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Cardiopulmonary bypass (CPB) has no significant impact on survival in patients undergoing nephrectomy and level III-IV inferior vena cava thrombectomy; a multi-institutional analysis

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Abstract

Purpose—The impact of cardiopulmonary bypass (CPB) usage in level III-IV tumor thrombectomy on surgical and oncologic outcomes is unknown. We sought to determine the impact of cardiopulmonary bypass (CPB) on overall and cancer specific survival, as well as surgical complication rates, and immediate outcomes in patients undergoing nephrectomy and level III-IV tumor thrombectomy with or without CPB.

Patients and Methods—We retrospectively analyzed 362 patients with RCC and with level III or IV tumor thrombus from 1992 to 2012 in 22 US and European centers. Cox proportional hazards models were used to compare overall and cancer-specific survival between patients with and without CPB. Perioperative mortality and complications rates were assessed using logistic regression analyses.

Results—The median overall survival was 24.6 months in non-CPB patients and 26.6 months in CPB patients. Overall survival and cancer-specific survival (CSS) did not differ significantly in both groups, neither in univariate analysis nor when adjusting for known risk factors. In multivariate analysis, no significant differences were seen in hospital LOS, Clavien 1-4 complication rate, intraoperative or 30 day mortality, and CSS between both groups. Limitations include the retrospective nature of the study.

Conclusions—In our multi-institutional analysis, the use of cardiopulmonary bypass did not significantly impact cancer specific survival or overall survival in patients undergoing nephrectomy and level III or IV tumor thrombectomy. Neither approach was independently associated with increased mortality in the multivariate analysis. Higher surgical complications were not independently associated with the use of CPB.

Keywords

renal cell carcinoma; cardiopulmonary by-pass; vena cava tumor thrombus; survival; surgical complication

Introduction

Renal cell carcinoma (RCC) is the third most common genitourinary malignancy, accounted 65000 new cases and caused 13600 death each year in the US [1]. Approximately 10% of the cases presented with tumor and/or thrombus involvement of the renal vein and vena cava. 1% of the patients with RCC presented with tumor thrombus above the level of the hepatic vein (Level 3 and 4) [1]. Without treatment, patients with caval thrombus have high mortality risk [2]. With aggressive surgical treatment, 5-year cancer specific survival reaches 50% in non-metastatic cases and overall survival approaches 40% [3, 4].

Surgical treatment of level III/IV thrombi is associated with high perioperative mortality and morbidity. These cases will often require the use of cardiopulmonary bypass (CPB) with/without hypothermia circulatory arrest. Previous studies have reported on the success of performing level III/IV thrombectomy without the use of cardiopulmonary bypass, given the associated morbidity when placing patients on CPB [1]. Most surgeons advocate for the use of CPB in complex cases involving tumor thrombus extending into the right atrium [5]. There is inconclusive evidence whether the use of CPB has any impact on short-term outcomes including intraoperative mortality, 30 days mortality, LOS, and immediate surgical complications. The impact of CPB on cancer specific mortality and overall mortality is also unclear.

To address these shortcomings, we aimed to analyze the impact of CPB on long-term oncologic outcomes and immediate surgical outcomes in patients undergoing radical nephrectomy with Level III/IV thrombectomy. We used a multi-institutional database from 22 US and European centers to report the largest series up to date.

Patients and Methods

Patient selection and data collection

This study was approved by the institutional review boards of all participating sites that provided the necessary institutional data-sharing agreements before initiation of the study. We retrospectively analyzed 362 patients with RCC and with level III or IV tumor thrombus who underwent radical nephrectomy and complete tumor thrombectomy from 1992 to 2012 in 22 US and European centers. The data was centralized via the International Renal Cell Carcinoma-Venous Thrombus Consortium (IRCC-VTC) to ensure data integrity and to address all data inconsistencies prior to the analysis as described previously [6]. Detailed surgical data, demographics, and pathological evaluation were available. Patients with incomplete records were excluded from the analysis.

Pathologic evaluation, tumor thrombus levels

Pathological staging was determined using the 2009 TNM classification. For patients who had surgery prior to 2009, their pathological staging were reclassified using the 2009 TNM staging [7]. Tumor thrombus levels were confirmed on preoperative MRI or trans-esophageal echocardiography. The level of the thrombus was classified using the Mayo classification system [8]. Level III thrombus involves the intrahepatic IVC but below the diaphragm and level IV tumor thrombus extends above the diaphragm or into the right atrium. Surgery times

were determined using start of incision to completion of incision. Surgical complications were within 30 days and classified using the 2004 Clavien-Dindo grading system. Low-grade and high-grade complications were further stratified using Clavien 1-2 and Clavien 3-4, respectively.

Management and Follow-up

Management included neoadjuvant targeted therapy, adjuvant immunotherapy and targeted therapy and were administered at the investigator's discretion to patients with metastatic disease. Preoperative angio-embolization and lymphadenectomy were also performed at the surgeons' discretion and did not follow a predetermined protocol. Follow-up was performed at least every 3 months for the first year, semiannually for the second year, and annually thereafter. Each visit included a physical examination, complete chemistry, hematology panels and diagnostic imaging (eg, ultrasonography, chest radiography, computed tomography of the abdomen/pelvis with intravenous contrast) at the discretion of the treating physician when clinically indicated [6]. The cause of death was determined by the treating physicians, by chart review corroborated by death certificates. The Martin criteria were used to qualify surgical complications and the Clavien-Dindo grading systems were used to classify complications [9, 10].

Statistical analysis

Cox proportional hazards models were used to compare overall and cancer-specific survival between patients with and without cardiopulmonary bypass (CPB). Median survival was estimated using the Kaplan-Meier method (log-rank test). The effects of CPB on length of stay were analyzed using quasi-Poisson models, which model count data while allowing for overdispersion. The effects of CPB on the odds of complications, intraoperative mortality, and 30-day mortality were analyzed using logistic regression. Analyses were conducted using R, version 2.15.1 (R Core Team, 2012), and version 3.1.0 (R Core Team, 2014, intraoperative mortality, 30-day mortality, and low- and high-grade complication analyses only) as described previously [11].

Results

Patient's characteristics

Median follow-up was 14.9 months in non-CPB patients (n=227) and 12.7 months in CPB patients (n=135). Table 1 shows patient characteristics dichotomized into with and without the use of CPB. The mean age was 63 years in both groups. CPB patients tended to have longer surgery duration, were more likely to have a level IV thrombus, and had a higher incidence of synchronous metastatic disease at presentation. As shown in Table 2, overall complication rate was 53% in patients undergoing level III/IV thrombectomy, the non-CPB cohort had a high-grade (major) complication (Clavien 3-4) rate of 28% while CPB patients had a high-grade complication rate of 23%. Intraoperative mortality for patients with or without CPB were both 2.2%. The 30 days mortality for non-CPB patients was 7.5% versus 10% for CPB patients.

Surgical outcomes

In univariate analysis, LOS was estimated to be 18% higher in CPB patients (p = 0.042), but when adjusting for other factors in multivariate analysis no significant difference was seen in LOS (p = 0.667). When looking at overall complications (Clavien 1-4), there was no significant difference in the odds of complication after adjusting for thrombus level, clinical and pathological characteristics, presence of metastasis, and time under surgery.

We further classified complications into low-grade (Clavien 1-2) and high-grade complications (Clavien 3-4) and analyzed their association with the use of CPB. The rates of high-grade or low-grade complications were not significantly associated with surgical approach when adjusted for thrombus level, time period of surgery and other factors. In addition, when analyzing level III and level IV thrombus separately, complication rate was not significantly associated with the use of CPB (supplemental table 1).

Next, we proceeded to determine if the role of CPB had any association with increase in the risk of intraoperative mortality and 30 day mortality. In univariate analysis, there was no significant association seen between CPB and intraoperative mortality (p = 0.995). There were 8 intraoperative mortalities, hence, not enough to fit multivariable models. Similarly, no significant association was seen between CPB and 30-day mortality in univariate analysis or multivariable analysis. Separate analysis of level III and level IV thrombus did not show any significant effect on perioperative mortality between CPB and non-CPB patients. In the level III thrombus cohort, longer surgery time was associated with increased risk of 30-days mortality after adjusting for other variables (supplemental table 2).

The use of CPB in level III thrombus patients was associated with lower requirement of blood transfusion (supplemental table 3). Liver mobilization was used in 40-55% of the time regardless whether patients were placed on by-pass and did not appear to affect surgical outcome.

Long-term oncologic outcomes

The median cancer-specific survival was 34.0months (95% CI [23.6, 64.7]) in non-CPB patients and 39.7months in CPB patients (95% CI [31.9, 80.0]), with 151 cancer-related deaths total in the two groups. Figure 1 shows a Kaplan-Meier plot of cancer-specific survival by CPB. (Note that the survival curves separate at the median, but are nearly superimposed elsewhere). Cancer-specific survival did not differ significantly based on CPB; neither in the univariate analysis (Wald test P = 0.942) nor when adjusting for thrombus level, age, sex, T stage, N stage, presence of metastasis, time under surgery, and time period of surgery (Wald test p = 0.771). Positive lymph node disease and metastasis were associated with both cancer specific survival and overall survival in the multivariate analysis, as shown in Tables 3-4.

The median overall survival was 24.6 months (95% CI [18.6, 34.5]) in non-CPB patients and 29.3 months in CPB patients (95% CI [12.7,35.7]), with 211 deaths total in the two groups. 93 patients were still alive as of last follow-up. Figure 2 shows a Kaplan-Meier plot of overall survival by CPB. Overall survival did not differ significantly based on CPB, neither in univariate analysis nor when adjusting for thrombus level, age, sex, T stage, N stage,

presence of metastasis, time under surgery and time period of surgery. In a separate analysis in which we segregated patients into level III and level IV thrombus, there was no statistically significant impact of CPB on CSS or OS (Supplemental figures 1 and 2).

Discussion

In patients undergoing level III/IV caval thrombectomy, the use of CPB allows the team of urologists and cardiac surgeons to meticulously remove the tumor, while having complete control over a bloodless field. When the tumor thrombus extends above the diaphragm, most surgeons are inclined to use CPB to allow maximal safety and oncological control in case of unpredictable difficulty during the thrombectomy. However, there are also associated hematological and neurological morbidities when placing patients on CPB with or without circulatory arrest. Two single-center series had reported on success of complete supradiaphragmatic tumor thrombus extraction without median sternotomy and CPB in 47 patients, with 30 day mortality of 9.2-15%, and 19.5% incidence of high grade complications [5, 12]. Patil et.al reported a median survival of 2.5 years for pT3cN0 patients without the use of CPB[5].

There are limited data on immediate surgical complications associated with the use of CPB in these patients, most were reported from single center series, with exception of one article that came from a 13 centers analysis [1, 13-18]. These series reported complication rate ranges from 18 to 47% and perioperative mortality ranges 7 to 22% in patients with level III/IV thrombus. In the present study, we report both oncologic and surgical outcomes in the largest cohort in the literature with level III/IV thrombus using International Renal Cell Carcinoma-Venous Thrombus Consortium (IRCC-VTC). As previously reported, patients with level III/IV thrombus often have significant complications associated with surgery, as high as 34% in the recent multicenter series using data from 162 patients [13]. In our analysis, 27% of the patients experienced high-grade complications. When we controlled for thrombus level, time period of surgery and other covariates, the use of CPB did not have any impact on LOS and low- or high-grade complications.

Granberg et al. reported a comparison of venovenous bypass (VVB) versus cardiopulmonary bypass in 41 patients with level II-IV thrombus (VVB = 13, CPB = 28) and did not find a significant difference in complication rate or in 5 year cancer specific mortality with either approach [16]. Similarly, we demonstrated that the use of CPB did not have any significant impact on short and long-term outcomes when compared to non-CPB counterparts. In our cohort of 362 patients with level III/IV thrombus, the intraoperative and 30-day mortality were 2.2% and 8.4% respectively, which are comparable to recently reported multicenter series [13]. Both CPB and non-CPB was associated with 2.2% intraoperative mortality. Neither intraoperative mortality nor 30 days mortality was associated with or without the use of CPB in the combined (level III and IV) or separated analysis (level III or IV alone). Patil et al. reported a 3.4% intraoperative mortality in their series of 87 patients with level III/IV tumor thrombus undergoing surgery without the use of CPB, while there is no report directly comparing CPB vs non-CPB with respect to intraoperative mortality [5]

In our long-term analysis of CSS and OS, we did not find any significant impact on these oncological outcomes associated with/without CPB in the multivariate analysis. Our findings suggest that the decision regarding the use of CPB during level III/IV thrombectomy should be made on the basis of surgeon experience, perioperative imaging, patient comorbidities, and availability of multispecialty team to maximize safety and cancer control. Limitations of our data were the retrospective nature of data collection, missing data and the analyses being subjected to confounding variable and selection bias that we cannot control for. However, this study offered insightful outcomes data based on a large international experience and may help guide decision in surgical approach.

Conclusions

In the analysis of the largest cohort of patients with RCC tumor thrombus, the use of cardiopulmonary bypass did not significantly impact cancer specific survival or overall survival in patients undergoing nephrectomy and level III or IV tumor thrombectomy. Surgical complications (Clavien 1-4), intraoperative and 30-day mortality, and hospital length of stay were not independently associated with surgical approach (non-CPB vs CPB).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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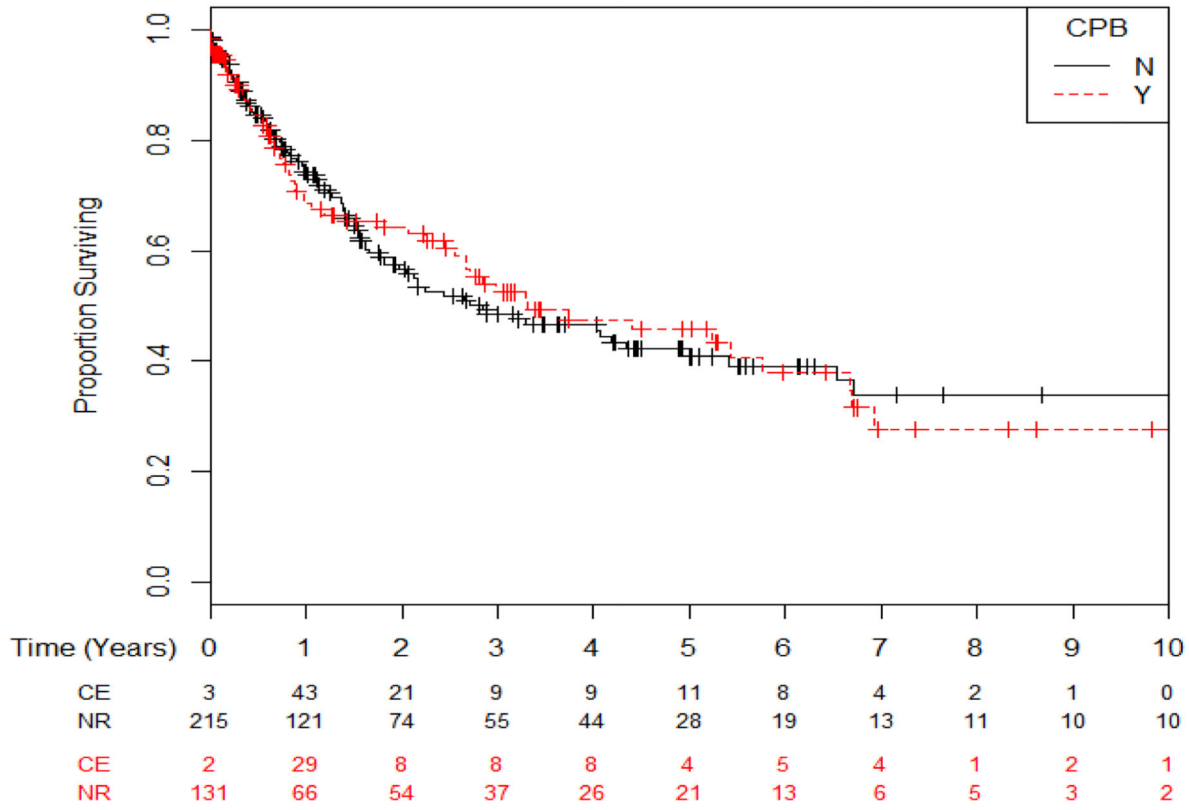

Figure 1.
Kaplan-Meier plot of cancer-specific survival by CPB, P = 0.942 (univariate).

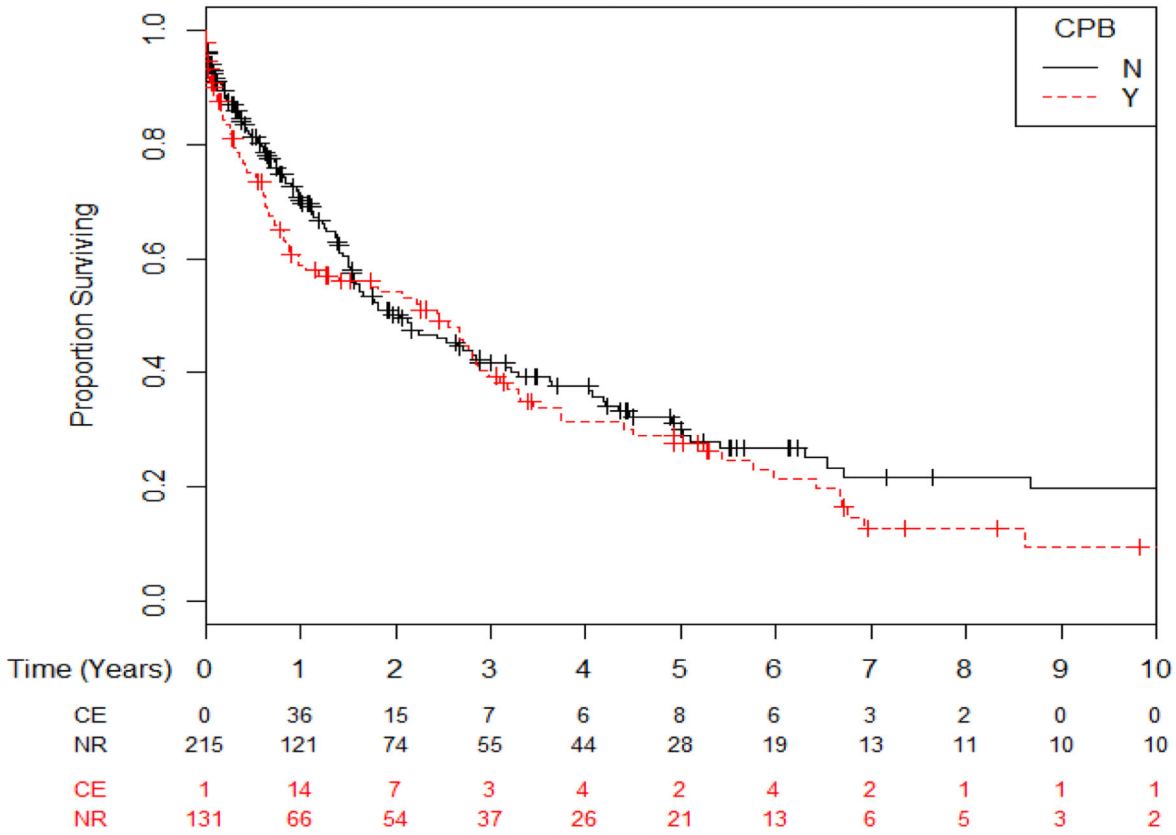

Figure 2.
Kaplan-Meier plot of overall survival by CPB, P = 0.235 (univariate)

Table 1

Patient Characteristics of 362 patients with RCC and with level III or IV tumor thrombus

	No CPB (n = 227)	CPB (n = 135)	All Level III and IV Patients (n = 362)	P-Value*
Age (Years)				0.904
Mean (SD)	63 (11)	63.2 (11.2)	63.1 (11.1)	
Median (Range)	64.3 (26--84)	64.4 (23--88.6)	64.4 (23--88.6)	
Time Under Surgery (Minutes)				<0.001
Mean (SD)	357 (149.1)	468.6 (161.1)	402.4 (163.3)	
Median (Range)	311 (110--831)	465 (141--965)	361 (110--965)	
Tumor Thrombus Level				<0.001
III	162 (71.4%)	49 (36.3%)	211 (58.3%)	
IV	65 (28.6%)	86 (63.7%)	151 (41.7%)	
Sex				0.436
F	83 (36.6%)	55 (40.7%)	138 (38.1%)	
M	144 (63.4%)	80 (59.3%)	224 (61.9%)	
T Stage				0.039
3	194 (88.6%)	121 (96%)	315 (91.3%)	
4	23 (10.5%)	5 (4%)	28 (8.1%)	
N Stage				0.005
N0	128 (56.4%)	61 (45.2%)	189 (52.2%)	
N1	28 (12.3%)	10 (7.4%)	38 (10.5%)	
N2	24 (10.6%)	13 (9.6%)	37 (10.2%)	
N3	1 (0.4%)	0	1 (0.3%)	
NX	46 (20.3%)	51 (37.8%)	97 (26.8%)	
M Stage				<0.001
M0	58 (25.6%)	67 (49.6%)	125 (34.5%)	
M1	57 (25.1%)	14 (10.4%)	71 (19.6%)	
MX	112 (49.3%)	54 (40%)	166 (45.9%)	
Synchronous Metastases				<0.001
No	159 (70%)	120 (88.9%)	279 (77.1%)	
Yes	68 (30%)	15 (11.1%)	83 (22.9%)	
Metachronous Metastases				0.095
No	194 (85.5%)	124 (91.9%)	318 (87.8%)	
Yes	33 (14.5%)	11 (8.1%)	44 (12.2%)	

Table 2

Patient Outcomes

	No CPB (n = 227)	CPB (n = 135)	All Level III and IV Patients (n = 362)	P-Value*
Complications				0.011
No	34 (40%)	21 (67.7%)	55 (47.4%)	
Yes	51 (60%)	10 (32.3%)	61 (52.6%)	
High Grade	24 (28.2%)	7 (22.6%)	31 (26.7%)	
Low Grade	27 (31.8%)	3 (9.7%)	30 (25.9%)	
Intraoperative Mortality				>0.999
No	219 (97.8%)	132 (97.8%)	351 (97.8%)	
Yes	5 (2.2%)	3 (2.2%)	8 (2.2%)	
30-Day Mortality				0.431
No	198 (92.5%)	118 (90.1%)	316 (91.6%)	
Yes	16 (7.5%)	13 (9.9%)	29 (8.4%)	
Follow-Up Duration (Months)				0.535
Median (Range)	14.9 (0—204)	12.7 (0—145)	14.2 (0—204)	

*P-value from Fisher's exact test for categorical variables, from t-test for age, and from the t-test conducted on log-transformed data for follow up duration and time under surgery

Table 3

Multivariable Cox Proportional Hazards Model of Cancer-Specific Survival By CPB

Variable	Hazard Ratio	95% Confidence Interval for Hazard Ratio	P-Value (Wald Test)
CPB (Yes vs. No)	1.573	(0.921, 2.686)	0.097
Level (IV vs. III)	1.131	(0.741, 1.725)	0.569
Age (Years)	0.998	(0.980, 1.018)	0.870
Sex (M vs. F)	0.745	(0.498, 1.115)	0.1526
T Stage (4 vs. 3)	1.934	(0.903, 4.143)	0.089
N Stage (N1 vs. N0)	**2.730**	**(1.503, 4.957)**	**0.001**
N Stage (N2 or N3 vs. N0)	**2.477**	**(1.362, 4.506)**	**0.003**
N Stage (NX vs. N0)	1.138	(0.648, 1.999)	0.653
Time Under Surgery (Hours)	1.057	(0.970, 1.151)	0.206
Metastases (M1 vs. M0)	**2.553**	**(1.470, 4.434)**	**0.001**
Metastases (MX vs. M0)	1.686	(0.968, 2.936)	0.065

Table 4

Multivariable Cox Proportional Hazards Model of Overall Survival By CPB

Variable	Hazard Ratio	95% Confidence Interval for Hazard Ratio	P-Value (Wald Test)
CPB (Yes vs. No)	1.544	(0.981, 2.430)	0.060
Level (IV vs. III)	1.055	(0.737, 1.510)	0.769
Age (Years)	1.009	(0.992, 1.025)	0.322
Sex (M vs. F)	0.935	(0.660, 1.323)	0.702
T Stage (4 vs. 3)	**1.968**	**(1.002, 3.865)**	**0.049**
N Stage (N1 vs. N0)	**2.237**	**(1.324, 3.782)**	**0.003**
N Stage (N2 or N3 vs. N0)	**2.045**	**(1.189, 3.518)**	**0.010**
N Stage (NX vs. N0)	1.357	(0.853, 2.158)	0.198
Time Under Surgery (Hours)	1.054	(0.979, 1.136)	0.164
Metastases (M1 vs. M0)	**1.889**	**(1.184, 3.014)**	**0.008**
Metastases (MX vs. M0)	1.206	(0.763, 1.906)	0.422