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Histologic Tumor Involvement of Superior Mesenteric Vein/ Portal Vein Predicts Poor Prognosis in Patients with Stage II Pancreatic Adenocarcinoma Treated with Neoadjuvant Chemoradiation

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Abstract

Background—Studies have shown that superior mesenteric vein/portal vein (SMV/PV) resection with pancreaticoduodenectomy (PD) is safe and feasible for patient with pancreatic adenocarcinoma (PAC). However, the prognostic significance of tumor involvement of the resected vein in patients who received neoadjuvant therapy is unclear.

Methods—We evaluated 225 consecutive patients with stage II PAC who received neoadjuvant therapy and PD with or without SMV/PV resection. The resected SMV/PV was entirely submitted for histologic assessment and reviewed in all cases. Tumor involvement of the SMV/PV was correlated with clinicopathologic features and survival.

Results—Among the 225 patients, SMV/PV resection was performed in 85 patients. Histologic tumor involvement of the resected SMV/PV was identified in 57 patients. Histologic tumor involvement of the SMV/PV was associated with larger tumor size, higher rates of positive margin and local/distant recurrence. By multivariate analysis, tumor involvement of the SMV/PV was an independent predictor of both disease-free survival (DFS) and overall survival (OS). However, addition of venous resection to PD itself had no impact on either DFS or OS compared to those with PD alone.

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Conclusion—Tumor involvement of the SMV/PV is an independent predictor of both DFS and OS in patients with stage II PAC treated with neoadjuvant therapy and PD. Complete histologic evaluation of the resected SMV/PV is important for the prognosis in patients with PAC who received neoadjuvant therapy and PD.

Keywords

pancreatic adenocarcinoma; survival; prognosis; SMV/PV

INTRODUCTION

In patients with pancreatic adenocarcinoma (PAC), tumor involvement of the superior mesenteric vein/portal vein (SMV/PV) was historically considered locally advanced, surgically unresectable disease because the complexity of such a radical procedure resulted in higher perioperative morbidity and often resulted in incomplete resection of the tumor, therefore conferring no survival benefit to the patient¹⁻³. The advent of the multidetector computed tomographic (CT) study has allowed for detailed assessment of the extent of disease to identify patients for whom a complete resection can be achieved. In addition, improvements in surgical technique have made the addition of vascular resection and reconstruction to pancreaticoduodenectomy (PD) safe and feasible, with peri-operative morbidity and mortality equaling those of standard PD⁴⁻⁷. Currently, a subset of patients with PAC and tumor abutment or short segment occlusion of the SMV/PV, short-segment involvement of the hepatic artery or its branches or <180° abutment of the superior mesenteric artery (SMA) which is amenable to resection and reconstruction is considered as borderline resectable⁸. Neoadjuvant therapy is increasingly recognized as an alternative to “surgery-first” approach in patients with potentially resectable disease because it potentially reduces tumor volume, thereby increasing the likelihood of a complete resection⁸. These recent advances in pancreatic imaging, surgery and oncology have given a subset of patients with potentially resectable PAC a chance for a more favorable outcome.

Analysis of the important prognostic factors predicting long-term survival in patients with borderline resectable or potentially resectable PAC has been hampered by the lack of a standardized approach to surgical resection, pathologic evaluation, and reporting of PD specimens that included a resected vein⁹. As a result, published data on the prognostic factors in patients with PAC who underwent PD with vascular resection are conflicting, with no consistent clinicopathologic parameters associated with a worse survival¹⁰. We therefore evaluated the prognostic significance of histologic tumor involvement of the resected SMV/PV and other clinicopathologic parameters in a cohort of 225 consecutive patients with stage II PAC who received neoadjuvant chemoradiation and underwent PD with or without SMV/PV resection. We found that histologic tumor involvement of the SMV/PV, but not the addition of SMV/PV resection, was an independent predictor of both disease-free survival (DFS) and overall survival (OS). We conclude that complete histologic evaluation of the resected SMV/PV is important in predicting prognosis in patients with PAC who were treated with neoadjuvant chemoradiation and subsequently underwent PD.

MATERIALS AND METHODS

Study population and patient characteristics

The study was approved by the Institutional Review Board of The University of Texas M. D. Anderson Cancer Center, Houston TX (MDACC). Two hundred twenty-five consecutive patients with stage II PAC who received neoadjuvant therapy and subsequently underwent PD at MDACC between January 1999 and December 2007 were included in the study. The posttherapy pathologic stage was determined according to the American Joint Committee on

Cancer (AJCC) Staging Manual, 7th edition¹¹. For the purpose of this study, patients who underwent PD for ampullary/periampullary carcinoma or other types of pancreatic neoplasms were excluded. Patients who underwent PD for posttherapy stage I PAC, those who did not receive neoadjuvant therapy, and those who underwent distal pancreatectomy were also excluded.

Our study group consisted of 89 females and 136 males with a mean age of 62.6 years at the time of surgery (median: 63.1 years, range: 38.5 – 85.4 years). Forty-one patients (18.2%) received neoadjuvant fluoropyrimidine-based chemoradiation (group 1), 69 (30.7%) received neoadjuvant gemcitabine-based chemoradiation (group 2), 72 (32.0%) received systemic chemotherapy followed by gemcitabine-based chemoradiation (group 3), 36 (16.0%) received systemic chemotherapy followed by fluoropyrimidine-based chemoradiation (group 4) and the remaining seven patients (3.1%) received neoadjuvant systemic chemotherapy alone (group 5). Among these patients, 141 of 225 patients (62.7%) were previously treated as part of clinical trials: 69 (30.7%) received gemcitabine-based chemoradiation¹² and 72 patients (32.0%) received systemic chemotherapy with gemcitabine and cisplatin followed by gemcitabine-based chemoradiation¹³. All other patients received various combinations of neoadjuvant chemotherapy and radiation therapy. All patients underwent restaging evaluation after completion of neoadjuvant therapy. PD was performed only in patients who had no disease progression and no contradiction to major abdominal surgery.

SMV/PV resection

Eighty-five patients (38%) with tumor adherence to the superior mesenteric vein (SMV), portal vein (PV), or superior mesenteric-portal vein confluence underwent either tangential or segmental resection of the involved vessel and reconstruction, as previously described¹⁴. The remaining patients (140 cases, 62%) did not undergo SMV/PV resection. Among the 85 patients who had SMV/PV resection, 34 patients (40%) underwent tangential resection and 51 patients (60%) underwent segmental resection of SMV/PV. A representative gross photograph of a pancreaticoduodenectomy specimen with segmental resection of SMV/PV and cholecystectomy is shown in Figure 1. The average intraoperative blood loss was 900 ml (range: 100 – 6,000 ml).

Pathologic evaluation of PD specimens and histologic assessment of SMV/PV

A standardized system for pathologic evaluation of PD specimens has been used at our institution since July 1990. Hematoxylin and eosin stained slides from all cases were reviewed by a gastrointestinal pathologist (H.W.) for tumor size, differentiation, extrapancreatic tissue involvement, margins status, and number of involved regional lymph nodes. The final margin status of PD specimens was recorded as R0 (all surgical margins were negative microscopically), R1 (all margins were grossly negative, but tumor cells were present at any of the resection margins microscopically) or R2 (tumor identified grossly and microscopically at any of the margins).

For PD specimens with SMV/PV resection, the resected portion or segment of SMV/PV was entirely submitted in all cases for histologic assessment. The inked vein margins were evaluated either perpendicularly for tangential SMV/PV resections or en face for segmental SMV/PV resections. As shown in Figure 1B-1D, the SMV/PV involvement by tumor was divided microscopically into four groups: a. no tumor involvement, including patients with fibrosis of perivascular soft tissue without viable tumor cells (Fig. 1B); b. tumor invasion of the tunica adventitia of SMV/PV, defined as tumor cells invading the perivascular soft tissue 1.0 mm from the tunica media (Fig. 1C); c. tumor invasion into the vein wall (the tunica media or intima, Fig. 1D); and d. tumor invasion into the lumen of SMV/PV, typically

associated with thrombus formation (Fig. 1E). For clinicopathologic correlations and survival analyses, we further grouped the patients who had SMV/PV resection, but no histologic tumor involvement of the resected SMV/PV and those who did not undergo SMV/PV resection as “no vein involvement”. The patients who had histologic tumor invasion into the tunica adventitia, media, intima, or lumen of SMV/PV were classified as “vein involved by histology”.

Follow-Up and Statistical Analysis

Clinical follow-up information through December 2009 was extracted from patient medical records and review of the U.S. Social Security Index. The first site or sites of disease recurrence were classified as either local/regional or distant recurrence. Local/regional recurrence was defined as recurrence in the region of the pancreatic bed, root of mesentery, soft tissues or lymph nodes adjacent to the pancreatic bed. Distant metastasis was defined as radiographic evidence of tumor spread to the liver, lungs, peritoneal cavity (including ascites), or other distant organs. Biopsy confirmation of metastasis was rarely performed. DFS was calculated as the time from the date of surgery to the date of first recurrence after surgery (in patients with recurrence) or to the date of last follow-up (in patients without recurrence). OS was calculated as the time from the date of diagnosis to the date of death or the date of last follow-up (if death did not occur).

Statistical analysis was performed using Statistical Package for Social Sciences software (for Windows 12.0, SPSS Inc., Chicago, IL). A two-sided significance level of 0.05 was used for all statistical analyses. Chi-square analysis or Fisher's exact test was used to compare categorical data and unpaired Student's t-test was used to compare continuous variables. OS and DFS curves were constructed using Kaplan-Meier method, and log-rank test was used to evaluate the statistical significance of differences. The prognostic significance of clinical and pathologic characteristics was determined using univariate Cox regression analysis. Cox proportional hazards models were fitted for multivariate analysis. After interactions between variables were examined, a backward stepwise procedure was used to derive the best-fitting model.

RESULTS

Clinicopathologic Features

Posttherapy tumor size ranged from 0.2 cm to 8.5 cm with an average of 2.7 cm (median: 2.5 cm). The overwhelming majority of our patients (221/225, 98%) had T3 disease while only two patients each (1%) had T1 or T2 disease. Dissection of regional lymph nodes from resection specimens yielded on average 22 lymph nodes (range: 5 to 50). The number of involved lymph nodes ranged from 1 to 21 nodes. Based on the AJCC (7th edition) Staging Manual¹¹, 85 patients (38%) had stage IIA disease and 140 patients (62%) had stage IIB disease. According to the World Health Organization (WHO) classification standards, 142 cases (63%) were well to moderately differentiated PAC and 83 cases (37%) were poorly differentiated PAC. R0 resection was achieved in 198 (88%) patients, 27 patients (12%) had microscopic tumor involvement of one or more surgical resection margins (R1); there were no R2 resections. In patients with R1 resection, six cases (3%) had tumor involvement of the SMV/PV margin; three cases (1%) had tumor at the common bile duct margin; eight cases (4%) had invasive carcinoma (5 cases) or carcinoma in situ/high-grade dysplasia (3 cases) at the pancreatic margin; and 15 cases (7%) had tumor at the retroperitoneal margin.

Patients who underwent PD with SMV/PV resection had higher intra-operative blood loss and larger tumor size than those who underwent PD without SMV/PV resection ($p < 0.05$). However, there were no differences in patient demographics, tumor differentiation, margin

status, lymph node status or other clinicopathologic parameters between these two groups (data not shown). Among 85 patients who underwent PD and SMV/PV resection, 57 patients (67%) had tumor involvement of the vein (18 cases had tumor invasion into the tunica adventitia, 35 cases had tumor invasion into the tunica media/intima and 4 cases had luminal involvement by tumor). The frequency of histologic tumor involvement was 59% (20/34) in patients who underwent tangential SMV/PV resection and 73% (37/51) in those underwent segmental SMV/PV resection ($p=0.24$). Clinicopathologic correlations of SMV/PV involvement by tumor are shown in Table 1. Patients with histologic tumor involvement of the SMV/PV had greater intra-operative blood loss, larger tumor size, and higher frequencies of positive resection margin (R1 resection), locoregional recurrence and distant metastasis compared to those who had no SMV/PV involvement, including patients who underwent PD without SMV/PV resection.

Survival Analysis

All patients were followed for a minimum of 12.7 months postoperatively or until death, with a median follow-up of 31.0 months (range: 7.6 – 122.3 months). At the time of last follow-up, 151 patients died of PAC, 11 patients died of other causes, 12 patients were alive with PAC and 51 patients were alive with no clinical or radiographic evidence of disease. Among all 225 patients, the DFS rates were 50% at 1 year and 29% at 3 years with a median DFS time of 11.8 months. The OS rates were 95% at 1 year and 43% at 3 years with a median OS time of 32.2 months.

The median DFS was 11.0 months in patients who underwent PD and SMV/PV resection (11.0 months in patients who underwent tangential resection and 10.1 months in patients who underwent segmental resection), which was not statistically different compared to those who underwent PD alone (median DFS of 15.2 months, $p>0.05$, Fig. 2A & 2B). Similarly, there was no difference in OS between the patients who underwent PD and SMV/PV resection and those who underwent PD alone. The median OS was 30.0 months among patients who underwent SMV/PV resection (31.2 months in patients who underwent tangential resection and 28.1 months in patients who underwent segmental resection) and 34.8 months among patients who underwent PD alone ($p>0.05$, Fig. 2C & 2D).

To examine the significance of SMV/PV involvement by tumor, we compared DFS and OS of patients who had tumor invasion into the tunica adventitia, the vein wall (tunica media or intima), or lumen of SMV/PV to those patients who had no tumor involvement of the resected SMV/PV and those who underwent PD without SMV/PV resection. The results are shown in Figure 3A and 3B. There was no difference in either DFS or OS among patients who had tumor invasion into the tunica adventitia, the vein wall, or lumen of SMV/PV (Figs. 3A and 3B). Similarly, there was no difference in either DFS or OS between the group of patients who had no tumor involvement of the resected SMV/PV and those patients who underwent PD without SVM/PV resection (Figs 3A and 3B). Patients with histologic tumor involvement of the resected SMV/PV had a significantly shorter DFS and OS (9.2 and 27.6 months, respectively) compared to the patients who had no histologic tumor involvement of the resected SMV/PV including those who underwent PD alone (15.9 and 35.7 months respectively, Figure 3C and 3D, $P=0.0001$).

Results from univariate Cox regression analysis for DFS and OS are tabulated in Table 2. DFS was associated with age ($p<0.001$), metastasis to regional lymph node ($p=0.004$) and tumor involvement of SMV/PV ($p<0.001$). OS was associated with intra-operative blood loss ($p=0.03$), tumor differentiation ($p=0.04$), metastasis to regional lymph node ($p=0.004$) and tumor involvement of SMV/PV ($p<0.001$). There was no significant correlation between either DFS or OS and gender, type of neoadjuvant therapy administered, tumor size, or type

of vein resection ($p>0.05$). By multivariate analysis, histologic tumor involvement of the resected SMV/PV was an independent predictor of both DFS and OS (Table 3).

DISCUSSION

In this study, we examined the prognostic significance of histologic tumor involvement of the resected SMV/PV in 225 consecutive patients with stage II PAC who received neoadjuvant therapy and subsequently underwent PD with or without SMV/PV resection. We found that histologic tumor involvement of the SMV/PV was an independent predictor of both DFS and OS. However, the addition of venous resection to PD itself had no significant impact on either DFS or OS. Our results highlight the clinical importance of careful histologic evaluation of the resected SMV/PV in PD specimens.

The current consensus in patients with borderline resectable PDAC is PD with venous resection if complete gross resection of tumor can be achieved.¹⁵ There is also growing evidence that the use of neoadjuvant therapy may be a rational treatment approach for patients with potentially resectable disease because it could potentially downstage the disease and increases the likelihood of a complete resection.⁸ However, data on the prognostic importance of tumor involvement of the resected vein in patients with PAC who underwent PD with venous resection are conflicting, with some reports demonstrating that histologic evidence of tumor in the vein conferred a worse survival duration by univariate analysis^{16–19} while other reports found no significant difference in survival between patients who had tumor involvement of the resected vein and those who did not.^{20–22} In addition, most of the above studies were smaller series with analysis of fewer than 50 patients who underwent SMV/PV resection^{16, 18, 20, 21, 23–30} and also lacked standardized evaluation of the resected SMV/PV. In this study, we included only patients with stage II PAC who received neoadjuvant therapy and PD with or without SMV/PV resection. The resected portion or segment of SMV/PV in the PD specimen was entirely submitted for histologic evaluation in all patients who underwent SMV/PV resection. Therefore, we not only had complete and accurate histologic evaluation of the tumor involvement in various layers of the resected SMV/PV, but also of the margin status of the resected vein. It is difficult to distinguish fibrosis involving the adventitia of SMV/PV secondary to inflammation or neoadjuvant therapy from fibrosis secondary to tumor involvement with complete response following neoadjuvant therapy. In this study, we defined the tumor involvement of the adventitia of SMV/PV as presence of viable tumor cells to 1.0 mm from the media with fibrosis extends to the media of the vein. We found tumor involvement of the resected SMV/PV in 67% of our patients who underwent SMV/PV resection. This result is similar to the reported vein involvement of 43% to 100% in a recent meta-analysis reported by Ramacciato et al. which included 12 studies^{16–18, 20, 21, 23–29} of patients with PDAC who underwent pancreatic resection (PD, distal pancreatectomy and total pancreatectomy) with or without SMV/PV resection published between 2000 and 2008.^{7, 16–18, 20, 21, 23–29} and 78% (86 of 110 patients) reported by Muller et al. However, only 16 of 110 patients in Muller's study and none of the patients in other 12 studies received neoadjuvant therapy. The average intra-operative blood loss reported by the 12 studies ranged from approximately 700 mL to 3100 mL, which is similar to average blood loss of 900 mL in our study. Among the four studies which included more than 30 patients who underwent SMV/PV resection,^{16–18, 27} the R1 resection rates were higher (14.3% to 38.4%), compared to 12% in our study. The median OS of 32.2 months in our patient population is better than the 13 to 22 months reported in the previous studies^{16–18, 21, 24–26}, this difference may be due to the highly selected population of patients reported here, all of whom underwent for PD with or without vein resection following neoadjuvant therapy in our study.

Many studies have shown that the addition of venous resection to PD is safe and feasible in the treatment of patients with PAC.^{5, 16, 18–21, 25, 26} In this study, we found that addition of SMV/PV resection itself to PD does not affect either DFS or OS when compared to the patients with PAC who underwent PD alone. Our data are in agreement with previous studies that SMV/PV resection can be safely performed with PD in patients with PAC. Patients with PAC invasion into the adventitia, vein wall or lumen of the resected SMV/PV (vein involved) had shorter DFS and OS than those who had no histologic tumor involvement of the resected SMV/PV or those who underwent PD alone. Our results demonstrate that histologic tumor involvement of the resected SMV/PV is an independent prognostic factor for both poorer DFS and OS by multivariate analysis. In addition, our data also demonstrate that tumor involvement of the resected vein is associated with larger tumor size, increased intra-operative blood loss, higher rates of positive margins and local/distant recurrence, which are similar to a previous study.¹⁷ These findings suggest that histologic tumor involvement of the resected vein can lead to an increased likelihood of residual tumor being present even after an attempted curative resection. In contrast to prior studies, which found that the depth of invasion into the resected SMV/PV correlated with the prognosis,^{31, 32} our data did not show significant differences in either DFS or OS in patients with tumor invasion into the adventitia, wall, or lumen of the resected SMV/PV ($p>0.05$).

In summary, we found that histologic tumor involvement of the resected SMV/PV is an independent predictor of both DFS and OS in patients with stage II PAC who received neoadjuvant therapy and subsequently underwent PD with or without SMV/PV resection. Patients with tumor involvement of the resected vein were more likely to have larger tumors, higher rates of positive resection margins and increased likelihood of local and distant recurrence. Therefore, complete pathologic evaluation of the resected SMV/PV in PD specimens is a predictor of prognosis in patients with PAC who received neoadjuvant therapy and subsequent PD.

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Figure 1.

A gross specimen of resected SMV/PV in pancreaticoduodenectomy specimen and criteria for histologic evaluation of the vessel wall for tumor involvement. A gross photograph of a pancreaticoduodenectomy and cholecystectomy specimen with a probe-patent segmental SMV/PV resection (A). Representative micrographs showing no histologic tumor involvement of SMV/PV (B), tumor invasion of the perivascular soft tissue to 1.0 mm from the tunica media (invasion of the tunica adventitia, C), the vein wall (invasion into the tunica media or intima, D), and lumen of the SMV/PV (E). The outmost media of the SMV/PV is indicated by the dotted lines in B, C and D. The deepest invasion of tumor cells into the SMV/PV is indicated by arrow(s). Original magnification 40X.

Figure 2.

Kaplan-Meier estimates of DFS (A and B) and OS (C and D) stratified by the presence or absence of SMV/PV resection or types of SMV/PV resection in patients with stage II PAC treated with neoadjuvant therapy and pancreaticoduodenectomy. The patients without SMV/PV resection have slightly better DFS and OS compared to patients who had SMV/PV resection but was not statistically significant. The two types of SMV/PV resection had similar outcome.

Figure 3.

Kaplan-Meier estimates of DFS and OS in patients with stage II PAC treated with neoadjuvant therapy and PD. Correlation of histologic tumor involvement of the adventitia, the wall, and lumen of the resected SMV/PV with DFS (A) and OS (B) are shown and compared to those with no histologic tumor involvement of the resected SMV/PV or those patients with PD alone. Histologic tumor involvement of the SMV/PV (vein involved) was associated with shorter DFS (C) and OS (D) compared to the patients who had no tumor involvement of the SMV/PV, including those who underwent PD without vein resection (no vein involvement).

Table 1

Clinicopathologic Features of Patients With and Without Histologic Tumor Involvement of the Superior Mesenteric Vein/Portal Vein (SMV/PV)

Characteristics	No vein involvement [§] (n=168)	Vein involved by histology (n=57)	p value
Age (mean ± SEM[*])	63.0 ± 0.8y	61.6 ± 1.4y	0.36
Gender			0.44
Female	69	20	
Male	99	37	
Blood loss (mean ± SEM)	788 ± 46 mL	1371 ± 160 mL	<0.001
Neoadjuvant Therapy			0.23
Group 1	30	11	
Group 2	55	14	
Group 3	53	19	
Group 4	23	13	
Group 5	7	0	
Tumor differentiation			0.53
Well-moderate	108	34	
Poor	60	23	
Tumor size			0.04
2 cm	64	13	
>2 cm	104	44	
Lymph node status (stage)			0.09
Negative	69	16	
Positive	99	41	
Margin status			0.008
Negative	154	44	
Positive	14	13	
Recurrence/metastasis			0.007
No	56	7	
Local recurrence	26	14	
Distant metastasis	86	36	

[§]Includes patients who underwent pancreaticoduodenectomy (PD) alone and those who underwent PD with SMV/PV resection but no tumor involvement of the SMV/PV;

^{*}SEM – standard error of mean

Table 2
Univariate Cox Regression Analysis of Disease-free and Overall Survival in Relation to Clinicopathologic Features

Characteristics	n	Disease-free Survival			Overall Survival		
		HR	95% CI	p value	HR	95% CI	p value
Age (years)	225	0.97 (0.96 – 0.99)	<0.001		0.99 (0.97 – 1.00)		0.09
Gender							
Female (reference)	89	1.00			1.00		
Male	136	1.00 (0.74 – 1.36)	1.0		1.09 (0.78 – 1.51)		0.62
Neoadjuvant therapy				0.11			0.80
Group 1	41	1.00			1.00		
Group 2	69	0.85 (0.53–1.36)	0.49		0.79 (0.48–1.28)		0.33
Group 3	72	1.31 (0.83–2.07)	0.24		1.00 (0.62–1.59)		0.98
Group 4	36	1.52 (0.90–2.56)	0.12		0.98 (0.56–1.73)		0.95
Group 5	7	1.21 (0.47–3.15)	0.69		0.97 (0.37–2.53)		0.95
Blood loss (mL)	225	1.00 (1.00 – 1.00)	0.07		1.00 (1.00 – 1.00)		0.03
Type of resection				0.17			0.14
No resection (ref)	140	1.00			1.00		
Tangential	34	1.38 (0.91 – 2.11)	0.13		1.33 (0.86 – 2.07)		0.21
Segmental	51	1.33 (0.92 – 1.93)	0.14		1.44 (0.98 – 2.11)		0.07
Tumor size							
2cm (reference)	77	1.00			1.00		
> 2 cm	148	1.15 (0.83 – 1.60)	0.40		1.01 (0.72 – 1.42)		0.95
Tumor differentiation							
Well-Moderate (ref)	142	1.00			1.00		
Poor	83	1.32 (0.96 – 1.81)	0.08		1.4 (1.01 – 1.94)		0.04
Margins							
Negative (reference)	198	1.00			1.00		
Positive	27	1.32 (0.84 – 2.07)	0.23		1.56 (0.99 – 2.46)		0.06
Nodal status (Stage)							
Negative (reference)	85	1.00			1.00		
Positive	140	1.61 (1.16 – 2.23)	0.004		1.67 (1.18 – 2.35)		0.004

Characteristics	n	Disease-free Survival		Overall Survival	
		HR (95% CI)	p value	HR (95% CI)	p value
Tumor involvement of SMV/PV					
No (reference)	168	1.00		1.00	
Yes	57	1.92 (1.37 – 2.70)	<0.001	1.97 (1.39 – 2.80)	<0.001

HR: hazard ratio; 95% CI: 95% confidence interval

Table 3
Multivariate Cox Regression Analysis of Disease-Free and Overall Survival in Relation to Clinicopathologic Features

Characteristics	n	Disease-free Survival			Overall Survival		
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age (years)	225	0.98 (0.96 – 0.99)	0.004	0.99 (0.98 – 1.01)	0.52		
Blood loss (mL)	225	1.00 (1.00 – 1.00)	0.82	1.00 (1.00 – 1.00)	0.65		
Tumor differentiation							
Well-Moderate (ref)	142	1.00				1.00	
Poor	83	1.29 (0.94 – 1.78)	0.12	1.44 (1.04 – 1.99)	0.03		
Margins							
Negative (ref)	198	--				1.00	
Positive	27	--		1.38 (1.02 – 2.62)	0.19		
Lymph node status							
Negative (ref)	85	1.00				1.00	
Positive	140	1.38 (0.98 – 1.94)	0.06	1.56 (1.11 – 2.21)	0.012		
Tumor involvement of SMV							
No (reference)	168	1.00				1.00	
Yes	57	1.79 (1.27 – 2.52)	0.001	1.97 (1.38 – 2.82)	<0.001		

HR: hazard ratio; 95% CI: 95% confidence interval