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Duodenal Adenocarcinoma: The Relationship between Type of Surgery and Site of Recurrence in a Spanish Cohort

Gerardo Blanco-Fernández [1,2,3], Daniel Aparicio-López [4], Celia Villodre [5,6], Isabel Jaén-Torrejimeno [1,2], Cándido F Alcázar López [5,6], Diego López-Guerra [1,2,3], Mario Serradilla-Martín [7,8,9,*] and José M. Ramia [5,6]

1 Department of Surgery, Hospital Universitario de Badajoz, 06080 Badajoz, Spain; gerardoblanco@unex.es (G.B.-F.); isabel.jaen@salud-juntaex.es (I.J.-T.); diegolopezg@unex.es (D.L.-G.)
2 INUBE: Instituto Universitario de Investigación Biosanitaria de Extremadura, 06006 Badajoz, Spain
3 Facultad de Medicina y Ciencias de la Salud, Universidad de Extremadura, 06006 Badajoz, Spain
4 Department of Surgery, Hospital Universitario Miguel Servet, 50009 Zaragoza, Spain; dapariciol@salud.aragon.es
5 Department of Surgery, Hospital General Universitario Doctor Balmis, 03010 Alicante, Spain; cvillodre@umh.es (C.V.); alcazar_can@gva.es (C.F.A.L.); ramia_jos@gva.es (J.M.R.)
6 ISABIAL: Instituto de Investigación Sanitaria y Biomédica, 03010 Alicante, Spain
7 Department of Surgery, Hospital Universitario Virgen de las Nieves, 18014 Granada, Spain
8 ibs.GRANADA: Instituto de Investigación Biosanitaria, 18012 Granada, Spain
9 School of Medicine, University of Granada, 18016 Granada, Spain
* Correspondence: mserradilla@ugr.es; Tel.: +34-636006184

Abstract: We present a multicenter retrospective study of patients undergoing surgery for duodenal adenocarcinoma, from January 2010 to August 2020, in order to determine the epidemiological characteristics and the oncological results after surgical resection obtained in this rare tumor. Variables: demographics; tumor location; surgical intervention and immediate postoperative period; and post-surgical follow-up information, such as recurrence, overall survival (OS), and disease-free survival (DFS). A total of 32 patients underwent surgery. The median age was 69.74 years (IQR 60.47–79.09) and the male/female distribution was 3:1. The surgeries performed were: pancreaticoduodenectomy (PD) in 16 (50%) patients, segmental resection in 13 (40.6%), and the local excision of the lesion in three (9.4%). The R0 rate was higher in PD (86.7% vs. 42.9%; $p = 0.013$). The OS and DFS rate at one, three and five years was 95%, 70%, and 60% and 86%, 55%, and 48%, respectively. There was a greater trend towards recurrence in patients who did not undergo PD (53.8% vs. 25%; $p = 0.14$) and conservative surgery seemed to be associated with more local recurrence than PD (57.1% vs. 33.3%; $p = 0.49$). PD and limited resection are both valid options in the cases of non-ampullary duodenal adenocarcinoma, although PD presented lower rates of loco-regional recurrence.

Keywords: adenocarcinoma; duodenum; surgery

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1. Introduction

Though a rare event [1], proximal (duodenal) adenocarcinoma is the most frequent tumor in the small bowel and accounts for 45% of all tumors in this region [2,3]. Duodenal cancer presents an increasing incidence. The number of cases of duodenal cancer diagnosed in North America is 3.0–3.7 per million population and in Europe 2.9–4.3 per million population [4–8]. In contrast, the incidence in Eastern countries is higher. According to data from the National Cancer Registry of Japan, in 2016 there was an extremely high incidence of 23.7 per million population [9].

Although the prognosis of duodenal adenocarcinomas is unfavorable and up to 25% of the cases are not resectable at the time of diagnosis [10], surgical treatment offers the possibility of a cure. Given the variety of locations, the surgical approaches available range from local excision to pancreatoduodenectomy (PD) [11].

The possible relationship between the type of the surgery and the site of recurrence in non-ampullary duodenal adenocarcinomas has not been studied in detail. The potential advantage of performing duodenal resection with pancreatic preservation is to avoid the complications of PD; however, the theoretical risk of this type of procedure is a higher rate of incomplete resections and a lower number of nodes removed. This could translate into a higher rate of local recurrence.

Here, we present a multicenter series from three hospitals in Spain in order to determine the epidemiological characteristics of this rare tumor and the oncological results after surgical resection obtained.

2. Materials and Methods

This is a retrospective study of patients undergoing surgery for duodenal tumors, from January 2010 to August 2020. The study was carried out at the Hepato-Pancreato-Biliary Surgery Departments of three university hospitals in Spain.

Patients with any duodenal cancer undergoing surgery with a final pathological diagnosis of adenocarcinoma were considered suitable for inclusion in the study. Patients with a secondary duodenal infiltration of adenocarcinoma of a different origin, such as the stomach, the pancreas, or the colon, were excluded.

Each participating center appointed a local manager to carry out the data collection and to liaise with the overall study coordinator. All the data were collected by this local manager. Researchers collected data from the electronic health records, and the project coordinator had access to medical data only. The study was approved by the Research Ethics Committee of the Hospital Universitario de Badajoz (Number Id: 27102020) and confirmed by the Research Ethics Committee of the other two hospitals. Patients' informed consent was not required since the study was retrospective and observational, and entailed no risk.

2.1. Preoperative Assessment

Diagnostic management included the establishment of a medical history and performance of clinical examination and imaging tests, including endoscopic exploration to confirm the tumor's origin and growth. To ensure that we were not dealing with ampullary cancer, during the endoscopy it was verified that the ampulla of Vater was free of tumor. Likewise, patients underwent an abdominal CT scan of the abdomen to ensure that it was not a pancreatic tumor as well as rule out any infiltration of the adjacent structures. In case of doubt, abdominal MRI was also performed. These tests also ruled out distant metastases and allowed us to assess resectability and the option of reconstruction according to the location. Prior to the intervention, the procedures of both conservative surgery and PD were explained to all patients, given that the final decision on the type of surgery to be performed might be altered by the intraoperative findings.

2.2. Definitions

The type of surgery performed was defined as PD using the Whipple technique in all cases [12], segmental resection, when a duodenal segment was resected with later intestinal anastomosis [13], or otherwise local excision.

The resection margins of the surgical specimen were categorized according to the definitions of the Royal College of Pathologists: R0 (margin to the tumor $\geq$ 1 mm), R1 (margin to the tumor < 1 mm), and R2 (macroscopically positive margin) [14]. Invasive tumors were staged according to the TNM Classification, 7th Ed. (TNM) [15]. Complications were assessed at 90 days using the Clavien–Dindo (CD) classification, and those defined as CD $\geq$ IIIa were considered major [16]. For the recording of complications, the medical and nursing notes of the electronic histories of each patient were consulted. For the specific complications of the pancreatic surgery, the definitions of the International Study Group on Pancreatic Surgery (ISGPS) of the delayed gastric emptying [17], post-pancreatic hemorrhage [18], bile leak [19], and pancreatic fistula [20] were used.

Follow up scheme: Long-term patient follow-up included physical examination, the determination of tumor markers (carcinoembryonic antigen [CEA] and carbohydrate antigen [CA] 19.9), and chest–abdomen–pelvis CT scan: every three months for the first two years, twice a year up to five years, and then annually. Local recurrence was defined as the reappearance of a tumor within the surgical field or regional lymph nodes, while systemic recurrence was defined as recurrent disease elsewhere.

2.3. Variables

The following variables were studied: epidemiological: age, sex, past medical history, medication, the American Society of Anesthesiologists (ASA) Classification; clinical: symptoms; diagnostic: Serological tests: hemoglobin (gr/dL), bilirubin (mg/dL), albumin (g/dL), ALT (U/L), AST (U/L), calcium (mg/dL), CEA (ng/mL), and CA 19-9 (U/mL); radiological and endoscopic diagnostic tests performed, preoperative biliary drainage if necessary, and preoperative biopsy. Surgical approach: the type of the resection and reconstruction, and intraoperative complications were recorded. The following details of the postoperative course were collected: morbidity and mortality according to the CD classification, re-operation, hospital length of stay, re-admission, and operative mortality (up to 90 days after operation). The histological data retrieved were TNM: tumor size and lymph nodes harvested, R status, and the degree of differentiation. Among the key long-term data recorded were the administration of chemotherapy and/or radiotherapy, the time of relapse, disease-free and overall survival, the cause of death, and postoperative follow-up (in months).

2.4. Statistical Analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were tested for Gaussian distribution by the Shapiro–Wilk test; those with normal distribution were presented as means and standard deviations (SD), and non-normal variables were reported as median and interquartile range (IR). Chi-squared analysis or Fisher's exact probability test was used to compare categorical variables. Non-parametric tests were used to compare medians. The Kaplan–Meier survival analysis was performed to model all-cause mortality and relapse-free survival from the day of surgery. The Cox proportional hazards model was used to assess the effect of the study variables in both univariate and multivariate survival analyses.

Data were analyzed using IBM SPSS v22.0. The level of significance was set at 0.05.

3. Results

During the study period, 32 patients with a diagnosis of duodenal adenocarcinoma underwent surgery (Table 1). The median age was 69.74 years (IQR 60.47–79.09) and the male/female distribution was 3:1 (24 men and 8 women). The most common symptoms at the time of diagnosis were constitutional syndrome in seven patients, vomiting in six, and gastrointestinal bleeding also in six; other less frequent symptoms were jaundice, pain, and anemia (Table 1).

CT scan was performed as a complementary test in all patients, while abdominal MRI and endoscopic ultrasound were performed in seven and two patients, respectively. Preoperative biopsy was obtained in 29 (90.6%) cases. Tumor site was the first duodenal portion in three patients (9.4%), second portion in fourteen (43.8%), third portion in six cases (18.8%), and fourth portion in the remaining nine (28.1%).

Four patients required preoperative biliary drainage. Mean laboratory test values were as follows: total bilirubin 69.74 (IQR 60.47–79.09) mg/dL; serum albumin 3.38 $\pm$ 0.78 g/dL; AST 22 IU (IQR 16–30) U/L; and ALT 28 UI (IQR 12–40) U/L. As regards tumor markers, only 8 of the 24 patients (33.3%) for whom preoperative determinations were available presented high figures. The surgeries performed were as follows: PD in 16 (50%) patients, segmental resection in 13 (40.6%), and the local excision of the lesion in 3 (9.4%). As for postoperative evolution, 65.7% of the patients presented complications (43.8% major) (Table 2).

Table 1. Demographic, neoplasm, and surveillance data.

N No.	Sex	Age (yr)	ASA	Location [a]	Type of Surgery [b]	Dindo–Clavien	PF [c]	AL [d]	R [e]	Size (cm)	TNM	LN [f]	Relapse	OS [g]	DFS [h]	Status [i]
1	M	79	3	D1	DS	No	--	No	R0	3.5	T1bNxM0	0/0	No	7.6	7.6	ANED
2	M	76	3	D2	PD	V	C	--	R0	4.7	T3bN1M0	1/13	--	0.4	0.4	
3	M	72	3	D3	PD	II	No	--	R0	2	T1bN0M0	0/1	No	4.4	4.4	ANED
4	M	66	2	D4	DS	No	--	No	R1	2	T4N0M0	0/1	No	1	1	ANED
5	M	66	2	D2	PD	Iva	C	--	R0	5	T3N0M0	0/20	Yes, jejunum	22.5	25.9	AWD
6	M	73	3	D2	PD	IIIa	Bc	--	R0	7	T1bN0M0	0/16	No	8.1	8.1	ANED
7	M	78	2	D2	PD	V	C	--	R0	3	T3N0M0	0/20	--	0.8	0.8	--
8	M	51	2	D2	DS	IIIa	--	Yes	R0		TisNxM0	0/0	No	26.8	26.8	ANED
9	F	81	2	D2	PD	V	B	--	R0	4	T2N0M0	0/8	--	0.5	0.5	--
10	M	68	2	D1	PD	V	No	--	R0	6	T4N1M0	2/11	--	0.8	0.8	--
11	M	44	1	D2	PD	No	No	--	R0	3	T3N1M0	2/28	No	69.5	69.5	ANED
12	M	49	2	D2	PD	IIIb	No	--	R0	3.50	TisN0M0	0/7	No	103.1	61.1	DND
13	M	68	3	D2	PD	I	Bc	--	R0	2.5	T1aN0M0	0/8	No	61.7	61.7	ANED
14	F	46	2	D2	PD	I	Bc	--	R0	5.3	T3N1M0	3/19	No	56.5	56.5	ANED
15	M	76	3	D4	DS	V	--	Yes	R1	2.9	T4NxM0	0/0	--	1.1	1.1	--
16	M	80	2	D3	DS	No	--	No	R1	3.4	T3N2M0	4/5	Yes, duodenum	16.8	11.3	DOD
17	M	34	1	D4	LR	V	--	--	R1	7	T3N1M0	2/3	--	0.03	0.03	--
18	F	81	3	D4	DS	No	--	No	R0	2	T3N0M0	0/1	No	26.2	26.2	ANED
19	F	44	1	D2	DS	II	--	No	R0	2	T4N0Mx	0/13	Yes, peritoneal and liver	35.4	32.3	AWD
20	M	76	3	D1	PD	IIIa	B	--	R0	3.5	T2N0M0	0/11	No	41.6	41.6	ANED
21	M	80	3	D3	LR	V	--	--	R1	2.8	T3NxM0	0/0	--	0.3	0.3	--
22	M	79	2	D2	LR	No	--	--	R1	1.7	T3NxM0	0/0	yes, retroperi-toneal nodes	16.9	16.3	DOD
23	M	77	2	D4	DS	IIIa	--	No	R1	3.2	T3N1M0	3/9	Yes, nodal, liver, and bone	23.5	18.3	DOD
24	M	63	1	D3	DS	I	--	No	R0	1.50	T3NxM0	0/0	Yes, pancreatic	52.7	42	DOD
25	F	79	2	D4	DS	No	--	No	R1	2.5	T3N0M0	0/4	Yes, liver	24.2	7.2	DOD
26	M	62	2	D4	DS	IIIb	--	No	R0	3	T3N0M0	0/1	No	92.9	92.9	ANED
27	M	63	2	D3	PD	I	Bc	--	R1	3.5	T4NxM0	0/0	Yes, liver and lung	22.6	12.7	DOD
28	F	59	2	D4	DS	No	--	No	R0	9.5	T3N0M0	0/10	No	55.5	55.5	ANED
29	M	63	3	D4	DS	No	--	No	R1	2.6	T3N1M0	1/12	Yes, locorregional nodes	33.4	24.4	AWD
30	F	59	3	D2	PD	No	No	--	R0	8	T2N1M0	3/22	No	31.8	31.8	ANED
31	F	67	3	D3	PD	No	No	--	R1	9	T2N2M0	9/25	No	22.7	22.7	ANED
32	M	71	3	D2	PD	I	No	--	R0	3.5	T3N2M0	3/20	Yes, bone	9.2	5.2	DOD

[a] Location of tumor: D1 first part of duodenum (superior duodenal flexure); D2 second part (descending part); D3 third part (inferior duodenal flexure); D4 fourth part of duodenum (ascending part). [b] Type of surgery: PD: pancreaticoduodenectomy; DS: duodenal segmentectomy; LR: lesion resection. [c] PF: pancreatic fistula; Bc: biochemical leak. [d] AL: anastomotic leak. [e] R: resection margin status. [f] LN: involved lymph nodes. [g] OS: overall survival. [h] DFS: disease free survival. [i] Status: AWD, alive with disease; DOD, death of disease; ANED, alive no evidence of disease; DND, death no disease. -- not applicable.

Table 2. Differences between the two groups according to the type of the surgery.

	Total (n = 32)	**Conservative (n = 16)**	**PD (n = 16)**	***p* Value**
Sex	M: 24 (75%) F: 8 (25%)	M: 12 (75%) F: 4 (25%)	M: 12 (75%) F: 4 (25%)	1
Age (median)	69.74 (IQR 60.47–79.09)	71.34 (IQR 60.4–79.85)	69.74 (IQR 60.66–76.50)	0.946
ASA	ASA 1: 4 (12.5%) ASA 2: 15 (46.9%) ASA 3: 13 (40.6%)	3 (18.8%) 8 (50%) 5 (31.3%)	1 (6.3%) 7 (43.8%) 8 (50%)	0.390
Kind of symptoms [a]	Vomits: 6 (18.8%) UGIB: 6 (18.8%) CS: 7 (21.9%) Jaundice: 3 (9.4%) Pain: 3 (9.4%) Anemia: 2 (6.3%) Other: 2 (6.3%) Asymptomatic: 3 (9.4%)	5 (33.3%) 4 (26.7%) 2 (13.3%) 0 (0%) 2 (13.3%) 1 (6.7%) 1 (6.7%) 1 (6.7%)	1 (6.3%) 2 (12.5%) 5 (31.3%) 3 (18.8%) 1 (6.3%) 1 (6.3%) 1 (6.3%) 2 (12.5%)	0.172
CT scan MRI EUS [b]	32 (100%) 7 (21.9%) 2 (6.3%)	16 (100%) 3 (18.8%) 1 (6.3%)	16 (100%) 4 (25%) 1 (6.3%)	1
Preoperative biopsy	29 (90.6%)	14 (87.5%)	15 (93.8%)	1
PBD [c]	4 (12.5%)	1 (6.3%)	3 (18.8%)	0.6
Total bilirubin Album (media) AST (median) ALT (median) Increased tumor markers	0.55 mg/dL (IQR 0.38–1.12) 3.38 ± 0.78 DS 22 UI (IQR 16–30) 28 UI (IQR 12–40) 9 (36%)	0.5 (IQR 0.34–0.69) 3.6 ± 0.64 23 (IQR 20–27) 28 (IQR 14–35) 3 (21.4%)	0.63 (IQR 0.43–1.8) 3.2 ± 0.86 22 (IQR 14–49) 23 (IQR 12–51) 6 (54.5%)	0.214 0.117 0.760 0.736 0.115
Postoperative morbidity Severe complication (CD ≥ IIIa)	21 (65.7%) 14 (43.8%)	8 (50%) 6 (37.5%)	13 (81.3%) 8 (50%)	0.135 0.722
Clavien–Dindo	CD I: 5 (15.6%) CD II: 2 (6.3%) CD IIIa: 4 (12.5%) CD IIIb: 2 (6.3%) CD IVa: 1 (3.1%) CD IVb: 0 (0%) CD V: 7 (21.9%)	1 (6.3%) 1 (6.3%) 2 (12.5%) 1 (6.3%) 0 (0%) 0 (0%) 3 (18.8%)	4 (25%) 1 (6.3%) 2 (12.5%) 1 (6.3%) 1 (6.3%) 0 (0%) 4 (25%)	0.532
POPF (pancreatic fistula)			Biochemical leak 4 (25%) B: 2 (12.5%) C: 3 (18.8%)	
Anastomotic leak		2 (12.5%)		
Biliary fistula			2 (12.5%)	
DGE [d]			A: 1 (6.25%) B: 0 (0%) C: 0 (0%)	
PPH [e]	A: 2 (6.3%) B: 3 (9.4%) C: 2 (6.3%)	A: 0 (0%) B: 2 (12.5%) C: 1 (6.3%)	A: 2 (12.5%) B: 1 (6.3%) C: 1 (6.3%)	0.792
Intra-abdominal abscess	8 (25%)	3 (18.8%)	5 (31.3%)	0.685
Postoperative mortality (90 days)	7 (21.9%)	3 (18.8%)	4 (25%)	1
Re-admission	5 (15.6%)	2 (15.4%)	3 (21.4%)	1
Hospital stay (median)	16 (IQR 10–24)	12.5 (IQR 9–19)	18.5 (IQR 11–42)	0.115

Table 2. *Cont.*

	Total (n = 32)	Conservative (n = 16)	PD (n = 16)	*p* Value
TNM	Tis: 2 (6.3%)	1 (6.3%)	1 (6.3%)	
	T1a: 1 (3.1%)	0 (0%)	1 (6.3%)	
T	T1b: 3 (9.4%)	1 (6.3%)	2 (12.5%)	0.190
	T2: 4 (12.5%)	0 (0%)	4 (25%)	
	T3: 17 (53.1%)	11 (68.8%)	6 (37.5%)	
	T4: 5 (15.6%)	3 (18.8%)	2 (12.5%)	
	Nx: 7 (21.9%)	6 (37.5%)	1 (6.3%)	
N	N0: 14 (43.8%)	6 (37.5%)	8 (50%)	0.227
	N1: 8 (25%)	3 (18.8%)	5 (31.3%)	
	N2: 3 (9.4%)	1 (6.3%)	2 (12.5%)	
Size (cm)	3.4 (IQR 2.5–5)	2.8 (IQR 2–3.4)	4.6 ± 2	0.112
Differentiation grade tumor	G1: 8 (25%)	5 (35.7%)	3 (20%)	
	G2: 10 (31.3%)	4 (28.6%)	6 (40%)	0.849
	G3: 9 (28.1%)	4 (28.6%)	5 (33.3%)	
	G4: 2 (6.3%)	1 (7.1%)	1 (6.7%)	
LN [f]				
Involved (median)	0 (IQR 0–3)	0 (IQR 0–2)	0 (IQR 0–3)	0.385
Resected (media)	11 ± 8 DS	6 ± 1.5	15 ± 7.6	0.015
R [g]	R0: 21 (65.6%)	7 (43.8%)	14 (87.5%)	0.23
	R1: 11 (34.4%)	9 (53.3%)	2 (12.5%)	
Neoadjuvant chemotherapy	0	0	0	
Adjuvant CT [h]	12 (37.5%)	6 (50%)	6 (50%)	1
Adjuvant RT [i]	4 (12.5%)	1 (7.7%)	3 (25%)	0.322
Relapse	10 (31.3%)	7 (53.8%)	3 (25%)	0.226

[a] Symptoms: UGIB: upper gastrointestinal bleeding; CS: constitutional syndrome; Other symptoms: gastroesophageal reflux disease and hypertransaminasemia. [b] EUS: endoscopic ultrasound. [c] PBD: preoperative biliary drainage. [d] DGE: delayed gastric emptying. [e] PPH: postpancreatectomy hemorrhage. [f] LN: lymph nodes. [g] R: resection margin status. [h] Adjuvant CT: chemotherapy. [i] Adjuvant RT: radiotherapy.

In patients undergoing PD, the specific complications of the pancreatic surgery were analyzed (Table 2). Type B pancreatic fistula was found in two of the 16 PD patients, and type C fistula in 3. Biliary fistula occurred in two cases. One patient presented delayed gastric emptying (type A). Postoperative bleeding was observed in seven patients (type A in two, type B in three, and type C in two), and intra-abdominal abscesses in eight (25%). Seven patients died in the postoperative period; four patients in the PD group and three patients in the conservative surgery group. Of the four patients in the PD group, the cause of death was pancreatic fistula in three of them, and in the other case, there was respiratory failure in an asthmatic patient. In the conservative surgery group, death was caused by duodenal suture dehiscence in two cases and the other by cardiac arrest. Mean postoperative stay was 16 (IQR 10–24) days and the re-admission rate was 15.6%.

Pathology analysis after resection revealed a mean tumor size of 3.4 (IQR 2.5–5) cm; it was larger in the cases of PD (4.6 vs. 2.8 (IQR 2–3.4); $p = 0.112$). Tumors were T3 or T4 in 68.7% of the patients, with a predominantly G2 or G3 degree of differentiation (Table 2). The mean R0 rate was 65.6% and was higher in PD (86.7% vs. 42.9%; $p = 0.013$).

The TNM distribution is shown in Table 2. Of the 16 patients who underwent PD, 4 presented the invasion of the pancreas. Twelve patients received adjuvant chemotherapy, in four cases in combination with radiotherapy. No patient had undergone neoadjuvant chemo- or radiotherapy.

Excluding patients who died in the immediate postoperative period, the mean survival time was 61.89 months (95% CI: 45.95–77.84) with a probability of survival at one, three, and five years of 95%, 70%, and 60%, respectively. Mean disease-free survival (DFS) was 59.98 months (95% CI 40.85–79.11) with a probability at one, three, and five years of 86, 55, and 48%, respectively. The factors related to overall survival (OS) and DFS are displayed in Tables 3 and 4. Survival curves according to the status of the resection margin, lymph node involvement, and the type of the surgery are shown in Figure 1. Ten patients suffered

recurrence: local in three, distant in five, and two patients presented lymph node recurrence (although one of these patients had periaortic recurrence which might also be considered "distant"). The most frequent site of distant recurrence was the liver, in three patients: in one of them in the liver alone, in another in the liver and lung, and the third in the liver and bone. There was a greater trend towards recurrence in patients who did not undergo PD (53.8% vs. 25%; $p = 0.14$).

Table 3. Univariate and multivariate Cox regression analyses: overall survival. [a] Clavien-Dindo.

Variable	Univariate		Multivariate	
	HR (CI 95%)	***p* Value**	**HR (CI 95%)**	***p* Value**
Sex (male)	3.53 (0.42–29.45)	0.244		
Age (years)	1.09 (1.02–1.19)	0.032		
Age ≥ 50	3 (0.36–25.29)	0.312		
Age ≥ 60	5.64 (0.69–46.39)	0.108		
Age ≥ 70	13.91 (1.62–119.75)	0.017	7.18 (0.73–70.35)	0.09
ASA	0.81 (0.3–2.2)	0.679		
Type of surgery	0.58 (0.13–2.51)	0.465		
Location of tumor	1.3 (0.61–2.79)	0.5		
Postoperative morbidity	1.04 (0.24–4.42)	0.956		
CD [a] ≥ IIIa	0.69 (0.14–3.46)	0.649		
Size of tumor	0.72 (0.41–1.27)	0.256		
≥2 cm	0.26 (0.5–1.36)	0.111		
≥3 cm	0.95 (0.22–4.03)	0.946		
≥5 cm	0.03 (<0.001–44.24)	0.349		
≥7 cm	0.04 (<0.001–261.15)	0.469		
Differentiation grade	1.64 (0.76–3.55)	0.208		
Involved lymph nodes	2.8 (0.46–17.13)	0.265		
R0/R1	14.78 (1.67–130.68)	0.015	6.84 (0.71–65.6)	$p = 0.095$
T	1.31 (0.72–2.37)	0.374		
T ≥ T2	2.17 (0.25–18.73)	0.479		
T ≥ T3	3.7 (0.45–30.46)	0.223		

Table 4. Univariate and multivariate Cox regression analyses: disease-free survival.

Variable	Univariate		Multivariate	
	HR (CI 95%)	***p* Value**	**HR (CI 95%)**	***p* Value**
Sex (male)	0.49 (0.1–2.33)	0.371		
Age (years)	1.07 (1.00–1.14)	0.042		
Age ≥ 50	3.53 (0.44–28.49)	0.236	0.75 (0.5–1.13)	0.166
Age ≥ 60	7.41 (0.93–59.27)	0.059	1904.68 (0.48–7.6 × 10^6)	0.074
Age ≥ 70	4.56 (1.18–17.71)	0.028	664.7 (0.76–580,133.8)	0.060
ASA	0.79 (0.33–1.91)	0.606		
Type of surgery	0.42 (0.11–1.63)	0.209		
Location of tumor	1.36 (0.72–2.56)	0.344		
Postoperative morbidity	0.86 (0.24–3.1)	0.821		
CD ≥ IIIa	0.49 (0.10–2.33)	0.371		

Table 4. *Cont.*

Variable	Univariate		Multivariate	
	HR (CI 95%)	***p* Value**	**HR (CI 95%)**	***p* Value**
Size of tumor	0.72 (0.46–1.13)	0.155		
≥2 cm	0.42 (0.09–2.14)	0.318		
≥3 cm	0.51 (0.15–1.77)	0.288	1.38 (0.58–3.27)	0.469
≥5 cm	0.27 (0.03–2.12)	0.212		
≥7 cm	0.04 (<0.001–49.48)	0.370		
Differentiation grade	1.52 (0.78–2.99)	0.217		
Involved lymph nodes	2.59 (0.57–11.80)	0.218		
R0/R1	23.19 (2.59–207.96)	0.005	6.43 (0.51–81.47)	0.151
T	3.09 (1.05–9.12)	0.040	11.86 (0.83–169.3)	0.068
T ≥ T2	29.30 (0.041–20,775.3)	0.313		
T ≥ T3	39.86 (0.17–9293.01)	0.185	39982.63 (<0.001–8.209 × 10^{174})	0.958

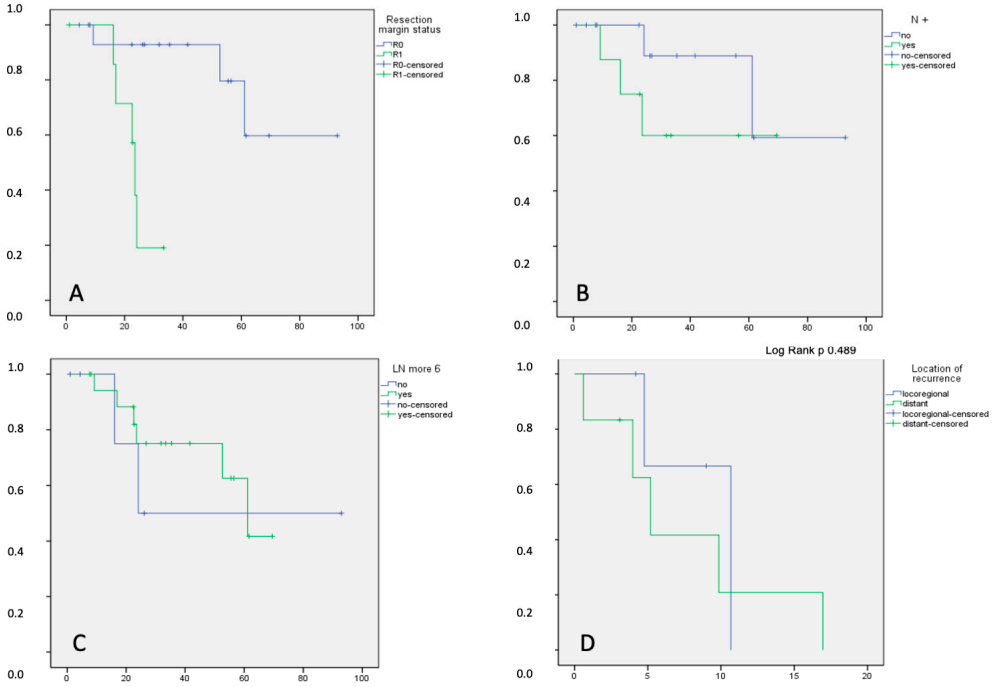

Figure 1. Kaplan–Meier survival curve of overall survival (OS) (**A**): following resection, grouped by resection margin status; (**B**): following resection, grouped by lymph node status; (**C**): following resection, grouped by number of lymph nodes resected; and (**D**): following recurrence, grouped by site of recurrence.

Conservative surgery seemed to be associated with more local recurrence than PD (57.1% vs. 33.3%; $p = 0.49$). Regarding survival post-recurrence, no differences were found between local and distant sites (9 vs. 7.6 m; $p = 0.48$) (Figure 1).

4. Discussion

Non-ampullary duodenal adenocarcinoma is a rare malignant neoplasm in which surgery is accepted as the treatment of choice and is considered to have curative potential [11]. Prognosis in these tumors is poor, although, at similar stages of evolution, it may be no worse than that of intestinal-type papilla of Vater adenocarcinomas [21]. However, it should be noted that duodenal adenocarcinoma has classically been studied alongside the rest of small bowel carcinoma. However, it is a separate malignant neoplasm that can be subdivided according to immunohistochemical reactivity into intestinal phenotype,

which is morphologically similar to colorectal adenocarcinoma and follows an adenoma-carcinoma sequence, and non-intestinal phenotype, mainly represented by the gastric phenotype and the pancreaticobiliary phenotype [22,23]. According to some authors, the cases of the intestinal-type duodenal adenocarcinoma, which originate most frequently in the supra-ampullary duodenum, have better postoperative results and longer survival [24].

Here we analyzed a multicenter series of the cases of duodenal adenocarcinoma undergoing surgical resection. Although PD has classically been considered the treatment of choice, from the first small series of the published cases to larger, more recent reports [25,26], the choice of the surgical technique for duodenal tumors varies according to the location, tumor size, or pancreatic infiltration [3,13,27,28]. In our series, 16 patients (50%) underwent PD. In the remaining 16 cases, a segmental bowel resection was performed in 13 and in the other 3 a local resection of the lesion due to its small size or the advanced age or high comorbidity of the patient. It should be noted that PD was performed in all sites except the fourth duodenal portion and that more conservative surgeries were also used in tumors in various sites, not only for distal locations. If possible, PD tends to be avoided due to the high associated morbidity and mortality rates; however, isolated duodenal resection is also accompanied by significant morbidity and even mortality [3,29]. In our series, the morbidity rates were high, and although there were no statistically significant differences between the groups, we found a trend towards greater morbidity in the PD group (81.3% vs. 50%). Nevertheless, the rate of severe complications was very similar in the two groups. Of the 32 patients, 7 presented Clavien–Dindo V complication, which resulted in an extremely high mortality rate in our series compared to that published in the literature. However, this is a series with a small number of cases in each surgical group, so when the cases of death occur, the rate is penalized.

In our assessment of the long-term evolution of our series after surgical resection, we excluded patients who died in the immediate postoperative period. This decision reduced the total number of the cases but we think that it avoided a possible bias with regard to the survival results. We found an OS of 61.89 months (95% CI 45.95–77.84) with a probability of survival at one, three, and five years of 95%, 70%, and 60%, respectively. These figures are similar to (or even higher than) those reported by other authors [3,29,30]. We did not find differences in survival according to the type of the resection performed, in agreement with the results of the previous studies [3,27,30]; indeed, in a propensity score-matched analysis performed to compare radical resection versus local resection, the authors were unable to demonstrate the superiority of the radical resection in terms of survival and so advocated the continued use of both techniques [27].

Factors recognized as having prognostic value include tumor size, degree of differentiation, or resection margin status [11]. In the univariate analysis we observed an influence of the status of the resection margin (R0 vs. R1) with a mean survival of 75.3 $\pm$ 8.35 vs. 23.4 $\pm$ 2.9 months, respectively, and survival rates at 1, 3, and 5 years of 93%, 93%, and 80% vs. 100%, 0%, and 0%. These differences, with survival rates of 0% at 5 years in cases of R1, have also been reported in other series [31]. In our cases we found an apparently high rate of R1 (34%) compared with recent publications [3], although the definition of R0/R1 is not always homogeneous. Other known independent prognostic factors include lymph node involvement and the invasion of the pancreas [28]. According to Nitta et al., the median survival outcomes for pancreatic invasion does not differ from those for pancreatic adenocarcinoma [28]. This may mean that in series in which this information is not specifically collected, the results of the PD group may be negatively affected since some of the cases could have pancreatic invasion and alter the mean survival of the group. In our series, we did not find any influence of pancreatic invasion, although its presence was very low. As for lymph node resection, the AJCC recommends removing a minimum of six nodes in duodenal adenocarcinoma surgery [3]. In our series, the mean number resected was 11 $\pm$ 8, with a higher number in the PD group (15 $\pm$ 7.6 vs. 6 $\pm$ 1.5; $p = 0.23$). The benefit of the adjuvant treatment is controversial. In a systematic review, the authors have investigated the role of the adjuvant and neoadjuvant therapy. In most of the studies

analyzed no benefit has been found on overall survival, either with chemoradiotherapy or chemotherapy alone. However, the authors conclude that could be a selection bias of the patients for adjuvant therapy and might suggest a benefit for the administration of the adjuvant therapy in patients with worse prognosis [32]. As regards recurrence, most of the series did not report the site of the recurrence or the possible factors that might influence its location. Ten of our patients presented recurrence: distant in six patients (four in the PD group and two in the non-radical surgery group), and loco-regional in four (one in the PD group and three in the non-radical surgery group). These findings do not suggest any relation between the site of the recurrence and the type of the surgery performed, nor that the site significantly affects patients' subsequent survival.

The main limitation of our study is its retrospective nature and the small number of cases. Larger sample sizes would provide more robust results. With only 32 patients included in the study, the power to detect significant differences between groups or to perform comprehensive multivariate analyses may be limited. Another limitation is the fact that the choice of the type of surgery is conditioned by the tumor site and characteristics as well as the patient's condition. This means that the results obtained may not be exclusively related to the type of the surgery performed. Furthermore, the absence of a non-surgical control group or comparison with alternative treatments limits the understanding of the relative efficacy of the surgical interventions studied.

5. Conclusions

We conclude that PD and limited resection are both valid options in the cases of non-ampullary duodenal adenocarcinoma. PD presented lower levels of loco-regional recurrence. Given the high rate of systemic recurrence, future efforts should focus on developing better systemic treatments to improve the control of the disease after resection.

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