ORIGINAL ARTICLE

Real Five Year Survival after Radical Surgery for Pancreatic Carcinoma: Can It Be Predicted with the Usual Prognostic Factors?

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ABSTRACT

Introduction Surgery of pancreatic adenocarcinoma with curative intent is the only treatment that offer a long-term survival possibility, with a reported 5-year overall survival rate ranging from 15% to 25%. However, it is only an estimation of long term survival in the majority of reports that could be higher than expected. Our aim is to report the real 5-year overall survival rate based on a large series from a single center and match it with similar reports. **Material and methods** This is a retrospective analysis of patients with pancreatic adenocarcinoma presenting with 5-year survival rate after the operation performed between 2004 and 2010. We also performed a review of the literature searching for similar series to compare to. **Results** A total of 128 patients had pancreatic adenocarcinoma resection. Seven patients were lost during the follow up and 4 passed in the early post operative period. The 5-year survival rate of the series is 7.69% (9/117). The analysis of our series and the 8 similar series (388 patients) found in literature shows that some of the well known bad prognostic factors as positive lymph node, poor differentiation grade, R1 resection may be present in these patients. None of long surviving patients was in post operative AJCC stage III and IV: it was the only bad prognostic factor. **Conclusions** Well known bad prognostic factors can be singled-out in patients with actual 5-year post pancreatectomy survival rates. We realize that the coexistence with some bad prognostic factors should be never taken in account to refute the potential curative surgical treatment except for T4 and/or M1 stage diagnosis.

INTRODUCTION

Complete surgical resection followed by adjuvant therapy is, up to now, the best treatment option for localized ductal pancreatic adenocarcinoma (DPAC) [1, 2, 3].

This strategy, performed in experienced centers, reports a general 5-year survival rate of 15-20% (defined as "long term survivors") (LTS). On the contrary, unresectable pancreatic cancers, shows a fluctuating 5-year survival rate that varies between 1-5% [4].

In literature there are some case series of pancreatic adenocarcinomas with LTS. However, most of them do a patient cohort that last long periods of time, from different centers and with different treatment types, therefore, with many biases [5].

Furthermore, most of these studies series present survival rates estimated using the Kaplan Meier method instead of a real survival rates of 5 year patient follow up [3, 6, 7, 8].

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Keywords Pancreatic Neoplasms; Pancreatectomy
Abbreviations SPNs solid pseudopapillary neoplasms
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As referred by some authors, [9] it is believed that estimated 5-year survival rate is higher than actual 5-year survival numbers. Given this data, there is still a need to present a series of LTS no estimated by statistics, but with real patient follow up.

The aim of this study is to show the series of LTS patients treated and followed at our center, to compare our findings with other previous published series and, finally, to analyze and correlate these findings with well known bad prognostic factors previously described.

MATERIALS AND METHODS

This is a retrospective study in which were included a total of consecutive 152 patients harboring a potentially resectable pancreatic cancer. Patients underwent surgery between March 2004 and October 2010. Only patients with histological or cytological confirmed adenocarcinoma have been definitely included in our analysis. A total of 24 patients with other diagnosis were excluded from the analysis: Pancreatic neuroendocrine tumors (n=19), chronic pancreatitis (n=3), Pancreatic intraepithelial neoplasms (n=1) and lymphoplasmocytic pancreatitis (n=1).

Pretreatment evaluation was standardized and consisted of physical examination, thoraco-abdominal CT scan with vascular reconstruction, FDG-PET scan measuring max standardized uptake value (SUV), pancreatobiliary MRI and endoscopic ultrasound with fine needle biopsy.

Jaundice, if present, is usually resolved preoperatively by biliary metallic stent placement.

Up to 2009 after surgery all patients received adjuvant chemotherapy (gemcitabine alone or in combination with other agents). Radiotherapy was administered only in cases with retroperitoneal involvement. Since January 2010 our institution has been exploring the use of protocol-based neoadjuvant therapy before surgical resection with Gemcitabine plus Nab-paclitaxel [1].

A prospective recording of the following data was performed: main demographic data (age, gender, co-morbidity, ASA stage, neoadjuvancy), main operative data (type of surgery, vascular resection), main post operative outcome (complications, hospital stay, adjuvancy), main pathological data (adenocarcinoma differentiation grade, tumoral size, number of retrieved lymphnodes and number of affected lymphatic nodes, neural invasion, lymphovascular invasion and both section and retropancreatic margin involvement) and finally long term follow up data (Overall survival, Disease free survival, site of recurrence).

Tumoral stage was defined according to the TNM stage of the AJCC [10].

Post operative follow up was performed both by surgery and oncology teams.

All pathological data have been independently reviewed by 2 pathologists. If they weren't in agreement, a third pathologist was asked to revise the specimen.

Surgeries were performed by 8 surgeons, two of them with high experience in HPB surgery. All procedures have been performed in a similar standard fashion in which a Roux-en-Y digestive tract reconstruction was performed with a duct to mucosa pancreatojejunostomy after duodenopancreatectomy.

We define mortality related to surgery if it occurred up to 60 days from the operation.

We define as long term survival patients alive (with or without recurrence) after 60 months from pancreatic resection date.

RESULTS

Outcome analysis was performed for 128 patients; 7 patients were lost during follow up. A total of 4 patients (3.3%) died during the post operative time and therefore were excluded from this series. The 5-year survival was 7.69% (9/117).

Overall mean survival of the remaining 108 patients who died before completing 60 months after the operation was 17 months.

Main patient demographic characteristics are shown in **Table 1**.

Jaundice is the more frequent diagnostic preoperative symptom (77.7%), followed by abdominal pain and weight loss (33.3%). All 7 patients with jaundice were successfully treated preoperatively by biliary plastic stent positioning, except one who needed metallic stent (wallflex type) as she underwent neoadjuvant treatment.

Main intra operative and post operative as well as pathological data are shown in **Table 2**.

Tumors were located in the pancreatic head in 7 patients, in the pancreatic body in one case and in the last case it was located in the pancreatic tail.

There were 3 concomitant vascular resections (1 case of superior mesenteric vein, 1 case of partially cava resection and one case of celiac trunk resection performing an Appleby technique).

Mean operative time was 370 min. Mean intraoperative blood loss was 300 cc. Mean perioperative blood transfusion was 2.1 units.

A total of 2 patients had post-operative complications. One patient suffered of an intrabdominal abscess treated successfully by radiological drainage; one patient presented left lateral liver ischemia and needed surgical reintervention. Mean hospital stay was 16 days (range: 10-85).

All specimen borders were free from disease (R0). In one case was found retroperitoneal involvement. In all cases, adenocarcinoma was confirmed by pathological and immunohystochemical analysis. One out of the 9 cases showed a clear cell subtype.

Mean tumoral size was 31 mm (range: 21-54 mm). One specimen was found to be a multifocal pancreatic tumor. From the 9 tumors, 6 were well differentiated and the 3 remaining specimens presented moderate differentiation. There was no pathological evidence of tumor involvement in the vascular resection specimens.

Mean number of retrieved lymph nodes was 15 (range: 9-20). In 4 cases (44%) there were positive lymph nodes.

TN staging is shown in **Table 2**.

Adjuvant treatment and type is shown in **Table 3**. Adjuvant radiotherapy was administrated only to the patient with retroperitoneal positive border.

The overall mean survival from the time of the operation was 79 months (range: 61-128 months). Today, 4 patients (44.4%) are still alive and without recurrence. One patient that is still alive presented local recurrence (after 90 months from surgery) and has been successfully managed with chemo-radiotherapy. One patient is still alive with pulmonary (presented 50 months after operation) and mediastinal metastases (presented 72 months after operation). A total of 3 patients died secondary to tumoral recurrence at 61, 63 and 73 months after operation, respectively.

Tables 4, 5 summarize our results in comparison with other eight series also collecting actual 5 years survivors after pancreatectomy for DPAC [4, 5, 11, 12, 13, 14, 15, 16].

DISCUSSION

Most series reporting patient survival after pancreatic resection for DPAC present only estimated survival,

Table 1. All patients demographic and clinical related data.

Patient number	Sex	Age	Surgical Date	Past Medical History	ASA	Clinical Symptoms	Stent Biliar Decompression
1	Male	56	2004 July	No	II	Jaundice; Abdominal pain; Weight loss	Yes (plastic prothesis)
2	Female	46	2005 April	No	II	Jaundice; Weight loss	Yes (plastic prothesis)
3	Male	52	2005 May	Atrial fibillation	III	Jaundice	Yes (plastic prothesis)
4	Male	52	2005 May	No	II	Jaundice; Abdominal pain	Yes (plastic prothesis)
5	Male	56	2006 April	No	II	Jaundice	Yes (plastic prothesis)
6	Female	61	2006 July	No	II	Jaundice	Yes (plastic prothesis)
7	Female	47	2007 May	No	II	Abdominal pain; Weight loss	No
8	Female	64	2008 August	No	II	Asymptomatic	No
9	Female	52	2010 February	chronic obstructive pulmonary disease (asthma)	III	Jaundice	Yes (short plastic prothesis)

Table 2. All patients pathological and surgery related data.

Patient number	Diagnosis	AJCC Stage	Grade	Size mm	Nodal Status	Invasion of AdjacentStructures	Localization and Surgical procedure	Vascular resection	Hospital days and complications
1	Ductal adencarcinoma	T3N1 (IIB)	Mod	28	N_1(1/16)	Duodenum	Head/ PD	No	14/No
2	Ductal adencarcinoma	T2N1 (IIB)	Well	21	N_1(1/19)	SMV*	Head/STP**	Yes (SMV)*	23/No
3	Ductal adencarcinoma	T2N1 (IIB)	Mod	22	N_1(2/16)	No	Head/TP**	No	18/No
4	Ductal adencarcinoma	T3N0 (IIA)	Well	30	N0(0/13)	Adipose peripancreatic tissue	Head/ (PD)	No	26/yes (intraabdominal collections)
5	Ductal adencarcinoma	T3N1 (IIB)	Well	54	N1(3/20)	Adipose peripancreatic tissue	Head/ STP**	No	16/No
6	Ductal adencarcinoma	T3N0 (IIA)	Well	52	N0(0/12)	Duodenum and Adipose peripancreatic tissue	Head/ STP**	No	16/No
7	Ductal adencarcinoma	T3N0 (IIA)	Well	32	N0(0/12)	Adipose peripancreatic tissue	Body and tail/ SDP**	Yes (celiac axis)	12/No
8	Ductal adencarcinoma	T3N0 (IIA)	Mod	multifocal	N0(0/15)	Visceral peritoneum and Adipose peripancreatic tissue	Body and tail/ SDP**	No	10/No
9	Clear cells Ductal adencarcinoma	T3N0 (IIA)	Well	45	N0(0/9)	Duodenum and Adipose peripancreatic tissue	Head/ PD	Yes (cava vein)	85/Yes(hepatic abscess and biliary fistule)

*SMV superior mesenteric vein; **TP totalpancreatectomy; SDP Splenodistalpancreatectomy; PD pancreatoduodenectomy; STP Spleno total pancreatectomy

calculated by Kaplan-Meier method. However, as referred by some authors, this method may over estimate data for LTS [9].

The aim of this study is to present and analyze the number of LTS after pancreatectomy for DPAC at our center.

In literature there are only few similar studies [4, 5, 11, 12, 13, 14, 15, 16]. However, these series, gathered data only up to 2004. As in the last decade there have been important improvement in surgical techniques and adjuvant treatment, there is need to present a newer study showing LTS after DPAC. Our series gathered data from 2004 up to 2010, describing those patients which achieves 5 years of survival.

Our series has incorporated the most important changes that occurred in the past decade treating resectable DPAC. These are the novel targeted drugs (nab-paclitaxel, erlotinib) [1, 2], as well as radiotherapy used before [17] and after operation [18]. As showed in **Table 3** patient nº 9 received neoadjuvant chemo-radiotherapy before surgery, patients nº 4, 5 and 7 received new agents as nab-paclitaxel in adjuvant regimen. Finally, in the last decade surgery for local recurrences is also being considered as longer survival terms are achieved after resection. In patients nº 3 and 7 the local relapse was surgically removed.

In the literature it has been reported that histopathology review of LTS can lead to a change in diagnosis in up to 6% of the cases [19]. Because the prognosis for adenocarcinoma of the pancreas is much worse than that of other peri-ampullar and pancreatic tumors, failure to accurately confirm the original pathologic diagnosis undoubtedly results in the inclusion of other tumor types, which can falsely inflate long term survival results. The histopathological specimens of all of our nine patients with a long term survival were re-evaluated by two pathologists specialized on pancreatic diseases. If there was no agreement the specimen was sent to a third one (it was only necessary in patient case nº 9)

Three out of 8 LTS series reviewed in this study, confirm that there has been some specimen misdiagnosis. The Conko-001 [5] study confirms the diagnosis of adenocarcinoma in all but one specimen in which the

Table 3. All patients follow-up and status related data.

Patient number	Surgery date	Neoadjuvanttreatmentt	Adjuvant	Status	Follow-up months	Observations
1	2004 July	No	Gemcitabine x 6 months	AFD*	128	Adherencial obstructive syndrome with conservative treatment at 75th month
2	2005 April	No	Gemcitabine x 6 months	DOD*	61	1st Local recurrence at 49th month: no surgical tentative
3	2005 May	No	Gemcitabine x 6 months 1st recurrence: Surgery + Gemox 2nd recurrence: radiotherapy + capecitabine	DOD*	63	1st Local recurrence at 40th month: surgical resection of VMS + adjuvant treatment 2nd local recurrence at 47th month: no surgical tentative. Only adjuvant treatment
4	2005 May	No	Gemcitabine x 6 months 1st recurrence: radiotherapy + capecitabine 2nd recurrence: Gemcitabine + MEK inhibitor/ Abraxane	DOD*	73	1st Local recurrence at 61th month: no surgical tentative. Only adjuvant treatment 2nd local recurrence at 70th month: no surgical tentative. Only adjuvant treatment
5	2006 April	No	Gemcitabine x 6 months 1st recurrence: Gemcitabine +Abraxane and Radiotherapy + Capecitabine	AWD*	107	1st Local recurrence at 90th month: no surgical tentative. Only adjuvant treatment
6	2006 July	No	Gemcitabine x 6 months	AFD*	104	2nd neoplasm at 57th month: rectal tumor T3N0 with also complete response and free of disease
7	2007 May	No	Gemcitabine x 6 months 1st recurrence: none 2nd recurrence: radiosurgery 3nd recurrence: Gemcitabine + Abraxane	AWD*	94	1st distant recurrence at 53th month: Left inferior pulmonary lobectomy 2nd distant recurrence at 72th month: lung hilum; no surgical tentative. Only adjuvant treatment 3rd distant recurrence at 83th month: mediastinum; no surgical tentative. Only adjuvant treatment
8	2008 August	No	Gemcitabine + Oxaliplatine + Radiotehrapy x 6 months	AFD*	79	Radial margin +
9	2010 February	Capecitabine + Radiotherapy (51.2 Gy)	No	AFD*	61	Chronic biliary fistula and severe desnutrition. No evidence of recurrence

*AFD alive free of disease; AWD alive with disease; DOD dead of disease

analysis was repeated and finally corrected to a high grade neuroendocrine carcinoma. Similarly, Katz *et al*. [12] led to a change in the diagnosis of 3 patients to biliary adenocarcinoma in 2 cases and intraductal papillary mucinous neoplasm in 1 case. Finally, Clearly *et al*. [15] withdrew one patient from the analysis because pathology revision revealed a diagnosis of duodenal adenocarcinoma.

Given this result, it is possible that other series may have LTS with no DPAC in the specimen, even if they do not address this issue.

The analysis of our series consists of correlate LTS to well known prognostic factors, as follow:

Blood Transfusion

In a number of solid tumors, perioperative blood transfusion has been reported as a negative prognostic factor [20, 21, 22]. An explanation for this finding could be that allogenetic blood transfusion could induce immunosuppression in the host, thus exhibiting a higher recurrence rate in the patient after tumor resection. It has also been advocated that the requirement for blood transfusion correlates with cases that present with advanced tumors and are more difficult to resect.

A meta-analysis conducted by Garcea *et al*. demonstrates that transfusion of less than 2 U is associated to a longer survival after DPAC operation [23]. Conversely, our nine patients received in the perioperative period a mean of 2.1 blood units, lightly superior.

Among the eight series consulted the only one showing blood loss as an independent factor for LTS was published by Dusch *et al.* [4].

No Prior Attempt at Resection

Katz *et al*. [12] include as an adverse factor associated with long-term survival a previous attempt at tumor resection before referral to his institution. Of the 88 5-year survivors, only 5 patients had undergone an unsuccessful attempt at tumor removal before referral. Conversely, 43 patients had undergone laparotomy for planned pancreatectomy before referral in the 241 non 5-year survivors; the effect of an unsuccessful prior laparotomy was profound and elucidates the importance of carefully selecting patients for PDAC surgery who are compatible with the skill set of the surgeon. Some studies and recent guidelines have suggested sending these patients to centers that perform more than 20 cases a year [24, 25]. In any of our nine patients, when referred from other institutions, a prior attempt for resection had been proposed.

R0 Resection

Margin status has been likely associated with the location and size of tumors. Tumors located in proximity to superior mesenteric vessels and celiac trunks are more

Table 4. Comparison of other series with actual 5-year survivors post-resection of pancreatic adenocarcinoma: demographic and follow up data; survival predictive factors.

Series	Publication year	Data collection years	Nº centres	Nº patients 5 year survivors (%)	Nº patients 10 year survivor (%)	Pathological accuracy (%)	Median global survival (months)	Median survival in 5-year survivors (months)	Complementary treatment (neoadjuvant or adjuvant) (%)	Deaths Follow up (%)	Predictivefactors
Conko-001 study [5]	2013	1998-2004	88	53/353 (15)	21/353 (5.9)	38/39** (97)	-	-	37/53 (69.81) Adjuvant gemcitabine	-	MVA**: Adjuvant treatment with gemcitabine; T_1:$T_{3,4}$; G_{well}:G_{poor}; N_0:N_1
Dusch *et al*. [4]	2013	1972-2004	1	69/360 (19.2)	22/360 (5.9)	69/69 (100)	17	-	23/69 (33.3) Adjuvant gemcitabine	33/69 (47.8) 28 DOD*(40.5) 2 DOC*(2.9) 3 unknown(4.4)	MVA**: Blood transfusion; LNR
Conlon *et al*. [11]	1996	1983-1989	1	12/118 (10.2)	-	12/12 (100)	14.3	83	No	6/12 (50) 6DOD* (50)	-
Katz *et al*. [12]	2009	1990-2002	1	88/329 (27)	-	88/91 (96.7)	23.9	91.2	65/88 (74) Neoadjuvant treatment 17/88(20) Adjuvant treatment	34/88(38.6) 17DOD*(19.3) 11DOC*(12.5) 6 unknown(6.81)	MVA**: R_0 resection; N_0; No prior attempt at resection
Schnelldorfer *et al*. [13]	2008	1981-2001	1	62/357 (17.36)	21/357 (5.88)	-	17	-	269/357(75) of the entire enrolled patients (5year survivors and not 5year survivors) adjuvant treatment	-	MVA**: N_0
Ferrone *et al*. [14]	2008	1983-2001	1	75/618 (11.8)	18/352§ (5)	-	-	-	16/75 (21.3) Adjuvant chemotherapy 13/75 (17.3) Adjuvant radiotherapy	43/75(57.33) 38DOD*(50.6) 5DOC*(6.6)	BVA**: Stage IB: Stage IIB; R_0 resection
Clearly *et al*. [15]	2004	1988-1996	5	18/123 (14.6)	5/123 (4.1)	18/19 (94.7)	13.6	106.8	5/18 (28) Adjuvant chemotherapy 4/18 (22) Adjuvant chemoradiotherapy	6/18(33.3) 4DOD(22.2) 2DOC(11.1)	MVA: Without symptoms at diagnostic; Small size; G_{well}:G_{poor}; Adjuvant radiotherapy
Han *et al*. [16]	2006	1985-1999	1	11/123 (9)	-	11/11 (100)	14.8	85	8/11 (72.72) Adjuvant treatment	2/11(18.18) 1DOD*(9.09) 1DOC*(9.09)	BVA**: N_0; Stage IIA: IIB/III/IV
Present study	2016	2004-2010	1	9/117 (7.69)	1/117 (0.85)	9/9 (100)	17	79	8/9 (88.88) Adjuvant treatment 1/9 (12.12) Neoadjuvant treatment	3/9(33.3) 3DOD*(33.3)	-

§352/618 are the potentially ten years survivors patients (collected until 1998 since the publication year is 2008)

*DOD dead of disease; DOC: dead of other causes; **MVA multi variant analysis; BVA: bi-variant analysis

likely to have specimen margin involvement. However, in the last decade, improvement of the vascular techniques allows for a marked decrease in margin involvement performing vascular resections [26].

In our series of 9 LTS, vascular resection was performed in 3 cases, with pathological vascular involvement in none of them. As reported by some authors, only 50% of resected vessels presented pathological tumoral involvement and only in this case it can be defined as poor prognostic factor [27]. Otherwise, LTS is still possible for these patients, as shown in our series.

In patient nº 2 the superior mesenteric vein was resected and reconstructed. This patient died secondary to the disease 61 months later. In patient nº 7 the celiac axis was resected by an Appelby technique. No vascular reconstruction was needed. Patient is still alive with mediastinum disease 94 months later. In patient nº 9 a segmental inferior vena cava resection was performed. Patient is alive without disease 61 months later.

Is mandatory to insist that vascular resection should not be considered anymore as a factor of poor prognosis unless tumoral pathological involvement of the resected vessel exists [26, 27].

Only in two of the consulted series [12, 14] the R0 margin was predictive of longer survival. Moreover, in 9.87% (36/365) of the 5-year survivors analyzed [4, 5, 12, 13, 14, 15] R1 resections were present. Thus, the presence of margin involvement should never preclude a LTS.

Lymph Node Status (N0)

In four of the listed 5-year actual survival patients the lymph node involvement was associated adversely with long-term survival [5, 12, 13, 16]. Also, lymph node metastases cannot exclude LTS. In fact we found that 44.37% (150/388) of all the 5-year survivors collected in the 8 series consulted had positive lymph nodes at the time of operation. Similarly, in our series 44.44% (4/9) of 5-year survivors had positive lymph nodes.

Table 5. Comparison of other series with actual 5-year survivors post-resection of pancreatic adenocarcinoma: pathological factors.

Series **Pathological factors**	Conko-001 study [5] n:53**	Dusch *et al.* [4] n:69**	Conlon *et al.* [11] n:12**	Katz *et al.* [12] n:88**	Schnelldorfer *et al.* [13] n:62**	Ferrone *et al.* [14] n:75**	Clearly *et al.* [15] n:18**	Han *et al.* [16] n:11**	**All series (mean)**	**Present study n=9****
Size (mm)*	-	24 (18-34)	29 (10-65)	30 (3-80)	27 +/- 10	-	23 +/- 3	30 (20-60)	27.16	31 (21-54)
T (%) n:225†	T1+T2:14/53 (26.4) T3:39/53 (73.6) T4:0/53 (0)	T1+T2:27/69 (39,1) T3:42/69 (60.9) T4:0/69 (0)	T1+T2:11/12 (91.66) T3:1/12 (8.33) T4:0/12 (0)	-	T1+T2:31/62 (50) T3:31/62 (50) T4:0/62 (0)	-	T1+T2:16/18 (88.88) T3:2/18 (11.12) T4:0/18 (0)	T1+T2:2/11 (18.18) T3:9/11 (81.82) T4:0/18 (0)	**T1+T2:101/225 (44.88) T3:124/225 (55.11) T4: (0)**	**T1+T2:2/9 (22.22) T3:7/9 (77.77) T4:0/9 (0)**
TNM (%) n:178†	-	-	Ia+Ib:6/12 (50) IIa:1/12 (8.33) IIb:5/12 (41.66) III+IV:0/12 (0)	-	Ia+Ib:21/62 (34) IIa:21/62 (34) IIb:20/62 (32) III+IV:0/62 (0)	Ia+Ib:36/75 (48) IIa:9/75 (12) IIb:30/75 (40) III+IV:0/75 (0)	Ia+Ib:13/18 (71.88) IIa:1/18 (5.55) IIb:4/18 (22.22) III+IV:0/18 (0)	Ia+Ib:2/11 (18.18) IIa:7/11 (63.63) IIb:2/11 (18.18) III+IV:0/11 (0)	**Ia+Ib:78/178 (43.82) IIa:39/178 (21.91) IIb:61/178 (34.26) III+IV: (0)**	**Ia+Ib:0/9 (0) IIa:5/9 (55.55) IIb:4/9 (44.44) III+IV:0/9 (0)**
Grade (%)†† n:225†	WD+MD: 44/53 (83.1) PD: 9/53 (16.9)	WD+MD: 54/69 (78.3) PD:15/69 (21.7)	WD+MD: 8/12 (67) PD: 4/12 (33)	-	WD+MD: 19/62 (31) PD: 43/62 (69)	-	WD+MD: 16/18 (88.88) PD: 2/18 (11.12)	WD+MD: 11/11 (100) PD: 0/11 (0)	**WD:152/ 225 (67.55) PD: 73/225 (32.45)**	**WD+MD: 9/9 (100) PD: 0/9 (0)**
N (%) n:388†	N0: 24/53 (45.3) N1: 29/53 (54.7)	N0: 41/69 (59.4) N1: 28/69 (40.6)	N0: 7/12 (58.4) N1: 5/12 (41.6)	N0: 56/88 (63.64) N1: 32/88 (36.36)	N0: 42/62 (67.75) N1: 20/62 (32.25)	N0: 45/75 (60) N1: 30/75 (40)	N0: 14/18 (78) N1: 4/18 (22)	N0: 9/11 (81.82) N1: 2/11 (18.18)	**N0: 238/388 (61.34) N1: 150/388 (44.37)**	**N0: 5/9 (55.55) N1: 4/9 (44.44)**
R margin (%) n:365†	R0: 46/53 (86.8) R1: 7/53 (13.2)	R0: 63/69 (91.3) R1: 6/69 (8.7)	-	R0: 80/88 (91) R1: 8/88 (9)	R0: 55/62 (89) R1: 7/62 (11)	R0: 68/75 (90) R1: 7/75 (10)	R0: 17/18 (94) R1: 1/18 (6)	-	**R0: 329/365 (90.13) R1: 36/365 (9.87)**	**R0 9/9 (100) R1 0/9 (0)**

*series [4, 11, 12, 16, present study]: median and range; series [13, 15]: mean and standard deviation

**n: actual 5years survivors in each series

†n: actual 5 years survivors enrolled in each topic

††WD: well differentiation; MD: moderate differentiation: PD: poor differentiation

AJCC Stage

As shown in 6 of the 8 series listed in **Table 4** [4, 5, 11, 12, 13, 15] AJCC stage was not a significant prognostic factor for 5-year survival rates. Therefore, even in patients with advanced stages, such as with large tumor size and/ or lymph node metastases, they have a chance for cure through surgical resection. None of the patients in our series were registered as early stages (IA-IB), but all of them were stage II (55.55% IIA; 44.44% IIB). We did not register Stage III-IV patients. Interestingly, none of the patients listed in the series consulted [4, 5, 11, 12, 13, 14, 15, 16], making a total count of 388 patients, were stage III-IV either. The issue is that we cannot understand if the specimen is going to be a pathological T4 stage, unless surgery is performed. Whenever an arterial resection was needed to complete pancreatectomy, pathological involvement of it (pT4) was confirmed only in 50% of cases [27]. Given this data, therefore, arterial resection should be performed in selected cases.

Tumoral Grade

Two studies [5, 15] revealed improved survival rates seen with well differentiated tumors compared with poorly differentiated neoplasms. This implies that the biologic behavior of the tumor affects patient outcomes. Accordingly to this statement, none of our nine patients were poorly differentiated. Moreover, some preclude tumoral grade to be included as an additional factor in the TNM staging system, in order to improve a better selection for patients to be included in further projects testing for new molecular markers [28]. However, we should mention that 32.45% (73/225) of the 5-year survivors analyzed [4, 5, 11, 13, 15, 16] had a contrasting poorly differentiated DPAC.

Adjuvant Chemotherapy

The CONKO-001 trial [5] didn't only demonstrate the benefit of adjuvant chemotherapy with gemcitabine in DPAC overall survival, but also elucidated this factor as an independent prognostic factor for the 5-year patient survivors. Unfortunately this series has to be interpreted with caution as chemotherapy was routinely given to patients only from 1998 resulting in a limited number of patients having undergone chemotherapy. Another drawback is the absence of standard protocols derived from the vast number of centers enrolled in the study. Similarities are found in the rest of the series consulted,

with only a few patients attending a formal chemotherapy regime, as they were treated in previous times when gemcitabine was not prescribed as a standard adjuvant treatment. Conversely, in our series with a recent initial data collecting date, all the patients received neoadjuvant or adjuvant treatment. As mentioned above, every time a disease recurrence was diagnosed, a new chemotherapy treatment regime was tested.

One consideration must be addressed about Katz series [12]. The incidence of patients with neoadjuvant treatment is really high, but is not an independent prognostic factor because very similar figures are present in both groups: 5 year survivors and under 5 year survivors (74% & 78% respectively).

LTS, Recurrence and Death

All of the series consulted registered recurrences and deaths. Most of the recurrences that can occur are local and distant, mainly in lungs, liver and brain [12]. Our series is also consistent with this pattern of late recurrences and deaths. Actual five years, or even ten years survival is not synonymous of cure [14]. The causes of these late recurrences are unclear and different theories have been proposed (occult lymph node or liver metastases, residual low-grade intraductal malignancies, or de novo tumors in the pancreas remanent).

Analysis of the clinical and histopathological variables in the 5-years survival group in the 8 studies selected demonstrates the enormous difficulty in defining prognosis for an individual patient. In a considerable number of these patients we realize the coexistence with really bad prognostic factors that never should be taken in account to refute the potential surgical treatment.

However, its noteworthy to mention that a AJCC stage III-IV is the only bad histopathological prognostic factor that was never present among the 397 patients (the eight 5-years survivors series consulted and ours) listed in this study. We can affirm categorically that a T4 or M1 stage are no longer associated with long term survivors.

CONCLUSIONS

According to our experience and the literature review, real LTS rate for patients that underwent pancreatectomy for adenocarcinoma is lower than estimated by KaplanMeier. On the other hand LTS is possible even if some of the well known bad prognostic factors are present.

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Conflict of Interest

The authors declare no conflict of interest

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