reviewed in the cohort of patients who had more than one procedure.

Patients were selected for CRS/HIPEC according to our previously published guidelines [8]. The primary goal of CRS/HIPEC was complete macroscopic cytoreduction prior to perfusion. R0 and R1 resections were grouped together as complete cytoreductions. Cytoreductions with residual macroscopic disease were characterized as R2 and subdivided based on the size of residual disease (R2a ≤ 5 mm, R2b ≤ 2 cm, R2c > 2 cm). The chemotherapeutic agent was chosen according to the primary malignancy, and HIPEC was performed using the closed abdominal technique [7].

Post-operatively, the majority of the patients were admitted to the intensive care unit (ICU). A smaller subset was admitted directly to the regular ward at the discretion of the operating surgeon. Insulin drips were only used in the ICU while sliding scales of regular insulin were ordered in the ICU and on the wards. In general, sliding scale insulin was preferred except in cases with markedly uncontrolled hyperglycemia. Strict protocols with narrow target blood

glucose ranges were not employed. Home regimens of oral hypoglycemic agents and long acting insulin were slowly added as patients' diets were advanced. Morbidity and mortality were classified according to the Clavien–Dindo grading system [9].

Statistical analyses were performed for patients with and without diabetes. Patient demographics, comorbidities, type of primary, hospitalization, morbidity, mortality, and distribution of complications were reviewed. Missing data are reported for each variable. Descriptive statistics are reported as count with percentage or mean with range as indicated. Comparisons were made with Fisher's exact test for nominal variables and Wilcoxon rank-sum test for continuous variables. Multivariate logistic regression was used to determine predictors of complications and mortality, and the final model was constructed using the backward selection method. Only significant variables from the univariate analysis were included in the multivariate mortality analysis. Survival was estimated from the date of CRS/HIPEC with the Kaplan–Meier method and compared with the log-rank test. Disease free survival (DFS) was estimated only in cases where a complete cytoreduction was achieved. Patients who suffered perioperative mortality were not included in survival analyses. Significance was defined as $P < 0.05$. All analyses were performed with SAS 9.3.

RESULTS

In total, 1065 CRS/HIPEC procedures were performed in 977 patients from 1991 to 2013 (Fig. 1). Diabetes status was known in all but 47 (4.8%) patients. We identified 91 diabetic and 844 non-diabetic patients that received CRS/HIPEC for PSD originating from 452 (48%) appendiceal and 220 (24%) colorectal primary lesions (Table I). While over 90% of the procedures in diabetics were performed in the year 2000 or later, there was no statistically significant increase in the rate of diabetes in patients undergoing CRS/HIPEC during the study period ($P = 0.32$). Diabetic patients were older ($P = 0.005$) and more likely to have lung disease ($P < 0.001$), heart disease ($P = 0.009$), higher body mass index (BMI) ($P < 0.001$), worse performance status ($P = 0.01$), and a higher initial Peritoneal Carcinomatosis Index (PCI) ($P = 0.003$) than non-diabetics. Preoperative ascites was present in 34 (37.5%) patients with diabetes. The extent of cytoreduction, as indicated by the mean number of visceral resections, was similar between diabetic and nondiabetic patients (3.2 vs. 3.1, respectively, $P = 0.40$).

Morbidity

Major complications (Clavien III–V) were more common in diabetics following CRS/HIPEC than in non-diabetics (27.5% or 25/91 vs 15.3% or 129/844, $P < 0.001$). In order to determine the effects of diabetes on major complications following CRS/HIPEC, analyses were performed in all patients looking for significant predictors of Clavien grade III complications or higher. Diabetes predicted Clavien III–V morbidity both on univariate and multivariate analyses (Table II). In fact a diagnosis of diabetes was the strongest identified independent predictor of a major complication in this cohort (odds ratio [OR] 3.7, 95% confidence interval [CI] 1.4–10, $P = 0.01$). Other independent predictors of a major complication included ECOG performance status greater than or equal to two and PCI score. Because the PCI score had incomplete data, a separate model was constructed excluding it

as a variable. In this model, diabetes remained a significant independent predictor of major complications following CRS/HIPEC (OR 2.5, 95% CI 1.3–4.8, $P = 0.006$). Besides just being associated with a higher frequency of major complications, the specific complication pattern observed in diabetics varied significantly from that seen in non-diabetics. More diabetic patients had infectious complications (OR 2.0, 95% CI 1.3–3.2, $P < 0.001$), thrombotic complications (OR 2.6, 95% CI 1.0–6.7, $P = 0.05$), arrhythmias (OR 3.8, 95% CI 1.6–9.4, $P = 0.007$), renal insufficiency or failure (OR 4.2, 95% CI 1.9–9.1, $P = 0.002$) and respiratory failure (OR 3.5, 95% CI 1.6–7.4, $P = 0.002$) than non-diabetics. A subset analysis of infectious complications demonstrated that diabetics were more likely to develop pneumonia (OR 2.5, 95% CI 1.1–5.3, $P = 0.03$) and sepsis from any source (OR 2.3, 95% CI 1.1–4.6, $P = 0.04$) than non-diabetic patients (Table III). In addition, diabetics spent twice as many days in the ICU as non-diabetics (6.8 vs. 3.1 days, $P = 0.009$) and demonstrated a trend towards increased length of hospital stay (18.1 vs. 13.9 days, $P = 0.07$).

Mortality

There were no intraoperative deaths in the study cohort. Perioperative mortality was significantly worse for diabetic patients both at 30-days (8.8% or 8/91 vs. 2.7% or 23/844, $P = 0.007$) and at 90-days (13.2% or 12/91 vs. 5.2% or 44/844, $P = 0.008$). To see if diabetes itself independently predicted mortality in CRS/HIPEC, we performed an analysis in all treated patients (Table IV). After adjusting for other predictors of mortality, a diagnosis of diabetes conferred more than twice the risk of mortality following CRS/HIPEC (OR 2.5, 95% CI 1.3–4.9, $P = 0.007$). Other independent predictors of mortality were older age (OR 1.7, 95% CI 1.4–2.2, $P < 0.001$), Eastern Cooperative Oncology Group (ECOG) performance status of two or greater (OR 2.5, 95% CI 1.4–4.5, $P = 0.003$), and the number of organs resected (OR 1.3, 95% CI 1.1–1.5, $P = 0.003$). Half (4/8) of diabetics 70 years of age or older undergoing CRS/HIPEC suffered mortality while the surviving four suffered major morbidity. Besides elderly age, enteric leak was also particularly detrimental in diabetic patients. While the rate of anastomotic leak was not significantly different between diabetics and non-diabetics (12.1% vs. 7.8%, $P = 0.16$), respectively, 45% of enteric leaks in diabetic patients eventually resulted in mortality.

Survival

Although perioperative outcomes were worse for patients with diabetes, no significant differences were observed in OS for patients with diabetes compared with patients without diabetes. Median OS for diabetic patients with LGA cancer was not reached compared to 101.9 months in patients without diabetes ($P = 0.61$). Median OS for diabetic and non-diabetic patients with colorectal cancer was 30.0 months versus 16.8 months ($P = 0.62$), respectively (Fig. 2). When analyzing only those who received a complete cytoreduction prior to HIPEC median OS remained similar for patients with LGA (median OS not reached versus 175.2 months, $p=0.82$) and colorectal cancer (median OS 32.3 months vs. 25.0 months, $P = 0.63$) with and without diabetes, respectively. Disease free survival (DFS) was also similar in patients with LGA (median DFS not reached vs. 139.2 months, $P = 0.37$) and in patients with colorectal cancer (median DFS 32.3 months vs. 23.0 months, $P = 0.79$) in diabetics compared with non-diabetics, respectively.

DISCUSSION

Diabetes may be present in up to 18% of cancer patients [10], and cancer patients with diabetes tend to present with a more advanced stage of disease than do similar patients without diabetes [11]. In fact, in patients with gastrointestinal malignancies, diabetes is associated not only with worse all-cause mortality, but also worse cancer related mortality [12]. Diabetic patients with PSD represent a challenging group to treat due to the inherent morbidity associated with each and due to the effects of both diseases on multiple organ systems. CRS/HIPEC is currently being offered in over 100 institutions across the country yet much remains unknown about which patients stand to benefit the most from this procedure. Identifying patients with acceptable (or unacceptable) risk profiles can help refine selection criteria and improve outcomes.

In this study, diabetes predicted both major complications and worse mortality following CRS/HIPEC even after adjusting for other significant predictors of morbidity and mortality. The specific complication pattern exhibited by diabetics may partially account for the increased mortality. It is difficult to know how much of these observations are due to the chronic effects of diabetes on multiple organ systems that results in depletion of necessary physiologic reserves to respond to surgical stress. Much debate has focused around perioperative glucose control. A recent large international multi-institutional randomized study reported that strict glucose control (81–108mg/dL) was associated with worse mortality than conventional glucose control with target blood sugars of less than 180 mg/dL [13]. Similarly, studies in cardiovascular surgical patients have shown no improvement in outcomes with strict glycemic control [14,15].

The data presented in this manuscript can help refine the selection of patients with PSD for CRS/HIPEC. A previous report has indicated that complications in elderly patients following CRS/HIPEC, negate any potential survival benefit, even in cases of complete cytoreduction [16]. While it is definitely possible to perform CRS/HIPEC safely in well-selected elderly patients, the current study was unable to identify any diabetic patient over 70 that did not suffer either major morbidity or mortality indicating that elderly diabetic patients are poor candidates for aggressive cytoreduction. In addition, the presence of preoperative ascites in patients with PSD has been shown to correlate with decreased chances of achieving a complete macroscopic cytoreduction [17]. Given that complete cytoreduction is the driving factor for prolonged survival following CRS/HIPEC, a diabetic patient with voluminous malignant ascites, from a non LGA primary, represents another poor candidate for CRS/HIPEC both because the risk of mortality is high and because the potential benefit from an incomplete cytoreduction is low.

Besides highlighting the need for stringent selection criteria in diabetic patients with PSD, the reported findings have implications on the selected intra-operative strategy. In general, once it has been determined that a complete cytoreduction is not feasible, extensive CRS should be avoided in order to prevent complications. This is even more important in diabetic patients where mortality is observed in nearly half of patients with an anastomotic leak. We currently favor a sigmoid colostomy or at least a diverting loop ileostomy for diabetic patients with any rectal resection. Our post-operative management has changed as well.

Coincidentally, at the conclusion of our study, an institution wide initiative has implemented a code sepsis screening protocol that helps clinicians identify and treat patients with early signs of sepsis [18]. This will hopefully facilitate timely recognition and treatment of infectious complications following CRS/HIPEC in diabetic patients and possibly improve mortality.

While diabetes does predict mortality in patients undergoing CRS/HIPEC procedures, meaningful survival benefits similar to those experienced by non-diabetic patients were observed for patients with colon and LGA primary lesions. Disease free survival was also similar between diabetics and those without diabetes further indicating that a carefully selected and treated diabetic patient can benefit from CRS/HIPEC when complications are avoided or treated successfully.

This study represents the first to directly evaluate the impact of diabetes on outcomes following CRS/HIPEC. Although the cohorts were large, the current study has several limitations. Primarily, detailed data regarding preoperative and postoperative blood glucose control, duration of diabetes, use of insulin, and hemoglobin A1c levels were not captured in the database and were unavailable on retrospective chart review. Diabetics are a heterogeneous population and the impact of meticulous medical management on outcomes following CRS/HIPEC is left unaddressed with the current study. That being said, PSD is universally fatal when left untreated and delaying CRS/HIPEC to medically optimize a diabetic patient must be weighed carefully against the natural history of PSD. A second limitation involves the possibility that power attenuation is responsible for an inability to identify variables with small but important effects on major complications and mortality rates following CRS/HIPEC in diabetic patients.

CONCLUSIONS

In conclusion, diabetes predicts increased major complications and a specific complication pattern associated with longer ICU stays and worse mortality in patients undergoing CRS/HIPEC. Left unaddressed, PSD is a rapidly and universally fatal process that must be weighed against what is considered acceptable operative risk. Patients with diabetes may still experience meaningful survival benefits following CRS/HIPEC procedures but efforts should be made in appropriate selection of operative candidates with acceptable perioperative risk.

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Abbreviations

PSD	peritoneal surface disease
CRS	cytoreductive surgery
HIPEC	hyperthermic intraperitoneal chemotherapy

ICU	intensive care unit
DFS	disease free survival
PCI	peritoneal carcinomatosis index
LGA	low-grade appendiceal
BMI	body mass index
OR	odds ratio
CI	confidence interval
ECOG	eastern cooperative oncology group
OS	overall survival

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Fig. 1.
Cohort inclusion and exclusion diagram.

Fig. 2. Survival following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with low-grade appendiceal and colon cancer as indicated based on diabetes status.

TABLE I

Characteristics of Diabetic and Non-Diabetic Patients Undergoing Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy

Characteristic	Non-diabetic (n = 844)	Diabetic (n = 91)	P
Age, mean (range), y	52.7 (11–87)	56.5 (32–76)	0.005
Male, n (%)	386 (45.7)	49 (53.9)	0.15
Race, n (%)			<0.001
White	746 (88.4)	64 (70.3)	
Black	72 (8.5)	22 (24.2)	
Other	26 (3.1)	5 (5.5)	
Heart Disease, n (%) (n = 934)	66 (7.8)	15 (16.7)	0.009
Lung Disease, n (%) (n = 934)	24 (2.8)	12 (13.3)	<0.001
Body Mass Index, mean (range) (n = 861)	27.4 (13.6–54.3)	31.8 (17.9–63.3)	<0.001
Smoking Status, n (%) (n = 907)			0.29
Current	126 (15.4)	12 (13.8)	
Past	134 (16.3)	20 (23.0)	
No	560 (68.3)	55 (63.2)	
ECOG Performance Status, n (%) (n = 921)			0.01
0/1	708 (85.2)	68 (75.6)	
2	94 (11.3)	20 (22.2)	
3	29 (3.5)	2 (2.2)	
Preoperative Albumin, mean (range) (n = 910)	3.8 (1.0–5.3)	3.7 (1.8–4.9)	0.46
Preoperative Ascites, n (%)	271 (32.1)	34 (37.5)	0.35
PCI at Exploration, mean (range) (n = 329)	13.4 (0–36)	18.4 (1–39)	0.003
Primary, n (%)			0.16
Appendiceal	412 (48.8)	40 (43.0)	
Colonic	198 (23.5)	22 (24.2)	
Mesothelioma	57 (6.8)	11 (12.1)	
Ovarian	56 (6.6)	6 (6.7)	
Unknown	20 (2.4)	5 (5.5)	
Other	101 (12.0)	7 (7.7)	
Total number of organs resected, mean (range)	3.1 (0–10)	3.2 (0–7)	0.40
Colon/rectal resection, n (%)	440 (52.1)	56 (61.5)	0.10
Resection status, n (%) (n = 925)			0.62
R0/1	399 (47.8)	37 (40.7)	
R2a	236 (28.3)	30 (33.0)	
R2b	119 (14.3)	14 (15.4)	
R2c	80 (9.6)	10 (11.0)	
Length of operation, mean (range), h (n = 670)	8.5 (4–19.5)	9.2 (4.5–25.6)	0.08
Estimated blood loss, mean (range), mL (n = 767)	755 (50–6500)	883 (100–3750)	0.16
Units transfused, mean (range) (n = 846)	1.01 (0–19)	1.36 (0–9)	0.12

ECOG, Eastern Cooperative Oncology Group; PCI, Peritoneal Carcinomatosis Index.

TABLE II

Predictors of Clavien Major Complications in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Characteristic	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	P	Odds ratio (95% confidence interval)	P
Diabetes	2.4 (1.4–3.7)	0.001	3.7 (1.4–10)	0.01
Age, 10year increments	1.1 (1.0–1.3)	0.18		
Male	1.5 (1.1–2.1)	0.02		
Race, non-white (versus white)	1.3 (0.8–2.1)	0.29		
Heart disease	1.0 (0.5–1.90)	0.97		
Lung disease	0.6 (0.2–1.7)	0.35		
Body mass index	1.0 (1.0–1.0)	0.40		
Any smoking history (past or current)	1.3 (0.9–1.9)	0.17	1.8 (0.9–3.5)	0.08
ECOG performance status 2	1.9 (1.2–3.1)	0.005	3.1 (1.4 – 8.5)	0.03
Preoperative albumin	0.7 (0.5–0.9)	0.005		
Preoperative ascites	1.1 (0.8–1.6)	0.60		
Total number of organs resected, each 1	1.4 (1.2–1.5)	<0.001		
Incomplete resection (R2) versus R0/R1	1.9 (1.3–2.7)	<0.001		
Length of operation	1.1 (1.0–1.2)	0.003		
Estimated blood loss	1.0 (1.0–1.0)	0.11		
Number of units transfused during procedure	1.0 (1.0–1.1)	0.42		
Peritoneal carcinomatosis index at exploration	1.0 (1.0–1.1)	0.002	1.0 (1.0–1.1)	0.01
Primary				
Colonic	Ref			
Appendiceal	1.7 (1.1–2.6)	0.03	0.9 (0.4–1.8)	0.68
Mesothelioma	1.4 (0.7–2.9)	0.41	0.1 (0.0–0.5)	0.008
Ovarian	0.3 (0.1–1.1)	0.08	0.6 (0.1–4.2)	0.57
Unknown	2.6 (1.0–6.5)	0.05	1.8 (0.2–21.3)	0.63
Other	0.6 (0.3 – 1.4)	0.23	0.2 (0.0–2.0)	0.19

ECOG, Eastern Cooperative Oncology Group.

TABLE III

Complication Patterns in Diabetic and Non-Diabetic Patients Following Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Complication	Non-diabetic (n = 844)	Diabetic (n = 91)	Odds ratio (95% confidence interval)	P
Any complication (Clavien I–V), n (%)	585 (69.3)	81 (89.0)	3.6 (1.8–7.0)	<0.001
Any infectious complications, n (%)	206 (24.4)	36 (39.6)	2.0 (1.3 – 3.2)	0.002
Intra-abdominal abscess	64 (7.6)	12 (13.2)	1.9 (1.0 – 3.6)	0.07
Wound infection	47 (5.6)	9 (9.9)	1.9 (0.9 – 3.9)	0.10
Urinary tract infection	17 (2.0)	3 (3.3)	1.7 (0.5 – 5.8)	0.43
Pneumonia	36 (4.3)	9 (9.9)	2.5 (1.1 – 5.3)	0.03
Sepsis	48 (5.7)	11 (12.1)	2.3 (1.1 – 4.6)	0.04
<i>Clostridium difficile</i> colitis	8 (1.0)	1 (1.1)	1.2 (0.1 – 9.4)	0.60
Bloodstream infection	19 (2.3)	1 (1.1)	0.5 (0.1 – 3.6)	0.71
Myocardial infarction, n (%)	4 (0.5)	2 (2.2)	4.7 (0.9 – 26.1)	0.11
Arrhythmia, n (%)	18 (2.1)	7 (7.7)	3.8 (1.6 – 9.4)	0.007
Deep vein thrombosis/pulmonary embolus, n (%)	22 (2.6)	6 (6.6)	2.6 (1.0 – 6.7)	0.05
Renal insufficiency/failure, n (%)	24 (2.8)	10 (11.0)	4.2 (1.9 – 9.1)	<0.001
Respiratory failure, n (%)	29 (3.4)	10 (11.0)	3.5 (1.6 – 7.4)	0.003
Enteric leak/perforation, n (%)	66 (7.8)	11 (12.1)	1.6 (0.8 – 3.2)	0.16
Fascial dehiscence, n (%)	19 (2.3)	2 (2.2)	1.0 (0.2 – 4.3)	1.0
30-Day readmission, n (%)	204 (26.4)	32 (36.4)	1.6 (1.0 – 2.5)	0.06

TABLE IV

Predictors of Mortality in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Characteristic	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	<i>P</i>	Odds ratio (95% confidence interval)	<i>P</i>
Age, 10yr increments	1.7 (1.4–2.2)	<0.001	1.7 (1.4–2.2)	<0.001
Male	1.0 (0.6–1.6)	0.92		
Race, non-white (versus white)	1.0 (0.4–2.3)	0.95		
Diabetes	3.1 (1.6–5.9)	<0.001	2.5 (1.3–4.9)	0.007
Heart disease	1.2 (0.5–2.8)	0.71		
Lung disease	1.3 (0.4–4.5)	0.63		
Body mass index	1.0 (0.9–1.0)	0.21		
Any smoking history	2.0 (1.2–3.4)	0.01		
Preoperative albumin	0.5 (0.3–0.7)	<0.001		
ECOG performance status 2	2.9 (1.7–5.2)	<0.001	2.5 (1.4–4.5)	0.003
Total number of organs resected, each 1	1.2 (1.1–1.4)	0.003	1.3 (1.1–1.5)	0.003
Preoperative ascites	2.1 (1.3–3.6)	0.005		
Incomplete resection (R2)	2.0 (1.2–3.6)	0.01		

ECOG, Eastern Cooperative Oncology Group.