

15-Year Experience with Surgical Treatment of Duodenal Carcinoma: a Comparison of Periapillary and Extra-Ampillary Duodenal Carcinomas

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Abstract

Background The aim of our study was to compare the outcomes of periampillary and extra-ampillary duodenal adenocarcinomas and segmental duodenal resection versus pancreatoduodenectomy and to evaluate prognostic factors.

Methods We performed a retrospective review of all adults treated for duodenal adenocarcinoma by operative resection at a large tertiary referral center from 1994 to 2009.

Results One hundred twenty-four patients had an operation for duodenal adenocarcinoma over a 15-year period (periampillary, $n=25$, and extra-ampillary, $n=99$). Ninety-nine patients (80%) underwent curative resection, including 24 (96%) with periampillary and 75 (76%) with extra-ampillary carcinomas. The average number of lymph nodes sampled was eight with segmental resection and 12 with pancreatoduodenectomy ($p<0.001$). Five-year overall survivals were 37% for the entire cohort ($n=124$), 37% in the extra-ampillary group, and 38% in the periampillary group. Tumor size ($p=0.20$), positive nodes ($p=0.60$), segmental resection versus pancreatoduodenectomy ($p=0.55$), adjuvant therapy ($p=0.23$), and R₁ versus R₀ resection ($p=0.21$) were not associated with survival. In contrast, advanced T stage and pathologic grade were associated with poor survival.

Conclusion Extra-ampillary and periampillary duodenal adenocarcinomas have similar survival after resection. For distal duodenal tumors, survival is improved by curative resection without being compromised by limited resection. The number of lymph nodes sampled was significantly less with segmental resection than pancreatoduodenectomy.

Keywords Duodenal adenocarcinoma · Periapillary carcinoma · Extra-ampillary carcinoma · Segmental resection · Pancreatoduodenectomy

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Introduction

Duodenal adenocarcinoma remains a rare malignancy that constitutes 0.4% of gastrointestinal malignancies but 45% of all small bowel adenocarcinomas.¹ Despite advancements in techniques of diagnosis and resection and decreased perioperative mortality and morbidity, 5-year survival is only 45–55%.^{1–3} Due to the rarity of the disease, reports are limited to small, single institution studies, and as a result, inconsistencies remain regarding the importance of various prognostic factors, including nodal status, margin status, grade of tumor, extent of resection, and use of adjuvant treatment. Thus, aggressive operative resection remains the mainstay of effective treatment.^{3,4} Experience at our institution with duodenal adenocarcinoma is similar with resectability rates of up to 67%,⁵ consistent with reported resectability rates of 43% to 87%.⁶

Periampullary and extra-ampullary duodenal adenocarcinomas have often been grouped together, and previously, periampullary duodenal adenocarcinomas were believed to have the same prognosis as other periampullary malignancies.^{7–9} Currently, however, some investigators maintain that the individual subtypes of periampullary malignancies confer different long-term prognoses, and therefore, authors have argued that they should be considered as distinct entities.⁴ In addition, controversy exists as to whether there is a prognostic difference in patients with tumors in the first and second portions of the duodenum (D1–2) not confined to the periampullary region versus distal tumors in the third and fourth portions of the duodenum (D3–4).^{3,10,11} This controversy concerning prognosis is perhaps due to the necessity of the extent of resection and nodal drainage basins in tumors located more proximally in the duodenum compared to those more distally located. Whether these two groups have significant differences both in clinical presentation and in terms of survival are yet to be defined. We hypothesized that periampullary duodenal adenocarcinomas are associated with better survival than extra-ampullary duodenal adenomas, whereas segmental duodenal resection for duodenal adenocarcinoma is associated with worse survival than pancreatoduodenectomy. Therefore, we sought to evaluate the results of operative treatment of this patient population in our large tertiary referral practice. In addition, we sought to compare the clinical features, prognostic factors, and outcomes in overall survival (OS) in patients with periampullary and extra-ampullary duodenal adenocarcinomas.

Materials and methods

With the approval from the Mayo Clinic Institutional Review Board, we reviewed all resected duodenal adenocarcinomas from January 1994 to January 2009 at Mayo Clinic, Rochester, MN, excluding all adenocarcinomas

arising within the ampulla of Vater, pancreas, distal bile duct, stomach, and jejunum and all non-adenocarcinomas of the duodenum. The patients were divided into the following two groups:

1. Duodenal adenocarcinomas arising in the periampullary duodenum (D2) within 2 cm of the ampulla of Vater or that were classified as such by the surgeon in agreement with the pathologist (periamp-DA group).
2. Extra-ampullary duodenal adenocarcinomas defined as those located greater than 2 cm from the ampulla of Vater (extraamp-DA group).

Tumor location was based on the four parts of the duodenum (D1–4). Only patients with periampullary and extra-ampullary tumors that were confirmed on histopathology to be duodenal adenocarcinoma were included in the study. Data abstracted included patient demographic information, clinical presentation, clinical stage, treatment, 30-day postoperative morbidity and mortality, and outcome after nonoperative therapeutic modalities. Relevant medical diagnoses, such as celiac sprue, familial adenomatous polyposis coli, and Lynch syndrome, were noted. Pathologic characteristics were used to stage the tumors according to the 2010 TNM system of the combined American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system.¹² Postoperative pancreatic leak/fistula was defined according to the International Study Group on Pancreatic Fistula Definition recommendations as a drain output of any measurable volume of fluid on or after postoperative day 3 with an amylase content greater than three times the serum amylase activity.¹³ Delayed gastric emptying was defined according to the International Study Group of Pancreatic Surgery guidelines.¹⁴ Postoperative tumor markers and computed tomography (CT) were used as surveillance in follow-up for evidence of cancer recurrence.

Descriptive statistics are reported as number (percentage) or mean and standard deviation as appropriate. Survival was estimated using the Kaplan–Meier method, reporting the estimate and 95% confidence interval (CI). Univariate associations of variables with patient survival were assessed using Cox proportional hazards regression, reporting the hazard ratio and 95% confidence interval. The alpha level was set at 0.05 for statistical significance.

Results

Demographics

Our study found 124 patients with duodenal adenocarcinoma who were explored for potential resection from January

1994 to January 2009. There were 75 males (59%) and 49 females (41%); the overall mean age was 65 years (range 33–87 years). Of the 124 patients, there were 25 patients with periamp-DA and 99 patients with extraamp-DA. The mean age-to-sex ratio of these patients was similar to the overall cohort (Table 1).

In the entire cohort, the most common clinical features were epigastric pain (23%), duodenal obstruction (18%), symptomatic anemia (15%), anorexia with weight loss (12%), obstructive jaundice (10%), and gastrointestinal bleeding (10%). The clinical presentation was, however, somewhat different for the periamp-DA and extraamp-DA. For periamp-DA, obstructive jaundice was more common than in extraamp-DA (24% versus 6%), while duodenal obstruction was less common (4% versus 21%) (Table 1). For the diagnosis, the majority (90%) was diagnosed by endoscopy, but CT played an important role in both diagnosis and staging.

Operative treatment

Of the 124 patients, 99 (80%) underwent curative resection, including 24 (96%) of the 25 patients with periamp-DA and 75 (76%) of the 99 with extraamp-DA. The type of resection was determined by location of the tumor: proximal duodenal lesions (D1 and D2) were treated with a pancreatoduodenectomy, while the more distal lesions (D3 and D4) were treated with segmental duodenal resection except for two patients with D3 tumors who underwent pylorus preserving pancreatoduodenectomy due to local invasion of the pancreas (Table 2).

Curative resection

Overall, of those undergoing curative resection, 70 patients (71%) underwent pancreatoduodenectomy, with 36 (51%) undergoing a classic resection and 34 (49%) undergoing a pylorus-preserving resection. Twenty-eight patients (28%) underwent segmental duodenal resection, and one patient with a D2 lesion underwent a transduodenal resection (Table 2). In the periamp-DA group, 24 patients (96%) underwent pancreatoduodenectomy. In the extraamp-DA group, 46 patients (61%) underwent pancreatoduodenectomy (all but two had D1 and D2 lesions), while 28 patients (37%) with D3 and D4 cancers underwent segmental duodenal resection (Tables 1 and 2).

Palliative procedures

Overall, 25 patients were managed by non-resectional, palliative operative treatment. In the periamp-DA group, 1 of 25 patients found to have unresectable disease related to vascular invasion and retroperitoneal infiltration was managed with

biliary and duodenal bypasses. In the extraamp-DA group, 24 of 99 patients had unresectable disease related to unrecognized distant disease to the liver and retroperitoneum (14 patients), superior mesenteric artery invasion (six patients), or peritoneal carcinomatosis (four patients). These patients were managed by some form of duodenal bypass.

Pathologic characteristics

In the entire cohort of 124 patients, the tumor locations were as follows: D1—8 patients (6%), D2—73 patients (59%), D3—24 patients (19%), and D4—15 patients (12%). Two patients had tumors at the junction of D1 and D2, one at the junction of D2 and D3, and two at the junction of D3 and D4 (Table 2).

The average tumor size for the entire cohort was 4.1 cm (range 0.2 to 10 cm) with an average size of 4.0 cm in the periamp-DA group and 4.2 cm in the extraamp-DA group. Of all those patients who underwent curative resection, 52 patients (52%) had lymph node-positive disease with the average number of lymph nodes evaluated of 11 (range 1–36) and an average number of positive lymph nodes of 2 (range 0–12). In the periamp-DA group, the average number of lymph nodes evaluated was 11 (range 1–36), while the average number of positive lymph nodes was 2 (range 0–12). In the extraamp-DA group, the average number of lymph nodes evaluated was 10 (range 0–46), while the average number of positive lymph nodes was 1 (range 0–9). For those patients undergoing a segmental resection for D3 and D4 neoplasms, the average number of lymph nodes evaluated was 8 (range 0–46) and the average number of positive nodes was 1 (range 0–6). In contrast, for patients undergoing pancreatoduodenectomy, the average number of lymph nodes evaluated was 12 (range 1–43) and the average number of positive nodes was 2 (range 0–12) ($p < 0.001$). Six patients had an R₁ resection, while 93 had an R₀ resection (Table 1). Of the 124 patients, 79 (64%) had grade 3 tumors, 27 (22%) had grade 2, and 15 (12%) had grade 4 tumors. Six patients had T1 tumors, 10 had T2, 47 had T3, and 41 had T4 tumors. Three patients were found to have metastatic disease not evident on preoperative staging. Nine patients were determined histopathologically to be stage 1, 55 patients to be stage 2, 38 patients to be stage 3, and 22 patients to be stage 4 disease (Table 1). The distribution of these pathologic characteristics was similar among patients in the periamp-DA and extraamp-DA groups. In the periamp-DA group, the majority of patients had grades 2 (32%) and 3 (48%) tumors, T3 (36%) and T4 (40%) lesions, and stages 2 (24%), 3 (32%) and 4 disease (28%). In the extraamp-DA group, the majority of patients had grades 2 (19%) and 3 (67%) lesions, T3 (38%) and T4 (31%) lesions, and stages 2 (49%) and 3 (30%) disease (Table 1).

Table 1 Patient and tumor characteristics and comparison of periampullary and extra-ampullary duodenal adenocarcinomas

Patient/tumor characteristics		Periampullary adenocarcinoma (n=25) n (%)	Extra-ampullary adenocarcinoma (n=99) n (%)	p value	All patients (n=124) n (%)
Sex (male)		15 (60)	60 (61)		75 (59)
Clinical presentation					
Asymptomatic		4 (16)	3 (3)		7 (6)
Anorexia with weight loss		3 (12)	12 (12)		15 (12)
Duodenal obstruction		1 (4)	21 (21)		22 (18)
Epigastric pain/discomfort		4 (16)	24 (24)		28 (23)
Gastric outlet obstruction		1 (4)	10 (10)		11 (9)
GI bleeding		2 (8)	10 (10)		12 (10)
HNPCC associated		2 (8)	5 (5)		7 (6)
Obstructive jaundice		6 (24)	6 (6)		12 (10)
Palpable mass		0	1 (1)		1 (1)
Symptomatic anemia		4 (16)	15 (15)		19 (15)
Operative procedure					
Whipple resection	PD	11 (44)	25 (25)		36 (29)
	PPPD	13 (52)	21 (21)	0.55	34 (27)
Segmental resection ^a		0	28 (28)		28 (23)
Transduodenal resection		0	1 (1)		1 (1)
Total pancreatectomy		0	0		0
Palliation		1 (4)	24 (24)		25 (20)
Grade					
1		0	0		0
2		8 (32)	19 (19)		27 (22)
3		12 (48)	67 (67)	0.002	79 (64)
4		4 (16)	11 (11)		15 (12)
Not evaluated		1 (4)	2 (2)		3 (2)
T stage					
0		0	0		0
1		2 (8)	4 (4)		6 (5)
2		3 (12)	7 (7)		10 (8)
3		9 (36)	38 (38)	<0.001	47 (38)
4		10 (40)	31 (31)		41 (33)
Not evaluated		1 (4)	19 (19)		20 (16)
Size of lesion					
<3 cm		5 (20)	14 (14)		19 (15)
3–4 cm		13 (52)	25 (25)	0.20	38 (31)
>4 cm		7 (28)	33 (33)		40 (32)
Missing		0	27 (27)		27 (22)
Nodal stage					
Negative (N0)		10 (40)	39 (39)	0.60	49 (40)
Positive (N1)		14 (56)	38 (38)		52 (42)
Not sampled		1 (4)	22 (22)		23 (19)
Stage ^b					
0 (Tis, N0, M0)		0	0		0
1 (T1 or T2, N0, M0)		4 (16)	5 (5)		9 (7)
2 (T3 or T4, N0, M0)		6 (24)	49 (49)		55 (44)
3 (Any T, N1 or N2, M0)		8 (32)	30 (30)		38 (31)
4 (Any T, any N, M1)		7 (28)	15 (15)		22 (18)
Margin status	R0	23 (92)	70 (71)	0.21	93
	R1	1 (4)	5 (5)		6

PD pancreaticoduodenectomy, PPPD pylorus-preserving pancreaticoduodenectomy, TP total pancreatectomy

^a All but one were located in D3 or D4

^b Staging according the 2010 TNM system of the combined AJCC/UICC system

Table 2 Tumor characteristics and operative treatment of duodenal adenocarcinoma by tumor location

	No. of patients (<i>n</i> =124)	D1 (<i>n</i> =8)	D2 peri-amp-DA (<i>n</i> =25)	D2 extraamp-DA (<i>n</i> =58)	D3 (<i>n</i> =23)	D4 (<i>n</i> =15)
Grade						
1	0	0	0	0	0	0
2	26	1	8	8	8	1
3	69	6	12	34	8	9
4	16	1	4	4	5	2
Nodal status						
Negative (N0)	44	2	10	15	10	7
Positive (N1)	46	3	14	20	5	4
T stage						
T1	6	0	2	3	1	0
T2	9	2	3	3	1	0
T3	44	0	10	12	13	9
T4	39	4	10	18	3	2
Margins						
R1	6	0	1	3	1	1
R0	87	5	23	34	15	10
Type of surgery						
PPPD	33	0	13	18	^a 2	0
PD	35	4	10	21	0	0
Segmental resection	28	1	0	0	14	13
Palliative bypass	24	3	12		7	2

PD pancreaticoduodenectomy, PPPD pylorus-preserving PD

^a Both had D3 tumors invading the pancreas and the colon mesentery

Morbidity and mortality

In the entire cohort, the overall morbidity rate was 46%. Sixty-four percent of patients in the periamp-DA group and 41% of patients in the extraamp-DA group had postoperative complications. The most common complication (24%) after operation in the entire cohort was delayed gastric emptying. In the periamp-DA group, delayed gastric emptying occurred in those patients who underwent either a standard pancreatoduodenectomy (50%) or pylorus-preserving resection (50%). Other complications in this group included wound infection in 16% of patients, intraabdominal hemorrhage in 12%, and pancreatic leak in 12%. In the extraamp-DA group, delayed gastric emptying (8%) and pancreatic leaks (6%) were the most common complications. Of the patients who had delayed gastric emptying, five (63%) had pancreatoduodenectomy, two (25%) had segmental duodenal resection, and one patient had a palliative bypass. Other clinically relevant complications occurring in the extraamp-DA group included enteric anastomotic leaks (9%), acute renal failure (5%), and cardiac complications (5%). Of the patients who underwent segmental duodenal resection (*n*=28), four (14%) had anastomotic leaks.

Overall in-hospital mortality for the entire cohort was 1.6% with both deaths occurring in the extraamp-DA group

(mortality rate of 2%). One death occurred due to intractable postoperative hemorrhage. The second death was due to disseminated disease and large tumor burden.

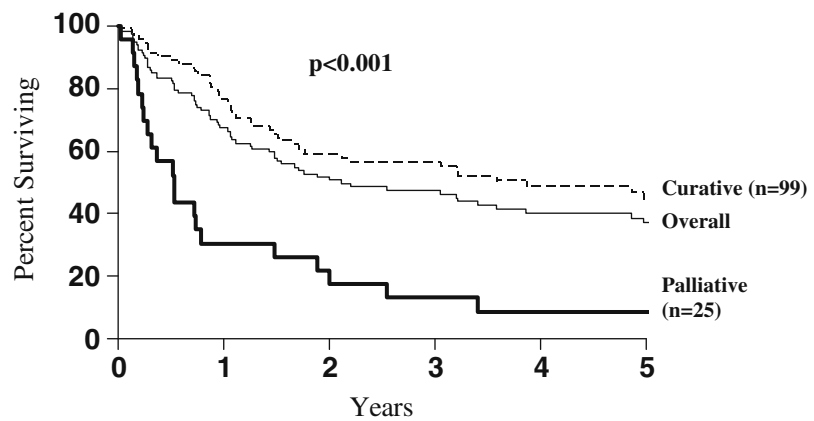
Adjuvant therapy

A total of 30 patients received adjuvant therapy in the entire cohort. Eight of these had periampullary duodenal tumors and 22 had extra-ampullary tumors. There was no difference in survival between patients who received adjuvant therapy and those who did not (*p*=0.23; HR 0.7).

Survival

The overall estimate for OS at 5 years for the entire cohort of 124 patients was 37% (95% CI, 28–48) (Fig. 1). The 5-year OS rates were 37% in the extraamp-DA group and 38% periamp-DA group. Lymph node involvement (N₁ versus N₀) (*p*=0.60) and margin status (R₁ versus R₀) (*p*=0.21) had no association with overall survival (Fig. 5a, b). In contrast, advanced tumor (T) stage (*p*<0.001) and advanced pathologic grade (*p*=0.002) were associated with poor survival (Fig. 5c, d). Importantly, there was no association of tumor location (periamp-DA versus extraamp-DA) and survival (*p*=0.77) (Fig. 2). Patients with a D1 tumor, however, when compared

Fig. 1 Overall estimate for OS at 5 years



to patients with a D2 tumor had an increased risk of death, (hazard ratio=2.6, 95% CI 1.1–6.2, $p=0.03$). There was no association with overall survival between patients with tumors in the first and second portions of the duodenum compared to those with tumors in the third and fourth portions of the duodenum ($p=0.58$, hazard ratio 1.2, 95% CI 0.7–2.0) (Fig. 3).

In the entire cohort, patients who had resectable tumors had 2-, 5-, and 10-year survival rates of 59%, 43%, and 39%, respectively, with a median survival of 3.2 years, while the unresectable group had 2- and 5-year survival rates of 30% and 15%, respectively, with a median survival of 6.4 months. As expected, patients undergoing curative resection when compared to patients undergoing palliative resection had better survival ($p < 0.001$ HR=0.3, 95% CI 0.2–0.4) (Fig. 1). Five- and 10-year survival estimates in patients who had segmental resection and those who had pancreaticoduodenectomy were 52% ($p=0.55$) and 43% ($p=0.55$) in the segmental group and 42% and 38% in the pancreaticoduodenectomy group, respectively ($p=0.50$) (Fig. 4).

Regarding association with survival, tumor size ($p=0.20$; HR=1.1 per 1 mm), positive nodal status ($p=0.60$; HR=1.2), extent of resection (segmental versus pancreaticoduodenectomy) ($p=0.55$; HR=1.3), adjuvant therapy ($p=0.23$;

HR 0.7), and R₁ versus R₀ resection ($p=0.21$; HR=2.0) were not associated with survival (Fig. 5). Patients who had a blood transfusion had no increased risk of death (hazard ratio=1.7, 95% CI of 0.7 to 4.2, p value=0.25).

Recurrence

Among the 99 patients who underwent a “curative” resection in the entire cohort, 30 patients developed recurrences, with a 5-year survival of 54% (95% CI 41–69). Of these, seven recurrences were identified among the 24 patients who had curative resection for periamp-DA group with a 5-year survival of 52%, while there were 23 recurrences identified among the curative resections in patients in the extraamp-DA group with a 5-year survival of 55%. In the periamp-DA group, four patients (57%) had loco-regional recurrence only, while three (43%) had distant metastases. In the extraamp-DA group, 16 (67%) recurred loco-regionally, 7 (29%) recurred distant, and 1 (4%) patient recurred locally and distant.

Discussion

Duodenal adenocarcinoma, though itself a rare disease, constitutes 35–50% of all the small bowel adenocarcinomas.¹⁵ The rarity of duodenal adenocarcinoma and small patient numbers have resulted in conflicting data regarding the impact on survival of the location of duodenal adenocarcinoma, extent of operative resection, and lymph node involvement by tumor. As a result, controversy persists in the literature in these areas. Similar to published literature,^{4,6,16} the second part of the duodenum was the most common site (59%) of duodenal adenocarcinoma in our study. Located on the medial wall of the second part of the duodenum, the periampullary area has been defined previously as the area within 2 cm of the ampullary of Vater¹⁵ with periampullary duodenal adenocarcinoma constituting 6–10% of all tumors in this area.¹⁵³ In the current

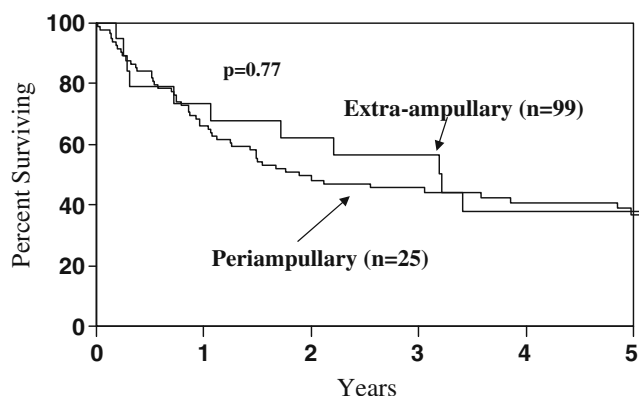
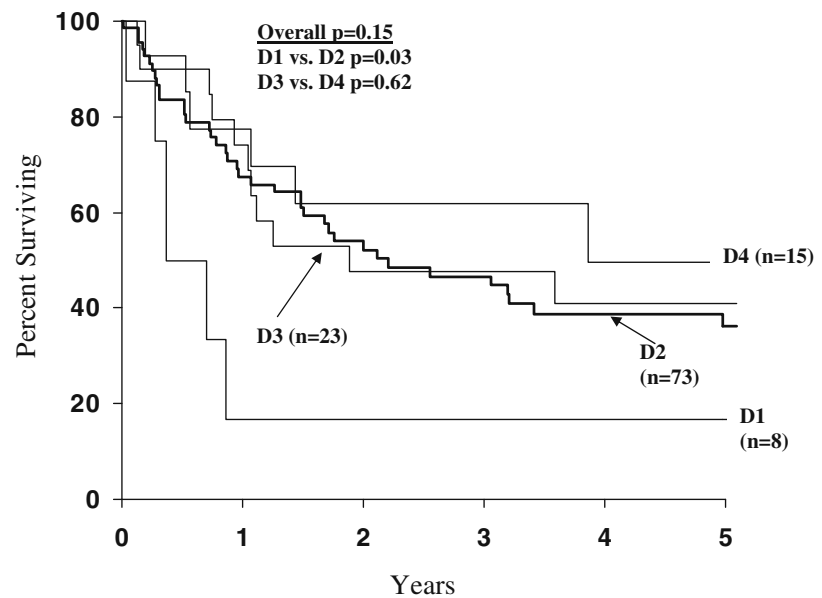


Fig. 2 Association of tumor location and survival

Fig. 3 Overall survival between patients with tumors in the first and second portions of the duodenum compared to those with tumors in the third and fourth portions of the duodenum



series, we looked specifically at periampullary duodenal carcinomas which were defined either as such by the surgeon and pathologist or as tumors within 2 cm of the ampulla of Vater because previous authors have reported that the location of duodenal adenocarcinoma affects survival.^{3,10,11} Our hypothesis was that periampullary duodenal carcinoma would have a better survival because of an earlier presentation with jaundice and more complete lymphadenectomy. The results in the literature have been conflicting with longer survivals being reported with both proximal (D1 and D2)^{3,10} and distal (D3 and D4) duodenal tumors.¹¹ Other authors, however, have not found a statistically significant difference in survival based on the location of duodenal tumor.^{17–19} In the current series, we found that there was no significant difference in survival based on tumor location in the four parts of the duodenum, proximal (D1 and D2) tumors versus distal (D3 and D4) tumors, and periampullary versus extra-ampullary tumors, although

there was an increased risk of death in patients with tumors in D1 when compared to D2.

The optimal extent of resection for duodenal adenocarcinoma remains a matter of debate. Not surprisingly, in our study and prior series, resectable duodenal cancer is associated with greater survival than unresectable tumors, and to date, resection is the only hope for cure for duodenal adenocarcinoma. Some authors have recommended pancreatoduodenectomy even for distal cancers located in D3 and D4 arguing that pancreatoduodenectomy is the procedure that satisfies the oncologic principles of adequate curative resection of duodenal adenocarcinoma by a concomitant en bloc lymphadenectomy^{3,16,20}; lymphadenectomy cannot be achieved with duodenal segmentectomy, however given that the duodenal mesentery is very short and the lymphatic drainage of the duodenum is via the superior mesenteric, celiac, and inferior mesenteric systems, the latter two being systems which are not removed during duodenal segmentectomy.^{16,21}

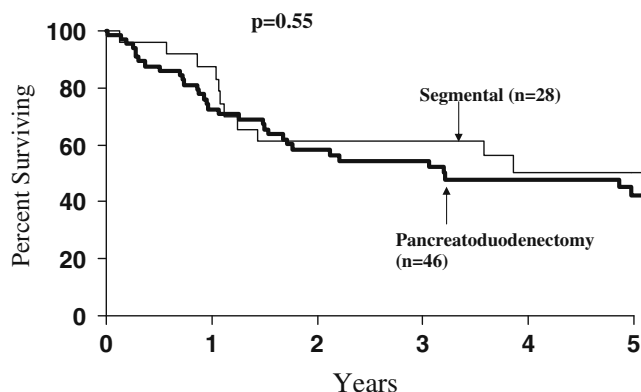
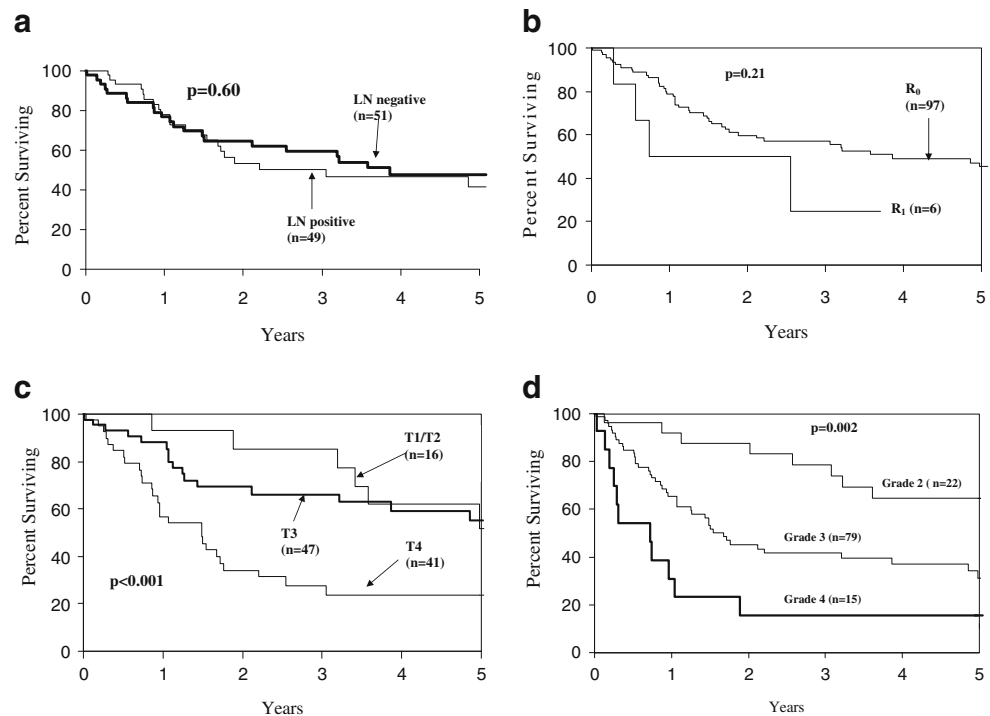


Fig. 4 Five- and 10-year survival estimates in patients who had segmental resection and those who had pancreatoduodenectomy

In contrast, others have reported that there is no demonstrable adverse effect on survival when comparing segmental resection to pancreatoduodenectomy.^{5,22} Tocchi et al. reported that segmental resection with intestinal derotation is adequate therapy for distal duodenal carcinomas and is associated with much less morbidity and mortality as compared to pancreatoduodenectomy.¹⁷ Bakaaen et al. also reported no adverse effect on survival with segmental resection of distal tumors because much of the lymphatic drainage of these distal portions of the duodenum is into the small bowel mesentery and only as a secondary level of lymphatic drainage along the superior mesenteric artery; lymphatic drainage from D3 and D4 lesions is not into the pancreatoduodenal basin and thus a pancreatoduodenectomy would, in theory, offer little added advantage.⁵ Kaklamanos et al.

Fig. 5 Lymph node involvement (a), margin status (b), tumor stage (c), and tumor grade (d) association with overall survival



found that the number of lymph nodes removed during segmentectomy was similar to that removed during pancreatoduodenectomy.²³ In the current study, we report that survival was improved by curative resection without being compromised by limited resection instead of pancreatoduodenectomy for distal (D3 and D4) tumors. In our series, 92% of patients with resectable distal tumors underwent segmental resection; only two (8%) patients underwent pancreatoduodenectomy because of local invasion into the pancreas. Segmental resection has been our procedure of choice because the extent of resection appears to be of a lesser importance in D3 and D4 cancers as long as an R₀ resection can be achieved. The number of lymph nodes sampled with segmental duodenal resection was less compared to pancreatoduodenectomy ($p < 0.001$).

Duodenal adenocarcinomas often present at a large size due to the vague nature of the clinical symptoms. The average size at presentation as reported in literature is at least 4 cm, as reported by Lee et al. and Sohn et al., who found that the average tumor size was 4.4 and 4.6 cm, respectively.^{3,6} Our study reported a similar finding. Larger tumor size, however, did not appear to affect resectability or survival of otherwise clinically resectable lesions. Hurtuk et al. have previously shown that size is not a determinant of resectability of duodenal adenocarcinoma; their results actually suggest that the smaller tumors at the time of presentation tend to be more aggressive than larger tumors.⁴

Given the location, the majority of these tumors appear to present early with symptoms consisting of pain, obstructive jaundice, upper gastrointestinal obstruction, gastrointestinal

bleeding with anemia, or anorexia and weight loss. Thus, most clinical tumors are resectable at presentation.

Historically, our resectability rate was 67%.⁵ Our current resectability rates for extra-ampullary and periampullary duodenal carcinoma are 73% and 96%, respectively. These rates are congruent with published literature with resectability rates ranging from 43% to 87%.^{6,16,18,19,24} This increase in resectability for “clinically resectable” neoplasms is secondary to the early development of symptoms, specifically in patients with periampullary tumors as well as the more widespread use of upper endoscopy and CT. Seventy-two percent of periampullary tumors and 84% of extra-ampullary tumors were detected at an early stage before distant metastasis had developed.

In-hospital mortality rate was low at 0–2% in both groups, a finding similar to prior studies.⁶ In contrast, extended operative resection with formal lymphadenectomy was associated with substantial morbidity, especially for patients undergoing operation for periampullary duodenal carcinomas who had a postoperative complication rate of up to 64% compared to 41% complications rate in patients with extra-ampullary duodenal carcinomas. The latter group, however, suffered more serious complications, including major cardiac complications, intraabdominal hemorrhage, anastomotic leaks, and thromboembolic events.

Literature regarding the prognostic effect of lymph node status has yielded conflicting results. Multiple series have shown that nodal metastases are associated with a poor prognosis and decreased survival.^{5,6,25} In contrast, other authors have shown that nodal status has no significant

impact on survival.¹⁹ In our study, lymph node involvement had no significant impact on survival (45% for negative nodes versus 52% for positive nodes). Failure of our study and others to show a prognostic effect of nodal status may be due to an inadequate number of lymph nodes sampled and examined. The AJCC fifth edition requires examination of at least six regional lymph nodes for assignment of the pN category (pN0, no nodal metastasis, and pN1, nodal metastasis present).²⁴ Sarela et al. demonstrated that after an R₀ resection of duodenal adenocarcinoma, examination of 15 lymph nodes resulted in improved prognostic discrimination by the pN category. He attributed such improvement in prognostic accuracy to a stage migration effect. Patients with accurately staged pN0 duodenal adenocarcinoma had excellent survival rates.²⁴ In contrast, pN1 disease was associated with a 5-year survival of 47%.²⁴

The median number of lymph nodes in the resected specimen in our study was similar between periampullary duodenal carcinoma and extra-ampullary duodenal carcinoma (11 nodes versus 10 nodes). Margin status (R₀ versus R₁) also had no significant effect on survival, but only six patients had positive margins making this comparison unreliable. In contrast to nodal involvement and margin status, pathologic grade and advanced tumor stage were associated with a significant decrease in survival in our study.

Despite the advances in the chemotherapeutic and surgical treatment of duodenal carcinoma, recurrence rates have changed only by a small margin. Since the prior review by Bakaeen et al. from our institution from 1976 to 1996, at which time a recurrence rate of 37% was found within a median period of 1.3 years after potentially curative resection, the recurrence rates have only decreased to 29% to 32% in the current series.

The rarity of duodenal adenocarcinoma and small patient numbers remain the limiting factors in most published studies on this disease. Our collective 75-year experience with a total of 329 patients provides the largest series to date.

Conclusion

Duodenal adenocarcinoma is a highly resectable malignancy. Most duodenal adenocarcinomas are situated away from the ampulla and tend to present as larger tumors and at an early stage with a slight male preponderance. The second portion of the duodenum is the most common site, away from the ampulla. Non-curative resection, higher pathologic grade, and advanced T stage are associated with poor prognosis, while tumor size, nodal status, location of the tumor, extent of resection, and margin status did not have a significant impact on prognosis and survival. Survival is improved by curative resection without being compromised by limited resection for D3 and D4 tumors. We were not

able to show a difference in survival with tumors associated with nodal metastases and positive margins, but the sample size was small.

Aggressive resection remains the most effective treatment modality with segmental resection being the treatment of choice for distal duodenal adenocarcinoma. Even though resection is associated with substantial morbidity, hospital mortality is low, and 5-year survival approaches 55%.

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References

1. Struck A, Howard T, Chiorean EG, Clarke JM, Riffenburgh R, Cardenas HR (2009) Non-ampullary duodenal adenocarcinoma: factors important for relapse and survival. *J Surg Oncol* 100:144–148
2. Howe JR, Karnell LH, Menck HR, Scott-Conner C (1999) The American College of Surgeons Commission on Cancer and the American Cancer Society. Adenocarcinoma of the small bowel: review of the National Cancer Data Base, 1985–1995. *Cancer* 86:2693–2706
3. Sohn TA, Lillmoie KD, Cameron JL, Pitt HA, Kaufman HS, Hruban RH, Yeo CJ (1998) Adenocarcinoma of the duodenum: factors influencing long-term survival. *Journal of gastrointestinal surgery: official journal of the Society for Surgery of the Alimentary Tract* 2:79–87
4. Hurtuk MG, Devata S, Brown KM, Oshima K, Aranha GV, Pickleman J, Shoup M (2007) Should all patients with duodenal adenocarcinoma be considered for aggressive surgical resection? *American journal of surgery* 193:319–324; discussion 324–315
5. Bakaeen FG, Murr MM, Sarr MG, Thompson GB, Farnell MB, Nagorney DM, Farley DR, van Heerden JA, Wiersema LM, Schleck CD, Donohue JH (2000) What prognostic factors are important in duodenal adenocarcinoma? *Arch Surg* 135:635–641; discussion 641–632
6. Lee HG, You DD, Paik KY, Heo JS, Choi SH, Choi DW (2008) Prognostic factors for primary duodenal adenocarcinoma. *World J Surg* 32:2246–2252
7. Pickleman J, Koelsch M, Chejfec G (1997) Node-positive duodenal carcinoma is curable. *Archives of surgery* 132:241–244
8. Sexe RB, Wade TP, Virgo KS, Johnson FE (1996) Incidence and treatment of periampullary duodenal cancer in the U.S. veteran patient population. *Cancer* 77:251–254
9. Wade TP, Coplin MA, Virgo KS, Johnson FE (1994) Periampullary cancer treatment in U.S. Department of Veterans Affairs hospitals: 1987–1991. *Surgery* 116:819–825; discussion 825–816
10. Stell D, Mayer D, Mirza D, Buckels J (2004) Delayed diagnosis and lower resection rate of adenocarcinoma of the distal duodenum. *Dig Surg* 21:434–438; discussion 438–439
11. Lowell JA, Rossi RL, Munson JL, Braasch JW (1992) Primary adenocarcinoma of third and fourth portions of duodenum. Favorable prognosis after resection. *Archives of surgery* 127:557–560
12. Edge SB, Compton CC (2010) The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Annals of surgical oncology* 17:1471–1474
13. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, Neoptolemos J, Sarr M, Traverso W, Buchler M (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 138:8–13

14. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR, Neoptolemos JP, Padbury RT, Sarr MG, Traverso LW, Yeo CJ, Buchler MW (2007) Delayed gastric emptying (DGE) after pancreatic surgery: a suggested definition by the International Study Group of Pancreatic Surgery (ISGPS). *Surgery* 142:761–768
15. Ross WA, Bismar MM (2004) Evaluation and management of periampullary tumors. *Curr Gastroenterol Rep* 6:362–370
16. Solej M, D'Amico S, Brondino G, Ferronato M, Nano M (2008) Primary duodenal adenocarcinoma. *Tumori* 94:779–786
17. Tocchi A, Mazzoni G, Puma F, Miccini M, Cassini D, Bettelli E, Tagliacozzo S (2003) Adenocarcinoma of the third and fourth portions of the duodenum: results of surgical treatment. *Archives of surgery* 138:80–85
18. Hu JX, Miao XY, Zhong DW, Dai WD, Liu W, Hu W (2006) Surgical treatment of primary duodenal adenocarcinoma. *Hepato-gastroenterology* 53:858–862
19. Ryder NM, Ko CY, Hines OJ, Gloor B, Reber HA (2000) Primary duodenal adenocarcinoma: a 40-year experience. *Archives of surgery* 135:1070–1074; discussion 1074–1075
20. Delcore R, Thomas JH, Forster J, Hermreck AS (1993) Improving resectability and survival in patients with primary duodenal carcinoma. *American journal of surgery* 166:626–630; discussion 630–621
21. Barnes G, Jr., Romero L, Hess KR, Curley SA (1994) Primary adenocarcinoma of the duodenum: management and survival in 67 patients. *Ann Surg Oncol* 1:73–78
22. Han SL, Cheng J, Zhou HZ, Zeng QQ, Lan SH (2010) The surgical treatment and outcome for primary duodenal adenocarcinoma. *J Gastrointest Cancer* 41:243–247
23. Kaklamanos IG, Bathe OF, Franceschi D, Camarda C, Levi J, Livingstone AS (2000) Extent of resection in the management of duodenal adenocarcinoma. *Am J Surg* 179:37–41
24. Sarela AI, Brennan MF, Karpeh MS, Klimstra D, Conlon KC (2004) Adenocarcinoma of the duodenum: importance of accurate lymph node staging and similarity in outcome to gastric cancer. *Annals of surgical oncology* 11:380–386
25. Joesting DR, Beart RW Jr, van Heerden JA, Weiland LH (1981) Improving survival in adenocarcinoma of the duodenum. *Am J Surg* 141:228–231