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Pathologic Response to Preoperative Therapy as a Novel Prognosticator for Ampullary and Duodenal Adenocarcinoma

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Abstract

Background: The prognostic impact of pathologic response to preoperative therapy in patients with duodenal adenocarcinoma (DA) and ampullary adenocarcinoma (AMPA) has not been established.

Methods: A retrospective review of 266 patients who underwent curative resection for DA (n=97) or AMPA (n=169) during 1993–2015 was performed. For patients who underwent preoperative therapy, pathologic response was systematically evaluated and classified as major (0%–49% of viable residual tumor cells) or minor (< 50% of viable residual tumor cells). Univariable and multivariable analyses were performed to identify predictors of pathologic response and disease-specific survival (DSS).

Results: In the 79 patients treated with preoperative therapy (DA n=34; AMPA n=45), concomitant use of radiation (67/79, 80%) was the sole independent predictor of major pathologic response (odds ratio: 8.17, 95% CI: 1.85–58.2, $P=0.005$). Patients with major pathologic response had a better 5-year DSS rate than patients with minor pathologic response (DA, 65% vs. 25%, $P=0.028$; AMPA, 85% vs. 43%, $P=0.016$). On multivariable analysis of DSS in the 79 patients who underwent preoperative therapy, major pathologic response was the sole predictor of improved DSS (hazard ratio: 2.88, 95% CI: 1.41–5.98, $P=0.004$). On multivariable analysis of DSS in the entire cohort, pathologic stage II was the sole predictor of better DSS.

Conclusion: Major pathologic response to preoperative therapy predicted improved DSS after resection of DA and AMPA and might represent a new prognosticator after resection of DA and AMPA.

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Keywords

pathologic response; preoperative therapy; ampullary adenocarcinoma; duodenal adenocarcinoma

INTRODUCTION

Periampullary cancers are a heterogeneous group of malignancies that include all neoplasms derived from the pancreaticobilio-digestive junction. Cancers usually classified as periampullary include ductal cancers from the pancreatic head, cholangiocarcinomas from the common bile duct, duodenal cancers, and ampullary cancers.¹ Of those, duodenal adenocarcinoma (DA) and ampullary adenocarcinoma (AMPA) are rare, accounting for 0.4% and 2.0% of gastrointestinal cancers, respectively.^{2, 3} AMPAs are histopathologically further subclassified as intestinal or pancreaticobiliary type.⁴ While several reports have suggested that pancreaticobiliary-type AMPA has a worse prognosis than intestinal-type AMPA,^{5–7} other reports did not find an impact of subtype on outcome.^{3, 8}

While today, resection remains the only potentially curative treatment for DA and AMPA, the precise role of perioperative therapy in the treatment of these diseases has not been established.⁹ Since prospective randomized studies of postoperative adjuvant chemotherapy for periampullary adenocarcinoma failed to show a survival advantage of postoperative chemotherapy in patients with DA and AMPA,^{8, 10} postoperative chemotherapy options for these diseases are extrapolated from the literature on pancreatic- and colon cancer. Similarly, because of the rarity of DA and AMPA, little has been reported in the literature concerning the impact of preoperative therapy for these diseases.^{2, 3} Previous retrospective study regarding localized AMPA demonstrated safety and feasibility of preoperative chemotherapy and/or chemoradiation, but suggested a limited role for the routine administration of preoperative therapies prior to intended resection.¹¹ In clinical practice at our institution, patients with DA or AMPA who frequently have bulky disease and/or regional adenopathy are likely to undergo preoperative therapy as recommended by the multidisciplinary care team.¹²

When preoperative therapy is used, pathologic response (as shown in other gastrointestinal cancers) to preoperative therapy correlates significantly with prognosis after surgery and can be used as a prognosticator; however, whether pathologic response to preoperative therapy correlates with prognosis in patients with DA and AMPA remains unclear.^{13–16} The aim of the current study was to determine the prognostic value of pathologic response to preoperative therapy in patients with DA and AMPA.

MATERIAL AND METHODS

Study Population

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study protocol (PA16–0530). A prospectively maintained hepatopancreatobiliary database of the Department of Surgical Oncology was reviewed to identify patients who underwent curative resection for DA and AMPA between January

1993 and December 2015. Patients with periampullary cancer considered to represent primary biliary or pancreatic adenocarcinoma and patients with Lynch syndrome diagnosed by Amsterdam II criteria were excluded. A total of 266 patients (97 with DA; 169 with AMPA) were identified (Figure 1). Among those patients, we identified patients treated with preoperative therapy followed by curative resection. The following data were extracted from electronic patient medical records: sex, age, body mass index, presence of diabetes mellitus, preoperative therapy characteristics (chemotherapy regimen and duration, and dose of radiation), operative characteristics (surgical procedure and margin status [R0, all margins clear of tumor on microscopic examination; R1, cancer on inked common bile duct, pancreatic neck, or superior mesenteric artery margin on microscopic examination, but margins clear of tumor on macroscopic examination]),^{17–19} primary tumor characteristics (differentiation, subtypes of AMPA [intestinal or pancreaticobiliary],⁴ perineural and lymphovascular invasion), lymph node metastases, pathologic stage based on the American Joint Committee on Cancer staging system, 7th edition,²⁰ and postoperative therapy characteristics. AMPA with mixed intestinal and pancreaticobiliary components was categorized on the basis of the predominant component.⁵ Pathologic response to preoperative therapy was systematically evaluated according to the method by Ribero et al²¹ and reported as major or minor according to the mean of the percentage of viable residual cancer cells within each tumor (major response, 0% to 49% of viable residual cancer cells; minor response, ≥50% of viable residual cancer cells).¹³ Hematoxylin-eosin stained sections were reviewed by two gastrointestinal pathologists (H.W. and J.Z.). The pathologists were blinded with respect to clinical information, treatment regimen, outcome, and the goal of the study.

Treatment

Decisions about the treatment strategy for each patient, including whether to use preoperative therapy, were made at a weekly specialty multidisciplinary conference. In general, patients were considered candidates for up-front resection when they were medically fit and able to undergo macroscopically curative resection. For patients with 1) pre-existing comorbidity, 2) disease perceived to be biologically advanced due to one or more well-defined clinical parameters (e.g., regional lymphadenopathy, advanced T stage, indeterminate liver/lung lesions), or 3) treatment of disease believed to be pancreatic ductal adenocarcinoma on the basis of existing clinical workup,^{11, 22, 23} preoperative therapy (chemotherapy alone or chemoradiation) was administered.^{11, 12, 24} Preoperative chemotherapy primarily consisted of regimens containing fluorouracil, capecitabine, or gemcitabine administered for 4 to 6 months.^{25, 26} When administered, external beam radiation was delivered using either a hypofractionated (10 fractions) or standard fractionated (28 fractions) regimen with concurrent fluorouracil, capecitabine, or gemcitabine. External beam radiation was delivered 5 days per week (Monday-Friday). CT-based three-dimensional conformal treatment planning was routinely used. Following preoperative therapy, the patient was restaged, and surgery was recommended in the absence of clinical or radiographic evidence of disease progression, the patient maintained an adequate performance status, and if a complete resection could be performed. Postoperative chemotherapy alone or chemoradiation was administered selectively based on the decision by multidisciplinary team of medical, surgical and radiation oncologists. In general, these

therapeutic modalities were recommended for patients with high risk features associated with their cancer, such as positive lymph nodes, advanced T stage, R1 margin status, poor tumor differentiation or lymphovascular/perineural invasion.¹¹ Patients were followed routinely after surgery with history, physical examination, laboratory evaluations, and axial imaging every 3 to 4 months for the first 2 years and every 4 to 6 months for the subsequent 3 years.

Statistical Analyses

Continuous variables were compared using the Wilcoxon rank-sum test, and categorical variables were compared using the χ^2 test. For the evaluation of predictors of pathologic response, univariable and multivariable analyses were performed by logistic regression analysis. Disease-specific survival (DSS) was measured from the date of resection to the date of death due to disease (DA or AMPA) or last follow-up. Patients who died of an unrelated cause were censored at the time of death. Survival curves were generated using the Kaplan-Meier method, and differences in survival were evaluated with the log-rank test. Univariable and multivariable analyses to identify predictors of DSS were performed by Cox proportional hazards regression models. Variables with $P < 0.1$ in univariable analysis were entered into each multivariable analysis. $P < 0.05$ was considered statistically significant in all analyses. Statistical analyses were performed with IBM SPSS software (version 23.0; SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

Table 1 lists the clinicopathologic and operative data for the 97 patients with DA and 169 patients with AMPA. Patients with AMPA were more likely than patients with DA to be male. In the present study period, there were 97 patients (41 with DA; 56 with AMPA) who were planned to receive preoperative therapy followed by curative resection. However, of those, 18 (7 with DA; 11 with AMPA) did not undergo planned resection due to disease progression (4 with DA; 6 with AMPA) and poor general status (3 with DA; 5 with AMPA). These 18 patients were therefore excluded from the analysis. The final study cohort exits of 79 patients treated with preoperative therapy and curative resection (34 with DA; 45 with AMPA). Among them, patients with AMPA vs. DA were more likely to receive chemoradiation and less likely to receive chemotherapy alone (Table 1). In patients with AMPA undergoing preoperative therapy followed by resection, 13% of cases (6/45) were considered preoperatively pancreatic ductal adenocarcinoma, which was significantly more frequent compared to patients with DA (0/34, $P = 0.027$).

The rate of major pathologic response after preoperative therapy did not differ significantly between patients with AMPA (64%) and DA (47%) ($P = 0.122$). There was no significant difference between the 2 groups with respect to preoperative chemotherapy regimen and duration. Among the 169 patients with AMPA, histologic subtyping (intestinal vs. pancreaticobiliary) was determined in 151 patients (89%), 35 of whom underwent preoperative therapy. There was no significant difference among patients with DA, intestinal AMPA, and pancreaticobiliary AMPA with respect to preoperative chemotherapy regimen

(Supplementary Table 1). Patients with AMPA were more likely than those with DA to undergo pancreaticoduodenectomy. Among patients with DA, pathologic stage III was predominant; among patients with AMPA, pathologic stage II was predominant.

Supplementary Table 2 lists the clinicopathologic characteristics of the patients who did (n=79) and did not undergo preoperative therapy (n=187). The patients who underwent preoperative therapy had significantly more poorly differentiated tumors. There was no other significant difference identified between the 2 groups.

Predictors of Pathologic Response

Among the 79 patients who underwent preoperative therapy, major pathologic response was observed in 45 patients (57%). Table 2 lists the results of univariable and multivariable analyses of potential predictors of major pathologic response in patients who underwent preoperative therapy. The singular independent predictor of major pathologic response was concomitant use of radiation. Among the patients with AMPA who underwent preoperative therapy, there was no significant difference in terms of rate of major pathologic response by histopathologic subtype (Table 2).

Predictors of Survival

The median follow-up duration was 57 months (range 1.0–267 months). On multivariable analysis of potential predictors of DSS after curative resection in the entire cohort (n=266), the sole independent predictor of worse DSS was pathologic stage III (Supplementary Table 3). Preoperative therapy independent of pathologic response was not a significant predictor of DSS in the entire cohort or in the subgroups of patients with DA and AMPA (Supplementary Figure 1). Similarly, presence of postoperative therapy was not a significant predictor of DSS in the entire cohort or in the subgroups of patients undergoing preoperative therapy (Supplementary Table 3 and Table 3).

However, among the 79 patients treated with preoperative therapy, DSS was significantly worse in patients with minor vs. major pathologic response (Figure 1B). Similar results were found in subgroup analyses of patients with DA (Figure 1C) and AMPA (Figure 1D). On multivariable analysis of factors associated with DSS after curative resection in patients undergoing preoperative therapy, major pathologic response was identified as the sole independent predictor of better DSS (Table 3).

Among the 187 patients without preoperative therapy, on multivariable analysis of factors associated with DSS after curative resection, absence of diabetes mellitus, R0 resection, and pathologic stage II were identified as the independent predictors of better DSS (Supplementary Table 4).

DISCUSSION

In this study, we found that among patients with DA and AMPA who underwent preoperative therapy, patients with major vs. minor pathologic response had a better 5-year DSS rate overall and in the DA and AMPA subgroups. Previous reports have shown the prognostic effects of pathologic response to preoperative therapy in patients with several

other gastrointestinal cancers,^{13–16} but to the best of our knowledge, this is the first report to show the impact of pathologic response to preoperative therapy on survival after curative resection of DA and AMPA.

We also found that in our cohort of resected DA and AMPA, concurrent radiotherapy was an independent predictor of major pathologic response among patients who underwent preoperative therapy. Previous reports have hinted towards an optimal pathological response of chemoradiation for DA and AMPA. Yeung et al reported a phase II study demonstrating the efficacy of preoperative chemoradiation for DA, which led to a resectability rate of 80% and revealed extensive necrosis and hyalinization in all cases undergoing resection.²⁷ Others have shown in patients with AMPA that downstaging secondary to preoperative chemoradiation was achieved in 67% (28%, pathologically complete response).²⁸ Further, patients with AMPA significantly more often received preoperative chemoradiation compared to patients with DA. This is in keeping with previous report suggesting a favorable chemoradiation sensitivity of AMPA.²⁸ Previous studies of unresectable biliary tract cancer suggested that chemoradiation produced better long-term outcomes than chemotherapy alone.²⁹ In recent years, a number of reports have shown the feasibility and tolerability of chemoradiation for locally advanced biliary tract cancer and DA.^{19, 30, 31} In the present study, histopathologic subtype of AMPA (intestinal or pancreaticobiliary) was not a predictor of major pathologic response to preoperative therapy. Previous studies that have addressed this topic have produced inconsistent results; some have shown that histomorphologic subtypes predict response to specific chemotherapy,^{9, 32} while others have shown no impact of subtype on chemotherapy response.^{3, 8, 33}

In the current study, on multivariable analysis of potential predictors of DSS in the entire cohort, use of preoperative therapy did not have a positive impact on prognosis, which is in line with the published literature.¹¹ However, this finding must be viewed in light of a possible selection bias: resectable patients with advanced disease were thought to possibly benefit from preoperative therapy due their comparatively higher disease burden. In fact, pathologic review of specimens following preoperative therapy and resection confirmed that poorly differentiated tumors were more common in patients with preoperative therapy compared to patients without preoperative therapy. A prospective randomized trial would provide robust evidence regarding the prognostic impact of preoperative therapy for DA and AMPA, but conducting such a trial would be challenging owing to the rarity of these diseases.^{2, 3}

Our results also suggested that the impact of traditional predictors of DSS after resection in patients with DA and AMPA might be mitigated by the effects of modern preoperative therapy. The multivariable analysis of DSS in the 187 patients without preoperative therapy identified R0 resection and pathologic stage II as the independent predictors of improved DSS. Conversely, on multivariable analysis of DSS in the 79 patients who underwent preoperative therapy, major pathologic response was the sole predictor of improved DSS instead of such traditional factors. Further research would be required to optimally choose postoperative therapy based on pathologic response to preoperative therapy rather than traditional prognosticators, which may aid clinicians in stratifying the need for postoperative therapy.

This study has several limitations. First, it is limited by its retrospective nature and associated biases, including selection bias since the analyzed cohort was limited to patients only who completed preoperative therapy followed by planned curative resection (79 of 97 [81%]). Second, histopathologic subtyping was not determined in a proportion of patients with AMPA (18/169, 11%), and the population of patients with histopathologic subtyping who were also treated with preoperative therapy was limited (n=35). Thus, our finding that histopathologic subtype of AMPA was not associated with pathologic response to preoperative therapy (Table 2) might potentially be underpowered to detect a difference. Third, our analyses grouped DA and AMPA together due to the rarity of these clinicopathologic disease entities, similar to previously published series¹⁻³. Fourth, among patients treated with preoperative therapy, patients with AMPA were less likely than patients with DA to receive chemotherapy alone and more likely than patients with DA to receive chemoradiation. The higher rate of chemoradiation in the AMPA vs. DA group may have in part been due to some AMPA having been considered to be pancreatic ductal adenocarcinoma preoperatively³⁴ and concerns regarding duodenal toxicity in concomitant radiation when treating DA³⁵. Finally, the present study did not include information concerning the genotype of tumors, including information about *KRAS* status, and also lacked information regarding microsatellite instability status. In the field of surgery for colorectal liver metastases, previous literature has demonstrated an association between mutant *KRAS* and suboptimal pathologic response to preoperative chemotherapy.³⁶ In addition, a study on AMPA³⁷ identified *KRAS* mutation as an independent predictor of poor prognosis following curative resection and others have suggested microsatellite instability was associated with improved survival in patients with AMPA and DA.^{38, 39} Further research is needed to identify biomarkers which can predict pathologic response to preoperative therapy in patients with AMPA and DA. This would not only allow patients who would benefit from preoperative therapy to be stratified towards receiving it, it would also help to avoid unnecessary preoperative therapy in patients who do not derive a survival advantage from it.

In conclusion, in patients with DA and AMPA treated with preoperative therapy followed by curative resection, pathologic response predicted postoperative DSS. Delivery of radiotherapy concurrently with preoperative chemotherapy was associated with major pathologic response. Pathologic response to preoperative therapy may be a new predictor of prognosis after resection of DA and AMPA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(A) Study population. Disease-specific survival by pathologic response to preoperative therapy in (B) all patients with duodenal adenocarcinoma (DA) and ampullary adenocarcinoma (AMPA) (n=279), (C) patients with DA (n=34), and (D) patients with AMPA (n=45).

Table 1.

Clinicopathologic characteristics of patients undergoing resection for duodenal adenocarcinoma and ampullary adenocarcinoma, 1993–2015*

Characteristic	Total	Duodenal adenocarcinoma	Ampullary adenocarcinoma	P value [†]
All patients	266	97 (36)	169 (64)	
Sex, M: F	153: 113	48: 49	105: 64	0.045
Age, y, median (range)	64 (28–88)	63 (28–88)	64 (28–88)	0.764 [‡]
Body mass index, kg/m ² , median (range)	27 (15–41)	27 (18–41)	26 (15–41)	0.631 [‡]
Diabetes mellitus	43 (16)	15 (15)	28 (17)	0.814
Preoperative therapy	79 (30)	34 (35)	45 (27)	0.148
Chemotherapy alone	12 (15)	10 (29)	2 (4.4)	0.002
Chemoradiation	67 (85)	24 (71)	43 (96)	0.002
Biologic equivalent dose, Gy, median (range)	45 (30–63)	35 (30–56)	45 (30–63)	0.908 [‡]
Chemotherapy regimen				
Fluorouracil-based	39 (49)	21 (62)	18 (40)	0.079
Capecitabine-based	37 (47)	13 (38)	24 (53)	
Gemcitabine-based	3 (3.8)	0	3 (6.7)	
Duration of preoperative chemotherapy, months, median (range)	2.7 (1.0–9.7)	2.8 (1.0–9.7)	2.7 (1.0–7.4)	0.344
Pathologic response				
Major (viable tumor 0–49%)	45 (57)	16 (47)	29 (64)	0.122
Complete (viable tumor 0%)	2 (2.5)	1 (2.9)	1 (2.2)	0.840
Minor (viable tumor 50–100%)	34 (43)	18 (53)	16 (36)	0.122
Surgical procedure				
Pancreaticoduodenectomy	250 (94)	82 (85)	168 (99)	<0.001
Other	16 (6.0)	15 (15)	1 (0.6)	
Differentiation, well/moderate/poor	17/182/67	5/67/25	12/115/42	0.816
Subclassification of ampullary carcinoma				
Intestinal type dominant	-	-	59 (35)	-
Pancreaticobiliary type dominant	-	-	92 (54)	
Undetermined	-	-	18 (11)	
Perineural invasion				
Positive/negative	131/135	49/48	82/87	0.754
Lymphovascular invasion				
Positive/negative	131/135	51/46	80/89	0.411
Surgical margin status				
R0/R1	259/7	92/5	167/2	0.057
Pathologic stage (AJCC staging system, 7th edition)				
0	8	0	8	<0.001
I	69	18	51	
II	100	33	67	

Characteristic	Total	Duodenal adenocarcinoma	Ampullary adenocarcinoma	P value [‡]
III	81	39	42	
IV	8	7	1	
Lymph node metastases				
Positive/negative	139/127	53/44	86/83	0.555
Postoperative therapy	91 (34)	30 (31)	61 (36)	0.393
Chemotherapy alone	30 (33)	10 (33)	20 (33)	0.958
Chemoradiation	61 (67)	20 (67)	41 (67)	0.958

* Values in table are number of patients (percentage) unless indicated otherwise.

[‡] χ^2 test unless indicated otherwise.

[‡] Wilcoxon rank-sum test.

AJCC, American Joint Committee on Cancer.

Table 2.

Univariable and multivariable analyses of major pathologic response in patients undergoing preoperative therapy (n=79)

Variable	n	Major pathologic response, n (%)	Univariable P value	Odds ratio (95% confidence interval)	Multivariable P value
All patients	79	45 (57)			
Sex *					
M	50	32 (64)	0.097	2.41 (0.86–7.06)	0.094
F	29	13 (45)			
Age, years *					
>60	49	32 (65)	0.056	2.74 (0.99–7.97)	0.052
60	30	13 (43)			
Body mass index, kg/m ²					
25	24	13 (54)	0.740	–	–
>25	55	32 (58)			
Diabetes mellitus					
Yes	15	9 (60)	0.792	–	–
No	64	36 (56)			
Entity					
Duodenal adenocarcinoma	34	16 (47)	0.122	–	–
Ampullary adenocarcinoma	45	29 (64)			
Subclassification of ampullary carcinoma					
Intestinal	8	5 (63)	0.724	–	–
Pancreaticobiliary	27	15 (56)			
Undetermined	10	9 (90)			
Type of preoperative therapy *					
Chemoradiation	67	43 (64)	0.002	8.17 (1.84–58.2)	0.005
Chemotherapy alone	12	2 (17)			
Preoperative chemotherapy regimen					
Fluorouracil-based					
Yes	39	21 (54)	0.581	–	–
No	40	24 (60)			
Capecitabine-based					
Yes	37	23 (62)	0.381	–	–
No	42	22 (52)			
Duration of preoperative chemotherapy					
<3	49	29 (59)	0.610	–	–
3	30	16 (53)			

* Variables entered into the multinomial logistic regression analyses.

Table 3.

Univariable and multivariable analysis of disease-specific survival in patients treated with preoperative therapy (n=79)

Variable	N	Disease-specific survival (%) [*]			Hazard ratio (95% confidence interval)	Multivariable P value [‡]
		3 years	5 years	Univariable P value [†]		
All patients	79	68	60	-	-	-
Sex						
M	50	70	62	0.305	-	-
F	29	65	57			
Age, years						
60	30	62	62	0.660	-	-
>60	49	72	60			
Body mass index, kg/m ²						
25	24	58	58	0.269	-	-
>25	55	73	61			
Diabetes mellitus						
Yes	15	65	65	0.958	-	-
No	64	69	60			
Entity						
Duodenal adenocarcinoma	34	62	45	0.246	-	-
Ampullary adenocarcinoma	45	73	70			
Type of preoperative therapy						
Chemotherapy alone	12	74	74	0.936	-	-
Chemoradiation	67	68	59			
Preoperative chemotherapy regimen						
Fluorouracil-based						
Yes	39	71	59	0.715	-	-
No	40	65	62			
Capecitabine-based						
Yes	37	65	61	0.604	-	-
No	42	71	59			
Duration of preoperative chemotherapy, months						
<3	49	74	67	0.122	-	-
3	30	59	48			
Pathologic response to preoperative therapy [§]						
Minor (viable tumor 50-100%)	34	42	34	<0.001	2.88 (1.41-5.98)	0.004
Major (viable tumor 0-49%)	45	86	79			
Differentiation						
Well/moderate	50	77	67	0.246	-	-
Poor	29	52	48			
Perineural invasion						

Variable	N	Disease-specific survival (%) [*]			Hazard ratio (95% confidence interval)	Multivariable P value [‡]
		3 years	5 years	Univariable P value [†]		
Yes	33	69	69	0.780	-	-
No	46	68	55			
Lymphovascular invasion						
Yes	35	64	60	0.962	-	-
No	44	72	61			
Lymph node metastases						
Yes	35	64	56	0.857	-	-
No	44	72	64			
Surgical margin status						
R1	2	100	0	0.832	-	-
R0	77	67	61			
Pathologic stage (AJCC staging system, 7th edition) [§]						
III	28	52	47	0.052	1.30 (0.63-2.65)	0.467
II	51	77	68			
Postoperative chemotherapy alone						
Yes	5	60	60	0.910	-	-
No	74	69	60			
Postoperative chemoradiation						
Yes	16	66	66	0.800	-	-
No	63	69	60			
Postoperative therapy						
Yes	21	65	65	0.886	-	-
No	58	70	60			

* Kaplan-Meier analysis.

[†] Log-rank test.

[‡] Cox regression model.

[§] Variables entered into the Cox regression model.

AJCC, American Joint Committee on Cancer.