Survival Predictors of Patients With Primary Duodenal Adenocarcinoma

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This single-institution experience retrospectively reviewed the outcomes in 21 patients with primary duodenal adenocarcinoma. Twelve patients underwent curative surgery, and 9 patients underwent palliative surgery at the Chiba University Hospital. The maximum follow-up period was 8650 days. All pathologic specimens from endoscopic biopsy and surgical specimens were reviewed and categorized. Twelve (57.1%) patients underwent curative surgery (R0): 4 pancreaticoduodenectomies (PD), 4 pylorus-preserving PDs (PpPD), 2 local resections of the duodenum and 2 endoscopic mucosal resections (EMR). Palliative surgery was performed for 9 patients (42.9%) following gastro-intestinal bypass. The median cause-specific survival times were 1784 days (range 160–8650 days) in the curative surgery group and 261 days (range 27–857 days) in the palliative surgery group (*P* = 0.0003, log-rank test). The resectability of primary duodenal adenocarcinoma was associated with a smaller tumor size, a lower degree of tumor depth invasiveness, and less spread to the lymph nodes and distant organs.

Key words: Duodenum – Cancer – Duodenectomy – Adenocarcinoma – Prognosis

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Primary adenocarcinoma of the duodenum is an uncommon disease, representing less than 0.5% of gastrointestinal malignancies and approximately 45% of small intestine adenocarcinomas.[1] Although nodal metastases, margins of resection, and depth of invasion are of prognostic importance in many malignant neoplasms, these factors have not consistently been shown to be of prognostic significance for patients with duodenal adenocarcinoma. The prognosis for patients with curatively resected duodenal adenocarcinoma is relatively better (5-year survival, 60%)[2] than for patients with ampullary carcinoma (46%),[3] distal bile duct (27%),[4] or cancer in the head of pancreas (10%).[5] The development of radiologic and endoscopic examination has led to an increased identification of earlier stages of duodenal cancer, but the oncogenic characteristics of primary duodenal cancer remain poorly understood. We herein demonstrate the outcomes of 21 patients with primary duodenal adenocarcinoma who were analyzed to clarify the predictive factors of patient survival.

Methods and patients

Patients

A total of 21 patients were retrospectively identified from the database of the Chiba University Hospital from October 1977 to July 2007. A total of 12 patients underwent curative surgery, and 9 patients who were admitted and underwent palliative surgery were pathologically or clinically diagnosed with duodenal adenocarcinoma.

Clinical presentation

The preoperative diagnosis was based on preoperative imaging studies, including an upper gastrointestinal X-ray series, gastro-intestinal endoscopy, percutaneous transhepatic cholangiography, magnetic resonance cholangiopancreatography, and conventional cross-sectional imaging studies [computed tomography (CT) and magnetic resonance imaging (MRI)]. The patients' medical records were reviewed for clinical symptoms, surgical procedures, and long-term outcome. Survival time was considered to be from the day of surgery to the day of death or the most recent follow-up visit or telephone questionnaire for survival, which were performed in March 2010. Patients who underwent palliative surgery were considered to be the control group for comparison with the curative surgery group.

Table 1   *Patients and treatment characteristics of 21 patients with duodenal adenocarcinoma*

	Number of patients (%)
Gender (male)	11 (52.4%)
Symptoms	
Epigastralgia	8 (38.1%)
Appetite loss	3 (14.3%)
Anemia	3 (14.3%)
Jaundice	3 (14.3%)
Hematemesis, vomiting	2 (9.5%)
Other symptoms	2 (9.5%)
Treatment	
Curative surgery	12 (57.1%)
PD	4 (33.3%)
PpPD	4 (33.3%)
PR	2 (16.7%)
EMR	2 (16.7%)
Palliation	9 (42.9%)
Bypass	9 (100%)

EMR, endoscopic mucosal resection; PD, pancreaticoduodenectomy; PpPD, pyrolus-preserving PD; PR, partial resection of duodenum; SD, standard deviation.

Cancer staging

The patient data were classified by the International Union Against Cancer (UICC) TNM Classification of Malignant Tumors of the small intestine by clinical or pathologic diagnoses (ICD-O C17.0).[6]

Statistical analysis

The results are expressed as the mean ± SD for the age of patients. Fisher exact probability test was used to compare categorical variables. The overall survival curves and the univariate analysis were evaluated by the Kaplan-Meier method. Comparisons of curves were analyzed using the log-rank test with 95% confidential interval (CI). Differences with P values of less than 0.05 were considered to be statistically significant. All the statistical analyses were carried out using the JMP software program, version 8.0.2. (SAS Inc, Cary, North Carolina).

Results

Comparison of clinicopathologic features

The mean age of the patients at the time of admission was 61.19 years of age, and 11 male subjects and 10 female subjects were evaluated in the present study. The initial patient symptoms included epigastralgia, appetite loss, anemia, jaundice, hematemesis, and vomiting, as well as others (Table 1).

Table 2 The comparison of tumor characteristics between patients who underwent curative resection and those who had palliative surgery

	Curative	Palliation	P value
Tumor location			
1st/2nd	10	7	1.000[a]
3rd/4th	2	2	
Tumor size			
<5 cm	8	1	0.024[a]
≥5 cm	4	8	
Tumor depth			
T1/T2	6	0	0.019[a]
T3/T4	6	9	
LN metastasis			
N0	6	0	0.019[a]
N1/N2	6	9	
Distant metastasis			
M0	11	0	<0.0001[a]
M1	1	9	
Tumor differentiation			
Well/mod	8	2	0.592[a]
Other types	4	3	
(Unknown)	0	4	

LN, lymph node; Well/mod, well or moderately differentiated adenocarcinoma.

[a]Fisher exact probability test.

Treatment procedures for duodenal adenocarcinoma

Surgical procedures were used to examine the invasiveness or metastasis of duodenal adenocarcinoma. Pancreaticoduodenectomy (PD) and pylorus-preserving PD (PpPD) were performed for patients with advanced carcinoma, and local resection was carried out in patients with less invasive cancers. Endoscopic mucosal resection (EMR) was performed for early-stage cancers that remained within the mucosal layer without lymph node (LN) metastasis. Twelve (57.1%) patients underwent curative resection (R0): 4 PDs, 4 PpPDs, 2 local resections of the duodenum, and 2 EMRs. A curative resection included T3/T4 (50%) and N2-positive tumors (16.7%). One portal vein reconstruction and one local colectomy were included in PD or PpPD. Palliative surgery was performed in 9 patients (42.9%), including a gastro-intestinal bypass for advanced cancers with infiltration and distant metastasis. From the pathologic diagnoses, all curative resections were found to be R0 (Table 1).

From the aspect of curative or palliative surgery, the results of the clinicopathologic features between the 2 groups are shown in Table 2. The tumor size, depth, LN metastasis and distant metastasis were found to be statistically significant between the

curative resection group and palliation surgery group ($P = 0.024$, $P = 0.019$, $P = 0.0186$, $P < 0.0001$, respectively, using Fisher exact probability test). The 12 curative resections indicated 8 well-to-moderately differentiated adenocarcinomas, but 4 palliative surgery patients had tumors that could not be identified according to the tissue differentiation type.

Survival after surgical resection

The mean survival rates of all patients with primary duodenal adenocarcinoma at 1, 3, and 5 years post-surgery were 66.2%, 48.2%, and 38.6%, respectively. The mean survival rates of the 12 patients who underwent curative surgery were 84.2%, 72.9%, and 65.7%, and the survival rates of the 9 patients who underwent palliative surgery were 24.9%, 1.0%, and 0.00029% at 1, 3, and 5 postoperative years, respectively.

The 21 patients include 7 patients who are alive without recurrence (median survival 3434 days; range 523–8650 days), 13 patients who died with recurrence (median survival 278 days; range 27–857 days), and 1 patient who died of another disease without recurrence (survival 2548 days), including 1 mortality within 30 days after palliative surgery (4.8%).

Cause-specific survival curves

The survival curves for the curative and palliative surgery groups are shown in Fig. 1. The median cause-specific survival times calculated using the Kaplan-Meier method were 1784 days (range 160–8650 days) in the 12 patients of the curative surgery group and 261 days (range 27–857 days) in the 9 patients of the palliative surgery group. The curative surgery group exhibited significantly better survival rates compared with the palliative surgery group ($P = 0.0003$, log-rank test).

The factors predictive of survival in 21 patients with primary duodenal adenocarcinoma

The tumor size ($P = 0.007$), tumor depth ($P = 0.007$), tumor differentiation ($P = 0.010$), and LN metastasis ($P = 0.009$) were found to significantly and negatively impact survival according to the univariate analysis (Table 3).

Factors affecting survival of 12 patients with curative surgery

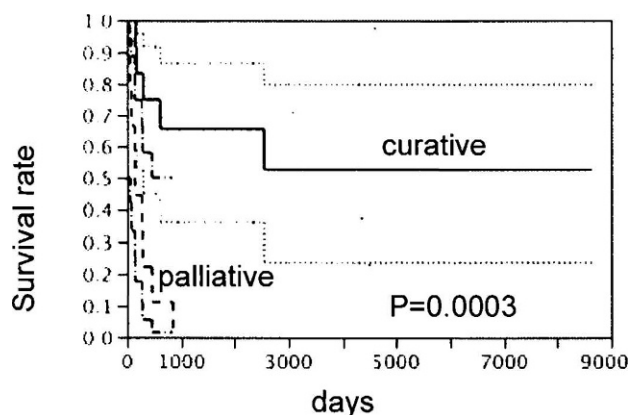PD, PpPD, partial resection of the duodenum, and EMR were performed in 4, 4, 2, and 2 patients,

Fig. 1 Kaplan-Meier survival curves in patients undergoing resection, with the overall survival defined from the time of the initial examination. Patients undergoing curative resection (n = 12, median survival 1784 days, range 160–8650 days) and palliative surgery (n = 9, median survival 261 days, range 27–857 months; $P = 0.0003$) were compared. Continuous line: Curative surgery group; dotted line: 95% confidential interval (CI) of curative surgery group; dashed line: palliative surgery group; long dashed dotted line: 95% CI of palliative surgery group.

respectively. A total of 4 male subjects and 8 female subjects were examined. The factors affecting survival of curative surgery are indicated in Table 4. In this group, the gender, tumor location, tumor size, macroscopic appearance, tumor depth, pancreas invasion, lymphatic vessel invasion, blood vessel invasion, LN metastasis, and surgical procedure did not significantly impact survival. The age and tumor differentiation factors only impacted overall survival ($P < 0.05$, log-rank test).

Discussion

The duodenum is anatomically located in the retroperitoneum. This anatomic characteristic complicates the treatment for duodenal cancer and leads to infiltrate in the pancreatic parenchyma directly and through retroperitoneal spaces.[7,8]

The primary patient symptoms are vague and not specific (epigastralgia, 38.1%; appetite loss, 14.3%), and the upper gastro-intestinal (GI) examinations by radiologic and endoscopic procedures may be useful for the prompt examination and earlier diagnosis of early-stage duodenal adenocarcinoma.[9]

Complete resection remains the only option for curability, but it is not always feasible in patients with locally advanced tumors or when tumors have invaded the retroperitoneal spaces. PD is the only appropriate operation to achieve complete resection when a tumor is located in the second portion of the duodenum. In the present study, curative resection was performed for 12 patients with duodenal cancer, and 4 PD and 4 PpPD resections were performed without mortality.

Several authors have suggested that duodenal adenocarcinomas should be treated by PD[1,10,11] because regional lymph nodes are most thoroughly extirpated by this method. Although it is difficult to perform a well-defined regional lymphadenectomy in the area owing to reduced duodenal mesentery, the removal of all periduodenal soft tissues removes an adequate number of lymph nodes in the majority of patients. For tumors located in the first, third, or

Table 3   *Univariate analysis of the factors affecting the survival of 21 patients with primary duodenal adenocarcinoma*

Factor	Category	Number of patients	5-year survival rate (%)	P value[a]
Age	<60	7	62.17	0.184
	≥60	14	22.71	
Gender	Male	11	22.25	0.265
	Female	10	52.33	
Tumor location	1st/2nd	17	33.95	0.450
	3rd/4th	4	56.51	
Tumor size	<5 cm	9	72.09	0.007
	≥5 cm	12	5.18	
Macroscopic type	Elevated	6	47.14	0.098
	Ulcerative	15	29.90	
Tumor depth	T1/T2	8	76.34	0.007
	T3/T4	13	18.57	
Tumor differentiation	Well/mod	10	72.76	0.010
	Other	7	7.55	
	(Unknown)	4	0.00	
LN metastasis	No	6	84.65	0.009
	Yes	15	21.99	

LN, lymph node metastasis; well/mod, well or moderately differentiated adenocarcinoma; other, exception of well/mod.

[a]P value, log-rank test.

Table 4   Univariate analysis of the factors affecting the survival of 12 patients with curative resections

Factor	Category	Number of patients	5-year survival rate (%)	P value[a]
Age	<60	8	100	0.043
	≥60	4	42.45	
Gender	Male	4	75.35	0.519
	Female	8	61.71	
Tumor location	1st/2nd	10	57.49	0.200
	3rd/4th	2	100	
Tumor size	<4 cm	8	79.27	0.123
	≥4 cm	4	23.44	
Macroscopic type	Elevated	6	65.86	0.886
	Ulcerative	6	65.20	
Tumor depth	T1/T2	6	83.34	0.223
	T3/T4	6	53.53	
Tumor differentiation	Well/mod	8	91.55	0.004
	Other	4	13.06	
Pancreas invasion	No	8	77.60	0.250
	Yes	4	45.40	
Lymphatic vessel invasion	No	5	80.45	0.318
	Yes	7	57.22	
Blood vessel invasion	No	8	82.22	0.070
	Yes	4	32.65	
LN metastasis	No	6	84.65	0.129
	Yes	6	49.49	
Surgery procedure	EMR/PR	4	100	0.066
	PD/PpPD	8	59.12	

EMR, endoscopic mucosal resection; LN, lymph node; Other, except of well/mod; PD, pancreaticoduodenectomy; PpPD, pyrolus-preserving PD; PR, partial resection of duodenum; Well/mod, well and moderately differentiated adenocarcinoma.

[a]P value, log-rank test.

fourth portions of the duodenum, a curative resection may be accomplished by removing the affected regional tissue. Several authors have reported excellent survival and considerably lowered postoperative mortality and morbidity following segmental resection.[2,7] However, it has been argued that a segmental resection results in inadequate resection margins and incomplete regional lymphadenectomy.[12] In the present study, 2 patients (9.5%) successfully underwent a local resection of the third portion of the duodenum, and 8 patients (38.1%) underwent PD/PpPD. In light of this potential limitation, PD/PpPD has been suggested as a standard approach to primary duodenal cancer, regardless of the primary site of the tumor.[13]

However, primary duodenal adenocarcinoma may be diagnosed at an advanced tumor stage, which results in a low local excision rate. Surgical palliation continues to play an important role in the management of periampullary carcinoma.[14] In the present study, palliative surgery was performed in 9 patients (42.9%). Surgical palliation can be accomplished with an acceptable perioperative mortality and morbidity with excellent long-term results.

There is general agreement that patients with resectable duodenal adenocarcinomas achieve better survival times than those with unresectable tumors.[1,15–18] In the present study, the resectability rate was 57.1%; other reported resectability rates ranged from 43% to 87%.[1,2,8,13,15,17,19] The survival figures for patients who undergo resection also vary widely. Several recent series have reported 5-year survival rates ranging from 25% to 44.1% in patients who have undergone curative resection.[2,8,15,17,19–21] In our study, the survival after curative surgery (R0) was good, with 3- and 5-year survival rates of 72.9% and 65.7%, respectively, which are consistent with the 5-year survival rates of published series even though our rate was in the range of the other studies. Moreover, the survival was significantly higher in patients who underwent curative surgery (median survival 1784 days, range 160–8650 days) than for those who underwent palliative resection (median survival 261 days, range 27–857 days) (P = 0.0003, log-rank test).

It has been reported that palliative surgery is not compatible with survival at 5 years.[2,20,22,23] The 1- and 3-year survival rates of the present 9 patients who underwent palliative surgery were 24.9% and 1.0%, respectively. In the present study, the resectability was found to be associated with a better survival rate in patients with duodenal adenocarci-

noma, thus indicating that an aggressive surgical approach that achieves complete tumor resection should be pursued whenever possible. Distant metastasis and local invasion are the main contraindications to curative surgery.

Regional LN metastases have been reported in 43% to 64.3%[8,24] of tumors, which is consistent with the present findings (52.3%). Rose et al[2] performed wide-ranging lymphadenectomies and achieved a 5-year survival rate of 43% in patients with a positive node. Therefore, a combination of PD/PpPD with wide-ranging lymphadenectomy may be appropriate for the detection of LN metastasis. Sarela et al[24] demonstrated that improved survival can be achieved for patients diagnosed early with no nodal involvement. In our study, the presence of LN involvement did not contribute to survival for curative resection ($P = 0.129$, Table 4). However, distant LN metastasis was more significant with palliative surgery than curative surgery ($P = 0.009$, Table 3). A randomized prospective trial is therefore warranted in the future to evaluate the ability of extended lymphadenectomy to increase patient survival rates. We were unable to demonstrate that this treatment confers a survival benefit and emphasize that the statistical analysis suffers from many limitations (nonrandomized, potential selection bias, and inadequate numbers), thus precluding a statistically powerful and reliable analysis.

The present study indicates that the 5-year survival rates of patients after a curative resection are favorable, but the respectability (R0) of patients with primary duodenal adenocarcinoma was not efficient. An increased resectability of primary duodenal adenocarcinoma, the ability to diagnose tumors at earlier stages, and radical resection are therefore considered to be essential predictors for the overall patient survival.

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