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Histologic Grading the Extent of Residual Carcinoma Following Neoadjuvant Chemoradiation in Pancreatic Ductal Adenocarcinoma: A Predictor for Patient Outcome

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Abstract

Background—Several grading schemes for the extent of residual tumor in post-treatment pancreaticoduodenectomy (PD) specimens have been proposed. However, the prognostic significance of these grading schemes is unknown.

Methods—Histopathologic slides of 223 cases who received neoadjuvant chemoradiation and PD were reviewed. The extent of residual tumor was graded using both the College of American Pathologists (CAP) and the Evans grading systems. The grading results were correlated with clinicopathological parameters and survival.

Results—Among the 223 patients, 6 patients (2.7%) showed pathologic complete response (pCR, CAP Grade 0 or Evans grade IV), 36 cases (16.1%) with minimal residual tumor (CAP Grade 1 or Evans grade III), 124 cases (55.6%) with moderate response (CAP Grade 2 or Evans grade IIb) and 57 cases (25.6%) with poor response (CAP grade 3, 18 with Evans Grade I and 39 with Evans Grade IIa response). Patients with pCR or minimal residual tumor (response group 1) had better survivals than those with moderate and poor response (response group 2). Response group 1 patients had lower post-therapy tumor and AJCC stages, lower rates of lymph node metastasis, positive resection margin, and recurrence/metastasis. Grading the extent of residual tumor is an independent prognostic factor for OS in multivariate analysis.

Conclusions—pCR or minimal residual tumor in post-treatment PD specimens correlate with better survival in patients with PDAC who received neoadjuvant therapy and PD. Histologic

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grading of the extent of residual tumor in PD specimen is an important prognostic factor in patients with PDAC who received neoadjuvant therapies.

Keywords

Pancreatic cancer; Pathologic response; Survival; Prognosis

INTRODUCTION

Pancreatic cancer is the 4th leading cause of cancer death in the United States for both males and females. The estimated number of new cases for pancreatic cancer in the year of 2010 was 43,140, and the number of deaths due to pancreatic cancer was 36,800.¹ Surgery offers the only chance for long term survival. However, 80% of patients with pancreatic ductal adenocarcinoma (PDAC) present with locoregionally advanced or metastatic disease and are not suitable for surgical resections.² The prognosis for patients with PDAC is poor. Despite significant improvements in surgery, peri-operative mortality rates, adjuvant systemic and radiation therapies, the prognosis for patients with PDAC has not changed significantly over the last four decades.³ Neoadjuvant chemoradiation therapy is increasingly used as an alternative to “surgery-first” approach in treatment of patients with potentially resectable PDAC, especially for patients with borderline resectable disease, because it potentially reduces tumor volume and treats early micrometastatic disease, thereby increasing the likelihood of a complete resection.

Few schemes for the histologic grading of the extent of residual tumor in post-treatment pancreatectomy specimens have been proposed. Ishikawa *et al.* proposed to group the tumor response into three categories based on the percentage of severely degenerative cancer cells (SDCC): one third or less, one-third to two-thirds, and greater than two-thirds, respectively.⁴ Evans *et al.* proposed a four-tiered grading system for the extent of residual tumor, based on the grading of residual tumors in other organs, by assessing the percentage of viable tumor cells (destruction of tumor cells) in the post-treatment pancreatectomy specimens: grade I, little (<10%) or no tumor cell destruction; grade IIa, destruction of 10%-50% of tumor cells; grade IIb, destruction of 51%-90% of tumor cells; grade III, few (<10%) viable-appearing tumor cells; and grade IV, no viable tumor cells.⁵ Similar to Evans grading system, White *et al.* also proposed to use the percentage of the residual carcinoma and grouped the tumor response into three grades: “large”, >90% viable tumor cells; “moderate”, 10% to 90% viable tumor cells; and “small”, <10% residual tumor cells, scattered foci of tumor cells or no residual tumor cells.⁶ The College of American Pathologists (CAP) proposes to use a four-tier grading system for the extent of residual carcinoma in post-therapy pancreatectomy specimens: grade 0, no viable residual tumor (pathologic complete response); grade 1, marked response (minimal residual cancer with single cells or small groups of cancer cells); grade 2, moderate response (residual cancer outgrown by fibrosis); and grade 3, poor or no response (extensive residual cancer).⁷ White *et al.* showed in a small cohort of 54 patients that eight patients who had large residual tumor load in the pancreatectomy after neoadjuvant therapy had shorter survival than 46 patients with no tumor or moderate residual tumor load.⁶ However, the prognostic significance of the grading systems mentioned above for the extent of residual tumor in post-therapy pancreatectomy specimens is largely unknown. Validation studies for histologic grading of the extent of residual tumor are needed.

In this study, we used both the Evans grading system and the CAP grading protocol to evaluate the extent of residual tumor in a cohort of 223 patients who received neoadjuvant chemoradiation therapy and subsequently underwent pancreaticoduodenectomy (PD). Histologic grading of the extent of residual tumor was correlated with clinicopathological

parameters, disease-free survival (DFS), and overall survival (OS). We found that patients with pathologic complete response (pCR) or minimal residual disease (<5% residual tumor cells) in post-treatment PD specimens had better survival than those patients who had little or moderate response. In this study, histologic grading of the extent of residual tumor is an independent prognostic factor for OS. Thus histologic grading of the extent of residual tumor in post-treatment PD specimens is a key prognostic factor of patients with PDAC who received neoadjuvant therapy. A modified grading system for the extent of residual tumor in post-treatment pancreatectomy specimens is proposed.

MATERIALS AND METHODS

Patient population and follow-up

Our study population consisted of 223 patients with histologically confirmed diagnosis of PDAC who received neoadjuvant chemoradiation therapy and subsequently underwent pancreaticoduodenectomy (PD). There were 130 male and 93 female patients with age ranging from 38.9 to 85.4 years (median age: 62.9 years). Thirty-nine patients (17.5%) received neoadjuvant fluoropyrimidine-based chemoradiation (group 1), 69 (30.9%) received neoadjuvant gemcitabine-based chemoradiation (group 2), 75 (33.6%) received systemic chemotherapy followed by gemcitabine-based chemoradiation (group 3), 35 (15.7%) received systemic chemotherapy followed by fluoropyrimidine-based chemoradiation (group 4) and the remaining five patients (2.3%) received neoadjuvant systemic chemotherapy alone (group 5). One hundred and forty-four (64.6%) of these patients (groups 2 and 3) were treated on previously published protocols.^{8, 9} Upon completion of neoadjuvant therapy, all patients underwent restaging evaluation and PD was performed only in patients with resectable disease without disease progression or metastasis, and who had no contraindications to major abdominal surgery. Patients who underwent distal pancreatectomy for PDAC and those who underwent PD for other types of pancreatic tumors were excluded.

The clinical and follow-up information through December 2009 was extracted from a prospectively maintained database at the Department of Surgical Oncology and verified by reviewing patient medical records and the U.S. Social Security Index. The first site or sites of disease recurrence were classified as either local/regional or distant recurrence based on the computer tomography (CT) scan. Biopsy confirmation of metastasis was rarely performed. 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. This study was approved by the Institutional Review Board of the University of Texas M.D. Anderson Cancer Center.

Histologic grading of the extent of residual carcinoma in pancreaticoduodenectomy specimens

To exclude the inter-observer bias, the archival H & E slides from all cases were uniformly reviewed by one pathologist (D.C.) for the extent of residual carcinoma, who has not reviewed the cases prior to this study and was blinded to all clinical and follow-up information. The grading of the extent of residual carcinoma in PD specimens was performed using two different grading schemes: the grading protocol recommended by the CAP which is based on the ratio of residual tumor cells and the stroma⁷ and the grading scheme reported by Evans et al which is based on the percentage of residual tumor cells.⁵ Representative micrographs for the extent of residual carcinoma in post-treatment PD specimens using the CAP and Evans grading systems are shown in Figure 1. The number of slides reviewed from the pancreas and tumor ranged from 3 to 45 (the mean number of

slides: 14). In addition, the gross tumor size, differentiation, margin status, and lymph node status were also reviewed. The post-treatment pathologic staging was grouped according to the American Joint Committee on Cancer (AJCC) Staging Manual, 7th edition.¹⁰ For all the cases with pCR, the pre-treatment cytology and imaging studies were reviewed.

Statistical analysis

Chi-square analyses were used to compare categorical data and analysis of variance (ANOVA) was used to compare continuous variables. Survival curves were constructed using the Kaplan-Meier method and the log-rank test was used to evaluate the statistical significance of differences. Disease-free survival (DFS) was calculated 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. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the date of last follow-up if death did not occur. 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 the variables were examined, a backward stepwise procedure was used to derive the best-fitting model. 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.

RESULTS

Pathologic evaluation and histologic grading of the extent of viable residual tumor

Post-therapy gross tumor size ranged from 0 cm to 8.5 cm with an average of 2.5 cm. Post-therapy tumor stages, ypT0, ypT1, ypT2 and ypT3, were present in 6 (2.7%), 12 (5.4%), 2 (0.9%), and 203/223 (91%) of patients respectively. For the six cases with pCR (ypT0), pre-treatment CT scan showed a mass lesion in the head of the pancreas and the pre-treatment cytology diagnosis of adenocarcinoma was confirmed in all cases. The number of regional lymph nodes ranged from 5 to 50 lymph nodes (median, 21). The number of involved lymph nodes ranged from 0 to 21 nodes (median, 1). According to the World Health Organization (WHO) classification standards, 136 of the 217 (62.7%) cases with viable residual PDAC were well to moderately differentiated and 81 (37.3%) cases were poorly differentiated. R0 resection was achieved in 199 (89.2%) patients, 24 (10.8%) patients had microscopic tumor involvement of one or more surgical resection margins (R1); there were no R2 resections. Based on the CAP protocol, 6 (2.7%) cases had complete response (grade 0), 36 (16.1%) had minimal residual tumor (grade 1), 124 (55.6%) had moderate response (grade 2), and 57 (25.6%) cases had poor response (grade 4). Using Evans grading system for tumor response, 18 (8.1%) cases had grade I response, 39 (17.5%) grade IIa response, 124 (55.6%) grade IIb response, 36 (16.1%) grade III response, and 6 (2.7%) cases had grade IV response. All the cases with Evans grade III response in this study showed minimal residual tumor (single cells or small cluster of cancer cells, <5% viable tumor cells), that was scored as grade I response by CAP protocol.

Correlation of histologic grading of the extent of residual tumor with survival

The correlations of histologic grading of the extent of residual tumor after neoadjuvant therapy with DFS and OS by the CAP and Evans grading systems are shown in Figure 2. None of the six patients with pathologic complete response (pCR) developed recurrence or died from disease during the follow-up. Patients with pCR had better DFS and OS than those with viable residual tumors by either CAP protocol or Evans grading system ($P < 0.05$). Patients with minimal residual tumor (CAP grade I or Evans grade III) had better OS than those with CAP grades 2 and 3, or Evans grades IIa, IIb and I (Figure 2b and 2d, $p < 0.05$).

However, no significant difference in either DFS or OS was observed between the patients with CAP grade 2 and grade 3 (Figure 2a and 2b, $p>0.05$). Similarly, there were also no significant differences in either DFS or OS among the patients with Evans grades I, IIa and IIb (Figure 2c and 2d).

Since only six cases showed pCR in our study and as there was no statistical difference in either DFS or OS between the CAP grade 2 response and those with CAP grade 3 response, we further classified our cases into two response groups: response group 1, which included the cases with pCR and those with minimal residual tumor (<5% viable residual tumor, CAP grade 1 response) and response group 2, composed of patients who had 5% or more viable residual tumor. The clinicopathologic correlations of the grading of the extent of residual tumor are shown in Table 1. Response group 1 patients had smaller tumor size, lower post-therapy tumor and AJCC stages, and lower incidence of lymph node metastasis and positive resection margin than response group 2 patients (Table 1). None of 42 (0%) response group 1 patients had positive resection margin compared to 24 of 181 (13%) response group 2 patients ($p=0.01$). Twenty-three of 42 (55%) response group 1 patients had local recurrence and/or distant metastasis, which was lower than 73% (132/181) in response group 2 patients ($p=0.03$). No statistical difference in the sites of recurrence/metastasis between these two response groups was observed (Table 1 footnote). There was also no significant difference in age, gender, tumor differentiation between response group 1 and 2 ($P>0.05$).

Response group 1 patients had better DFS and OS than response group 2 patients (Figure 3a and 3b). The mean DFS and OS were 55.8 and 79.2 months in response group 1 patients compared to 36.8 months ($p=0.01$) and 48.2 months ($p=0.0002$) in response group 2 patients, respectively. The results from univariate Cox regression analysis for DFS and OS are shown in Table 2. Both DFS and OS were significantly associated with ypT, lymph node status, AJCC stage and histologic grading of the extent of residual tumor. In addition, DFS was also associated with tumor size ($p=0.04$) and OS was associated with margin status ($p=0.005$) and blood loss ($p=0.046$). There was no significant correlation of either DFS or OS with gender, tumor differentiation or among the patients who received different neoadjuvant therapies. Two multivariate analysis models were used to determine the prognostic significance of histologic grading of residual tumor for DFS and OS and the results are shown in Table 3. Histologic grading of the extent of residual tumor was an independent prognostic factor for OS in both models. The correlation of histologic grading of the extent of residual tumor with DFS was not significant in multivariate analysis. In addition, our data showed that ypT, lymph node status, and AJCC stages were also independent prognostic factors for both OS and DFS (Table 3). Tumor size, blood loss, and margin status was not significant for either DFS or OS in the multivariate analysis.

DISCUSSION

In this study, we used two histologic grading systems to evaluate the extent of residual tumor in 223 patients who received neoadjuvant chemoradiation therapy and subsequently underwent PD. We found that patients with pCR and minimal residual tumor (response group 1) had better survivals than those with moderate and poor response (response group 2). Response group 1 patients had lower post-therapy tumor and AJCC stages, less frequent lymph node metastasis, lower rate of positive resection margin, and lower rate of recurrence/metastasis than response group 2 patients. Histologic grading of the extent of residual tumor is an independent prognostic factor for OS in this group of patients. Thus histologic grading of the extent of residual tumor in PD specimen was important in predicting the prognosis in patients with PDAC who receive neoadjuvant therapies.

The Evans grading system of the extent of residual tumor in post-treatment PD is the most widely used in various clinical studies and clinical trials.⁵ In this study, we used Evans grading system to evaluate the percentage of residual tumor and the CAP protocol to evaluate the ratio between residual tumor cells and the stroma in a large cohort of 223 post-therapy PD specimens. We found only six patients (2.7%) who had pCR (no residual tumor) in post-treatment PD specimens (Evans grade IV, CAP grade 0). All six patients with pCR had confirmed pretreatment cytologic diagnosis of adenocarcinoma and a pancreatic mass by pretreatment CT scan. None of these patients had recurrence or died of PDAC with a follow up ranging from months to 6.0 months to 106 months (median 70.1 months). Patients with pCR had better DFS and OS than patients with residual tumor in their post-treatment PD specimens. Our study also showed that patients with minimal residual tumor (<5% residual tumor cells, CAP grade 1) had better OS than those with CAP grade 2 or grade 3 residual tumor. This finding was consistent with results reported by Moutardier *et al.* which showed major pathologic response in 9 of 40 patients, including three with pCR, and better survival in patients with major pathologic response than those without major response.¹¹ In our study, we did not observe significant difference in either DFS or OS among the patients who had the Evans grade I, grade IIb or IIa residual tumor, in contrast to the study by White *et al.* that patients who had large residual tumor load (Evans grade I) in the post-treatment pancreatectomy specimens had shorter survival than those with no tumor or moderate residual tumor load.⁶ Similar results were obtained using the CAP grading system, we did not observe significant differences in either DFS or OS between the groups of patients with CAP grade 2 and grade 3 residual tumor. Based on our findings, we propose to modify the current CAP grading system into a three-tier grading system for the extent of residual tumor: Grade 0, no residual carcinoma; Grade 1, patients with minimal residual carcinoma (single cells or small groups of cancer cells, <5% residual carcinoma); and Grade 3, patients with 5% or more residual carcinoma. This modified grading system is simple and easy to apply by the pathologists, thus may produce more consistent and reproducible histologic grading for the extent of residual tumor in post-treatment pancreatectomy specimens for future studies.

Neoadjuvant chemoradiation therapy is increasingly used as an alternative to “surgery-first” approach in treatment of patients with potentially resectable PDAC.^{8, 9} For patients with PDAC who received neoadjuvant chemoradiation and PD, studies on the prognostic factors are limited. In our previous study, we found that posttherapy tumor stage (ypT), lymph node metastasis and AJCC stage are independent prognostic factors for survival in patient with PDAC who received neoadjuvant chemoradiation and PD.¹² Histologic grading of the extent of residual carcinoma in post-therapy resection specimens has been shown to correlate with the prognosis in patients with carcinoma of several organ sites, including breast, rectum, esophagus and gastroesophageal junction region.^{13–20} Consistent with these finding, we found that histologic grading of the extent of residual tumor in post-treatment PD correlated significantly with both DFS and OS in patients who received neoadjuvant therapy by univariate analysis and is an independent prognostic factor for OS in multivariate analysis. In addition, we found that patients with pCR and minimal residual tumor (response group 1) had lower post-therapy tumor and AJCC stages, less frequent lymph node metastasis, lower rate of positive resection margin, and lower rate of recurrence/metastasis than response group 2 patients. However, no significant difference in the sites of recurrence was observed between these two groups of patients in our study.

In summary, we showed that pCR or minimal residual tumor (<5% residual tumor) in post-treatment PD specimens is associated with better DFS and OS than those patients with moderate or poor response (≥ 5% residual tumor cells) and is an independent prognostic factor for OS in patients with PDAC who received neoadjuvant chemoradiation therapy. Since no difference was present in either DFS or OS between the group of patients with

CAP grade 2 and those with CAP grade 3 residual tumor in our study, we propose that the current CAP grading protocol for the extent of residual tumor should be modified. Histologic grading of the extent of residual tumor is an important prognostic factor for patients with PDAC who received neoadjuvant chemoradiation therapy and pancreatectomy.

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Figure 1.

Panel a, representative micrographs show the post-treatment scar with fibrosis, but no residual carcinoma cells (pathologic complete response, CAP grade 0 and Evans grade IV); panel b, post-treatment scar with fibrosis and individual tumor cells (arrows mark the tumor cell, CAP grade 1 and Evans grade III), which is positive for pan-cytokeratin (insert); panel c, post-treatment scar with fibrosis and microscopic focus of residual tumor cells (arrows mark the tumor cells, CAP grade 1 and Evans grade III); panel d, post-treatment tumor bed with residual tumor cells outgrown by stroma and mucin pools (approximately 20% of viable residual tumor cells, CAP grade 2 and Evans grade IIb); panel e, post-treatment tumor bed with residual tumor cells outgrow the stroma (approximately 70% of viable residual

tumor cells, CAP grade 3 and Evans grade IIa); panel f, poorly differentiated adenocarcinoma with minimal treatment effect, more than 90% of the tumor cells are viable (CAP grade 3 and Evans grade I).

Figure 2. Kaplan-Meier estimates of disease-free survival (Panels a and c) and overall survival (Panels b and d) in patients with pancreatic ductal adenocarcinoma treated with neoadjuvant chemoradiation followed by pancreaticoduodenectomy. The CAP grading (a and b) and the Evans grading (c and d) of the extent of residual tumor correlate with disease-free and overall survival.

Figure 3.

Kaplan-Meier estimates of disease-free survival (a) and overall survival (b) in response group 1 patients who had pathologic complete response or minimal residual tumor (<5% of residual tumor cells) and response group 2 patients which had moderate to poor response (≥ 5% residual tumor).

Table 1

Clinicopathological correlation of the extent of residual tumor after neoadjuvant therapy

Characteristics	Response group 1 (%) (n=42)	Response Group 2 (%) (n=181)	<i>p</i> value
Age			0.76
<60 yrs	16 (38)	76 (42)	
60– 70 yrs	15 (36)	67 (37)	
>70 yrs	11 (26)	38 (21)	
Gender			0.39
Female	20 (48)	73 (40)	
Male	22 (52)	108 (60)	
Neoadjuvant therapy			0.40
Group 1	4 (10)	35 (19)	
Group 2	14 (33)	55 (30)	
Group 3	15 (36)	60 (33)	
Group 4	9 (21)	26 (14)	
Group 5	0 (0)	5 (3)	
Tumor differentiation			0.85
Well-Moderate	22 (61)	114 (63)	
Poor	14 (39)	67 (37)	
Tumor size			<0.001
2cm	28 (67)	61 (34)	
>2cm	14 (33)	120 (66)	
Lymph node(s)			0.01
Negative	26 (62)	69 (38)	
Positive	16 (38)	112 (62)	
Pathologic tumor stage			0.00
ypT0	6 (14)	0 (0)	
ypT1	6 (14)	6 (3)	
ypT2	0 (0)	2 (1)	
ypT3	30 (72)	173 (96)	
Resection margin			0.01
Negative	42 (100)	157 (87)	
Positive	0 (0)	24 (13)	
AJCC stage			<0.001
Stage 0	6 (14)	0 (0)	
IA and IB	6 (14)	5 (3)	
IIA	14 (33)	64 (35)	
IIB	16 (38)	112 (62)	
Recurrence			0.07
No	19 (45)	49 (27)	
Local ^a	6 (14)	35 (19)	

Characteristics	Response group 1 (%) (n=42)	Response Group 2 (%) (n=181)	<i>p</i> value
Distant ^a	17 (41)	97 (54)	

^aLocal recurrence, metastasis to the peritoneal cavity or abdominal wall, liver, lung and other sites were present in 6, 3, 9, 4 and 1 patients in response group 1, and 35, 15, 47, 31 and 4 patients in response group 2 (p=1.00).

Table 2

Univariate Cox Regression Analysis of Disease-free and Overall Survival

Characteristics	No. of patients	Disease-free survival			Overall survival		
		HR (95% CI)	p value		HR (95% CI)	p value	
Gender							
Females (ref)	93	1.00			1.00		
Males	130	1.02 (0.74, 1.40)	0.92		1.13 (0.81–1.58)	0.48	
Age (years)			0.04			0.57	
<60 (ref)	92	1.00			1.00		
60– 70	82	0.84 (0.59, 1.18)	0.31		0.96 (0.67, 1.38)	0.82	
>70	49	0.56 (0.36, 0.88)	0.01		0.78 (0.49, 1.25)	0.30	
Neoadjuvant therapy			0.36			0.73	
Group 1 (ref)	39	1.00			1.00		
Group 2	69	0.83 (0.51, 1.34)	0.44		0.76 (0.46, 1.24)	0.27	
Group 3	75	1.17 (0.74, 1.86)	0.50		0.88 (0.55, 1.43)	0.62	
Group 4	35	1.26 (0.73, 2.16)	0.41		0.85 (0.48, 1.52)	0.59	
Group 5	5	1.50(0.52, 4.29)	0.45		1.33 (0.46, 3.83)	0.60	
Tumor differentiation							
Well-Moderate (ref)	136	1.00			1.00		
Poor	81	1.23 (0.89, 1.70)	0.22		1.29 (0.92, 1.80)	0.14	
Tumor size							
2cm (ref)	89	1.00			1.00		
>2cm	134	1.40 (1.01, 1.95)	0.04		1.36 (0.96, 1.93)	0.08	
Pathologic tumor stage							
ypT0-ypT1-ypT2 (ref)	20	1.00			1.00		
ypT3	203	2.90 (1.42, 5.92)	0.004		5.60 (2.07, 15.19)	0.001	
Margin							
Negative (ref)	199	1.00			1.00		
Positive	24	1.56 (0.98, 2.48)	0.06		1.94 (1.22, 3.10)	0.005	
Lymph node (s)							
Negative (ref)	95	1.00			1.00		

Characteristics	No. of patients	Disease-free survival			Overall survival		
		HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Positive	128	1.78 (1.28, 2.48)	0.001	2.01 (1.41, 2.87)	<0.001		<0.001
AJCC Stage			0.001				<0.001
Stage 0, IA and IB (ref)	17	1.00		1.00			
Stage IIA	78	2.81 (1.20, 6.56)	0.02	7.92 (1.92, 32.74)	0.004		
Stage IIB	128	4.23 (1.85, 9.68)	0.001	12.32 (3.03, 50.14)	<0.001		
Blood loss	223	1.00 (1.00, 1.00)	0.126	1.00 (1.00, 1.00)	0.05		
Extent of residual tumor							
Response group 1 (ref)	42	1.00		1.00			
Response group 2	181	1.81 (1.15, 2.84)	0.01	2.65 (1.55, 4.54)	<0.001		

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

Table 3

Multivariate Cox Regression Analysis of Disease-free and Overall Survival

Characteristics	No. of patients	Disease-free survival			Overall survival		
		HR (95% CI)	p value		HR (95% CI)	p value	
Age (years)			0.06				
<60 (ref)	92	1.00			NA		
60–70	82	0.88 (0.62, 1.27)	0.50		NA		
>70	49	0.57 (0.36, 0.91)	0.02		NA		
Blood loss	223	NA	NA		1.00 (1.00, 1.00)	0.18	
Pathologic tumor stage							
ypT0-ypT1-ypT2 (ref)	20	1.00			1.00		
ypT3	203	2.95 (1.34, 6.50)	0.007		3.35 (1.20, 9.37)	0.02	
Margin							
Negative (ref)	199	1.00			1.00		
Positive	24	1.35 (0.84, 2.17)	0.22		1.52 (0.95, 2.43)	0.08	
Lymph nodes							
Negative (ref)	95	1.00			1.00		
Positive	128	1.42 (1.00, 2.02)	0.05		1.57 (1.10, 2.26)	0.01	
Extent of residual tumor							
Response group 1 (ref)	42	1.00			1.00		
Response group 2	181	1.43 (0.90, 2.28)	0.13		1.89 (1.09, 3.28)	0.01	
Age (years)			0.05				
<60 (ref)	92	1.00			NA		
60–70	82	0.89 (0.62, 1.28)	0.53		NA		
>70	49	0.57 (0.36, 0.90)	0.02		NA		
Blood loss	223	NA	NA		1.00 (1.00, 1.00)	0.19	
Margin							
Negative (ref)	199	1.00			1.00		
Positive	24	1.36 (0.84, 2.19)	0.21		1.53 (0.96, 2.46)	0.08	
AJCC stages			0.001		0.001		
Stage 0, IA and IB (ref)	17	1.00			1.00		

Characteristics	No. of patients	Disease-free survival			Overall survival		
		HR (95% CI)	p value		HR (95% CI)	p value	
Stage IIA	78	3.79 (1.50, 9.56)	0.005		6.00 (1.43, 25.2)	0.01	
Stage IIB	128	5.18 (2.10, 12.78)	<0.001		9.03 (2.18, 37.4)	0.002	
Extent of residual tumor							
Response group 1 (ref)	42	1.00			1.00		
Response group 2	181	1.38 (0.87, 2.20)	0.17		1.79 (1.03, 3.11)	0.04	

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