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ORIGINAL ARTICLE

Treatment characteristics and outcomes of pure Acinar cell carcinoma of the pancreas – A multicentric European study on radically resected patients

Ruben Bellotti[1], Salvatore Paiella[2], Florian Primavesi[1,3], Carsten Jäger[4], Ihsan E. Demir[4], Fabio Casciani[2], Peter Kornprat[5], Doris Wagner[5], Christiane S. Rösch[6], Giovanni Butturini[7], Alessandro Giardino[7], Peter E. Goretzky[8], Martina Mogl[8], Tim Fahlbusch[9], Jörg Kaiser[10], Oliver Strobel[10,11], Anna Nießen[9], Andreas M. Luu[9,12], Roberto Salvia[2] & Manuel Maglione[1]

[1]Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, 6020 Innsbruck, Austria, [2]General and Pancreatic Surgery Unit, Pancreas Institute, University of Verona, Verona, Italy, [3]Department of General, Visceral and Vascular Surgery, Salzkammergut Hospital, 4840 Vöcklabruck, Austria, [4]Department of Surgery, Klinikum Rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany, [5]Department of General Surgery, Medical University of Graz, Graz, Austria, [6]Department of Surgery, Ordensklinikum Linz, Linz, Austria, [7]Department of Surgery, Pederzoli Hospital, Peschiera, Italy, [8]Department of Surgery, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin 13353, Germany, [9]St. Josef Hospital, Department of General and Visceral Surgery, Ruhr-University Bochum, Germany, [10]Department of General, Visceral and Transplantation Surgery, Heidelberg University Hospital, Heidelberg, Germany, [11]Division of Visceral Surgery, Department of General Surgery, Medical University of Vienna, Vienna, Austria, and [12]Klinikum für Allgemein, Viszeral- und Minimalinvasive Chirurgie, HELIOS Klinikum, Krefeld, Germany

Abstract

Background: Acinar cell carcinomas (ACC) belong to the exocrine pancreatic malignancies. Due to their rarity, there is no consensus regarding treatment strategies for resectable ACC.

Methods: This is a retrospective multicentric study of radically resected pure pancreatic ACC. Primary endpoints were overall survival (OS) and disease-free survival (DFS). Further endpoints were oncologic outcomes related to tumor stage and therapeutic protocols.

Results: 59 patients (44 men) with a median age of 64 years were included. The median tumor size was 45.0 mm. 61.0% were pT3 (n = 36), nodal positivity rate was 37.3% (n = 22), and synchronous distant metastases were present in 10.1% of the patients (n = 6). 5-Years OS was 60.9% and median DFS 30 months. 24 out of 31 recurred systemically (n = 18 only systemic, n = 6 local and systemic). Regarding TNM-staging, only the N2-stage negatively influenced OS and DFS (p = 0.004, p = 0.001). Adjuvant treatment protocols (performed in 62.7%) did neither improve OS (p = 0.542) nor DFS (p = 0.159). In 9 cases, radical resection was achieved following neoadjuvant therapy.

Discussion: Radical surgery is currently the mainstay for resectable ACC, even for limited metastatic disease. Novel (neo)adjuvant treatment strategies are needed, since current systemic therapies do not result in a clear survival benefit in the perioperative setting.

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Correspondence.

Manuel Maglione, Department of Visceral, Transplant and Thoracic Surgery, Center of Operative Medicine, Medical University of Innsbruck, Anichstr. 35/8, 6020 Innsbruck, Austria E-mail: manuel.maglione@i-med.ac.at

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Introduction

In the panorama of pancreatic exocrine tumors, neoplasms with acinar differentiation represent rare entities. Even though pancreatic parenchyma consists mainly of acinar cells, pancreatic acinar cell carcinomas (ACC) account for only 1–2% of adult pancreatic tumors.[1] They occur more frequently in males, usually in their sixth or seventh decade.[2–6]

Due to its rarity, there are no clear treatment guidelines. Therapeutic strategies and staging system for ACC are still considered inadequate, since they mostly rely on findings and conclusions derived from pancreatic ductal adenocarcinoma (PDAC) evidence.[7,8]

ACC represents a different entity from PDAC, and this fact is reflected by its general better prognosis compared to the classical PDAC.[8–10] Currently, surgery still represents the mainstay in patients where radical resection can be achieved.[2,4,6,11,12] However, with regard to systemic treatment modalities the available literature reports are controversial, and the role for adjuvant as well as neoadjuvant strategies is still debated.[3,4,6,10,11,13–16]

The majority of available studies have limitations either in the small number of patients included in most case series, naturally leading to low statistical power, or in the lack of detailed data on histopathologic subtyping, surgical margins and (neo)adjuvant treatment regimens as it is in national registries.[4–6,12,17,18] Furthermore, published series frequently include both resected and unresected tumors, as well as other entities like mixed acinar-neuroendocrine neoplasms (acinar MiNEN) or pancreatoblastomas,[12,14,15,19] and these commonly not share the same clinical behavior as pure ACCs. The aim of this study therefore was to capture the experience of 9 European institutions on radically resected pure ACCs, hereby contributing to the available body of knowledge in how to best treat these rare malignancies.

Methods

Study design

This is a multicenter, retrospective study of patients who underwent surgical resection for pure ACC of the pancreas at 9 different European centers between August 2002 and September 2020. Data were obtained from prospectively maintained databases. The study was approved by the ethics committee of the Medical University of Innsbruck (EC-1210/2022). Patient consent was waived according to the statement of the ethics committee, concerning the retrospective nature of the study. Reporting is consistent with the principles of the Declaration of Helsinki.

Patient selection

Patients included were older than 18 years and had a verified histopathologic diagnosis of pure ACC of the resected primary tumor (selection criteria are shown in Fig. S1).

Patients were selected from each institutional database if diagnosis included the terms acinar cell carcinoma and pancreas. Before inclusion, samples of all patients were reviewed by the attending pathologists at each institution to confirm the diagnosis and to exclude possible confounding entities like acinar structured adenocarcinomas, mixed acinar-neuroendocrine neoplasms (acinar MiNEN) or pancreatoblastomas. Specimens from institutions with smaller case-load were reviewed by referral pathology centers with higher experience in this rare tumor entity. Trypsin and since 2011 anti-BCL10 were the immunohistochemical markers used to diagnose ACC. The use of synaptophysin and chromogranin-A was described for each single sample, in order to exclude the diagnosis MiNEN, even though they can be also expressed in ACC.[20] Moreover, different combinations of other markers, like CK 7 and CK 19, beta-catenin, PAS and/or alpha-AFP were also used at different institutions.

Data extracted from the medical records included: age, sex, date of diagnosis, co-morbidities, family history for pancreatic cancer, symptoms at presentation, histopathologic tumor characteristics (location, size, regional lymph node metastases, lymphovascular invasion, perineural invasion - where available), biochemical data at time of diagnosis (bilirubin, lipase, CA19-9), surgical data, any systemic treatment regimen, date and localization of any relapse, and date of death or last follow-up. Tumor, regional lymph node metastases, and distant metastasis (TNM) staging as well as the margin status (R) were classified as for other exocrine malignancies of the pancreas according to the AJCC Cancer Staging Manual, 8th edition.[7]

Statistical analysis

Statistical analyses were performed using IBM SPSS 24 (SPSS Inc., Chicago, IL, USA). Two-sided (p) values of 0.05 or less were considered statistically significant. The Pearson's chi-squared test and Wilcoxon test were used in the univariable analysis. Survival and comparison of univariable analyses were performed using the Kaplan–Meier method with the log-rank test. Multivariable analysis was conducted using a Cox proportional hazard model to identify factors affecting patients' overall survival (OS) and disease-free survival (DFS). A binary logistic regression was used to identify risk factors for regional lymph node metastases.

Results

Patients' and tumor characteristics

In total, 59 patients with a median age of 64 years were included, and their characteristics are shown in Table 1.

Liver resections were performed in cases with up to three metastatic lesions. Specific surgical and pathologic data are shown in Table 2. R0 resection rates were significantly higher for tumors of the pancreatic body and tail (58.0%), compared to those of the pancreatic head (36.0%; p = 0.005).

Tumor dimensions were not related to the presence of regional lymph node (any N status) or distant metastases (p = 0.267 and p = 0.927, respectively). Local lymphatic vessel (L) and perineural (Pn) invasion were significantly related to a positive nodal

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Table 1 Patient characteristics (n = 59)

Characteristics	n (%)
Age[a]	64 (25–86)
Male Sex	44 (74.6)
Episodes of acute pancreatitis	4 (6.8)
Diabetes mellitus type II	15 (25.4)
Family history for pancreatic malignancies	5 (8.5)
Pain	24 (42.4)
Weight loss	22 (37.3)
Jaundice	5 (8.5)
Biliary drainage/stenting	3 (5.1)
Serum bilirubin (mg/dl)[a] **(n = 56)**	0.5 (0.2–9.0)
Serum CA19–9 (U/ml)[a]**(n = 44)**	11.2 (1.0–372.0)
Serum lipase (mg/dl)[a] **(n = 40)**	53.5 (16.0–6556.0)
Surgery	
Whipple/PPPD	26 (44.0)
Distal pancreatectomy	24 (40.7)
Total pancreatectomy	8 (13.6)
Central pancreatectomy	1 (1.7)
PV/SMV/LGV resection	7 (11.9)
Arterial resection[b]	1 (1.7)
Tumor localization	
Head	26 (44.1)
Body	18 (30.5)
Tail	12 (20.3)
Overlapping	3 (5.1)

PPPD: pylorus-preserving pancreatoduodenectomy; PV: portal vein; SMV: superior mesenteric vein; LGV: left gastric vein.
[a] Median value (range).
[b] Accessory hepatic artery (Michels IV).

status rather than to tumor dimensions, both in the univariable and multivariable analysis (see Table S2, supplementary materials). Serum markers like lipase and CA19-9 did not show any correlation to the tumor burden (p = 0.721 and p = 0.749, respectively). Other data concerning histopathologic features are shown in Table 2.

Neoadjuvant treatments

Concerning neoadjuvant treatments, 8 patients, 6 with locally advanced disease and 2 with synchronous distant metastases, received chemotherapy. In one case of borderline-resectable disease chemo-radiation was administered. Resectability following neoadjuvant treatment was based on the clinical and radiological response (CT scan restaging). Radical surgical resection (R0) was achieved in 6 patients, while resection of the other 3 resulted in R1 resection. The most frequently administered protocols were FOLFOX and FOLFIRINOX (Table 2).

In the final histopathologic analysis, one case showed a complete response (grade 0 of the CAP regression scoring system), while two patients showed a CAP grade 2. In three patients, the observed reduction of the cell proliferation rate to approximately 50% was considered as partial tumor regression and in other three cases histopathological tumor regression was not documented.

Follow-up and adjuvant strategies

The median follow-up period was of 48 months. The 1-, 3- and 5-year overall survival (OS) rate was 84.7%, 66.6% and 60.9%, respectively (median OS: n. a.). The 1-, 3- and 5-year disease-free survival (DFS) was 82.5%, 51.3%, 38.3% (median 30 months). One patient was excluded from the survival analysis because he died from myocardial infarction 15 days following resection.

Nodal status N2 was associated with significantly shorter OS and DFS compared to N1 or N0 stage ($p < 0.001$ and $p < 0.0001$) (Fig. 1 A, B). This finding was independently confirmed in the multivariable cox regression analysis (HR:4.31 and HR: 3.64, respectively; Tables 3 and 4). In contrast, no difference was observed between N1 and N0 status (OS and DFS: $p = 0.429$ and $p = 0.289$, respectively). Overall, patients with regional lymph node metastases (N1 or N2) experienced significantly higher recurrence rates (72.2%) than nodal negative patients (38.9%; $p = 0.015$).

Concerning the localization of the lesions, tumors overlapping more parts of the pancreas presented significantly shorter OS and DFS as well ($p = 0.05$ and $p < 0.001$, respectively, Fig. S2). They were associated with more frequent rate of synchronous distant metastases ($p = 0.014$); however, the nodal status was not different compared to primaries involving only one anatomical part of the gland ($p = 0.117$).

The local resection status (R-status) and the local involvement of vessels (V), lymphatic vessel (L) or nerves (Pn) did not correlate with local and/or systemic relapse ($p = 0.387$, $p = 0.324$, $p = 0.395$, $p = 0.494$, respectively).

Synchronous metastatic disease undergoing surgical simultaneous resection did not influence the OS ($p = 0.466$), however, correlated significantly with shorter DFS ($p = 0.007$).

The majority of patients received adjuvant treatment (62.7%), with gemcitabine-based protocols representing the most common regimen (33.9%). With regard to the disease recurrence, within a median follow-up time of 48 months, 31 patients relapsed: 7 only locally, 6 locally and systemically and 18 only systemically. The liver was the most frequent site of distant metastases (74.4%). Data regarding adjuvant protocols and follow-up data are shown in Table 2.

Information on therapeutic strategies concerning disease relapse were only available for 23 of these 31 patients, whereby most received a systemic therapy (Table 2).

No significant differences were observed concerning OS and DFS in relation to any performed adjuvant therapy ($p = 0.542$ and $p = 0.159$, respectively). Similarly, the chemotherapeutic protocol administered in the adjuvant setting did not differ in OS and DFS ($p = 0.750$ and $p = 0.153$, respectively). Adjuvant

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Table 2 Histopathological findings, Systemic treatment, and Follow-up

Characteristics	n (%)	Characteristics	n (%)
pT stage (AJCC 8th Edition) (n = 59)		Neoadjuvant Therapy (n = 59)	
TX	1 (1.7)	No	50 (84.7)
T1	10 (16.9)	Gemcitabine based	2 (3.4)
T2	11 (18.6)	5-Fluorouracile based	5 (8.5)
T3	36 (61.0)	5-Fluorouracile based + RT	1 (1.7)
T4	1 (1.7)	Protocol not known	1 (1.7)
Tumor dimension (mm) (n = 55)	45.0 (0.0[c]-180.0)[a]	**Adjuvant Therapy (n = 59)**	
pN stage (AJCC 8th Edition) (n = 59)		No	22 (37.3)
N0	37 (62.7)	Gemcitabine-based	18 (30.5)
N1	13 (22.0)	Gemcitabine-based + RT	2 (3.4)
N2	9 (15.3)	5-FU-based	8 (13.5)
Removed lymph nodes (n = 58)	24.0 (1.0–62.0)[a]	5-FU-based + RT	1 (1.7)
Involved lymph nodes (n = 59)	0.0 (0.0–37.0)[a]	Platin-based	1 (1.7)
Lymphnode-Ratio (n = 58)	0.0 (0.0–0.77)[a]	Platin + RT	1 (1.7)
M stage (n = 59)		Tramafenib/Dabrafenib	1 (1.7)
M0	53 (89.8)	Protocol not known[b]	5 (8.)
M1	6 (10.2)	**First relapse (n = 59)**	
Local resection status (R) (n = 59)		No relapse	28 (47.5)
R0	50 (84.7)	Local	7 (11.9)
R1	9 (15.3)	Local + systemic	6 (10.1)
Perineural invasion (Pn) (n = 37)		Systemic	18 (30.5)
Pn0	15 (40.5)	**Metastases localization**	
Pn1	22 (59.5)	Liver	17 (74.0)
Vascular invasion (V) (n = 44)		Liver + Peritoneum	2 (8.7)
V0	17 (38.6)	Liver + Lung	1 (4.3)
V1	27 (61.4)	Paraaortic Lymphnodes	2 (8.7)
Lymphovascular invasion (L) (n = 44)		Paraaortic Lymphnodes + Peritoneum	1 (4.3)
L0	26 (59.1)	**Therapy of the relapse (n = 23/31)**	
L1	18 (40.9)	5-FU-based	7 (30.3)
Stadium (AJCC 8th Edition) (n = 59)		Gemcitabine-based	8 (34.7)
0	1 (1.7)	Gemcitabine + RT	1 (4.4)
IA	5 (8.5)	Temozolomide	1 (4.4)
IB	4 (6.8)	Tramafenib/Dabrafenib	1 (4.4)
IIA	25 (42.3)	Surgery	1 (4.4)
IIB	11 (18.6)	Local ablation	2 (8.7)
III	7 (11.9)	BSC	2 (8.7)
IV	6 (10.2)		

[a] Median value (range).
[b] Only chemotherapy.
[c] CAP 0 following neoadjuvant treatment; RT: radiotherapy; BSC: best supportive care.

treated patients presented higher rates of regional lymph node metastases (p = 0.004).

Of note, even though the type of administered neoadjuvant therapy did not influence OS and DFS following radical resection (p = 0.161 and p = 0.481, respectively), it led to conversion surgery in 9 patients.

The entire set of performed survival analyses is shown in Fig. 1 und Fig. S2).

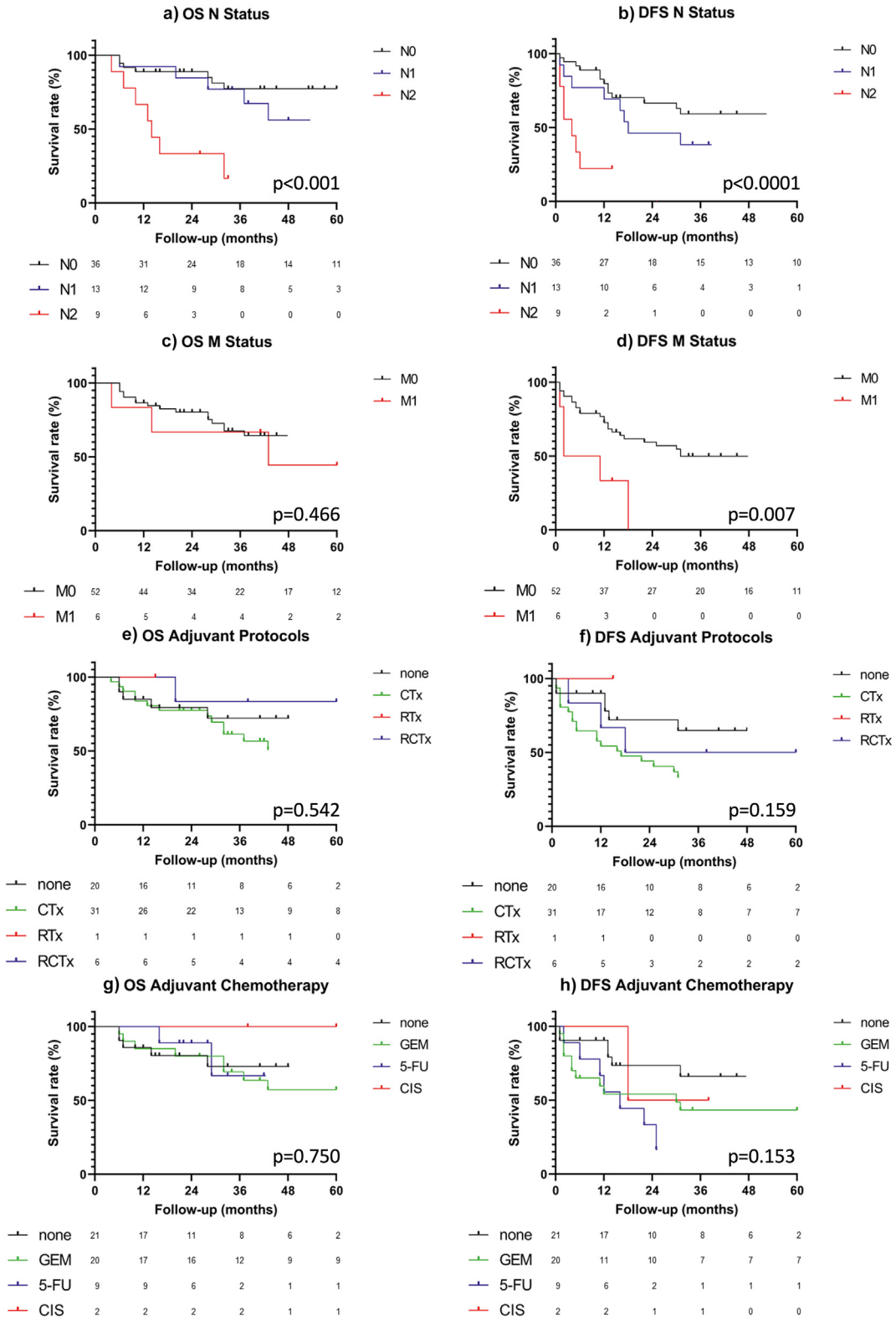

Figure 1 Kaplan–Meier survival curves with regard to the TNM staging accordingto the AJCC 8th Edition and to adjuvant therapies. **a)** OS and **b)** DFS in relationto N stage. **c)** OS and **d)** DFS in relation to M stage. **e)** OS and **f)** DFS with regard to adjuvant therapy protocols **g)** OS and **h)** DFS considering different adjuvant chemotherapy regimens (OS: overall survival; DFS: disease-free survival).

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Table 3 Survival analysis for factors affecting patients' overall survival using a Cox proportional hazard model

Factor	Univariable		Multivariable		
	Median survival (Months)	p	HR	95% CI	p
Female sex	Not reached	0.042	0.33	0.072-1.485	0.148
Age >70	32.0	0.012	2.78	1.094-7.064	0.032
Neo-adjuvant Therapy	Not reached	0.624			
DM type II	Not reached	0.493			
Loss of weight	Not reached	0.194			
Jaundice	Not reached	0.743			
Elevated CA19–9	Not reached	0.638			
R1 resection	37.0	0.200			
Tumor dimension > 40 mm	Not reached	0.642			
Nodal status					
N1	Not reached	0.429			
N2	14.0	<0.001	4.31	1.094-12.905	0.027*
Distant Metastases	43.0	0.525			
Lipase > 60 mg/dl	Not reached	0.429			
Adjuvant therapy	Not reached	0.816			

DM: diabetes mellitus; R1: resection status 1; *corrected according to Bonferroni.

Discussion

The present study represents one of the largest case series of surgically resected pure ACC of the pancreas in the currently available literature. The presented OS and DFS is comparable to other previous studies with similar patient cohorts and confirms that the prognosis of resected ACC tends to be better than that of resected PDAC.[3,5,6,16,19,21,22] Nevertheless, the reported 5-year OS in the available literature varies between 17,5% and 72%.[2,6,10,11,13,14,21–27] This wide range reflects probably the limitations of the mostly small (retrospective) case series, the bias of registries that lack data like, e.g., detailed adjuvant treatment regimens and, last but not least, the different inclusion criteria of

Table 4 Survival analysis for factors affecting patients' disease-free survival using a Cox proportional hazard model

Factor	Univariable		Multivariable		
	Median survival (Months)	p	HR	95% CI	p
Female sex	Not reached	0.003	0.29	0.082-1.001	0.050
Age >70	31.0	0.952			
Neo-adjuvant Therapy	25.0	0.527			
DM type II	Not reached	0.547			
Loss of weight	Not reached	0.194			
Jaundice	25.0	0.869			
Elevated CA19–9	31.0	0.921			
R1 resection	25.0	0.492			
Tumor dimension > 40 mm	Not reached	0.225			
Nodal status					
N1	18.0	0.237			
N2	4.0	<0.001	3.64	1.413-9.315	0.021*
Distant Metastases	2.0	0.008	2.03	0.708-5.833	0.187
Lipase > 60 mg/dl	25.0	0.804			
Adjuvant therapy	18.0	0.044	1.95	0.754-5.069	0.168

DM: diabetes mellitus; R1: resection status 1; *corrected according to Bonferroni.

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the studies ranging from resectable to non-resectable patients (See Table S1).

A major finding of this study is that N2 status revealed itself as the only significant, negative prognostic factor. Many previous studies defined the presence of regional lymph node metastases a negative prognostic factor.[2,8,14] We also observed worse OS for patients with positive N-status, however, only N2 was significantly related to shorter survival. Interestingly, between N0 and N1 there was no significant difference regarding OS and DFS.

As others already reported,[14,28] we also observed that OS is not related to tumor dimensions. There were also no associations between tumor dimension and the presence of regional lymph node metastases and/or synchronous hepatic metastases. In contrast, La Rosa et al. observed worse survival by very large tumors (>6.5 cm).[2] The reported minor importance of tumor dimension might reflect the more expansive rather than infiltrative growth pattern of ACC compared to PDAC which in regards to the prognosis is probably less crucial than the tumor capacity of blood and lymphatic vessel invasion. Though its expansive growth tendency – rather than infiltrative – the ACC shows indeed the microscopic tendency to invade local blood and lymphatic vessels, which is responsible for its systemic spread.

A peculiarity of ACC in comparison to PDAC is reflected by the survival advantage achieved performing radical surgery, even in case of limited metastasized disease.[22,29] Since so far no defined systemic therapy protocol was shown to positively influence the disease prognosis, surgery is also recommended for resectable stage IV ACC.[30] In our study, surgery in presence of up to three liver metastases resulted in a median OS which was not significantly different compared to survival rates of stages I-III. This is in line with other data that suggest local treatment strategies for stage IV ACC, even in a palliative setting.[9]

Despite a better OS, ACC shows high recurrence rates (52.5% in our study and up to 71.5% in previous series[14]) and it shows a quite short DFS, which was described to be similar to a comparative cohort of resected PDAC.[10] Given the frequent presence of regional lymph node metastases in these patients, the use of adjuvant systemic treatments seems preferable. However, only few studies showed improved prognosis after adjuvant treatments,[5,13,17] and our observations reflect these observations[5,8,11,12,14,17] not showing any advantage regarding OS and DFS for both gemcitabine and 5-FU based adjuvant therapy protocols. Furthermore, in contrast to previously observed beneficial effects of systemic therapy for resected stage IIB patients[31] we could not observe any beneficial survival effect of adjuvant therapies in the context of stage I, II disease. However, it is worth to mention that protocols like FOLFOX and FOLFIRINOX resulted in an increased OS in palliative, non-resectable stages.[11,32] Therefore, while radical surgical resection should always be attempted to achieve better prognosis in ACC patients there is currently no evidence for any adjuvant systemic treatment to sustain the curative approach.

Our series includes the currently largest patient group that underwent neoadjuvant therapies. Currently, there is no evidence available for applying neoadjuvant protocols for ACC. In the literature there are some studies, which observed the efficacy of 5-FU based protocols (principally FOLFOX and FOLFIRINOX) both for locally unresectable and limited metastatic disease,[16,21,23,29] however always in upfront not resectable patients. In those cases, radical resection (R0) after chemotherapy was reached. Also in 8 patients, neoadjuvant chemoradiation lead to tumor regression and finally R0 resection.[22,23] In our study, all 9 patients included had at least a radiologic partial response following neoadjuvant treatment resulting in conversion surgery and radical resection, with comparable OS to primarily operated patients. Altogether, these data suggest that neoadjuvant protocols might be of value in patients with advanced disease burden. However, in this series in only 2 ACC were biopsy-proven before starting neoadjuvant treatment. In 2 cases biopsy revealed initially PDAC while final diagnosis was ACC, and in 5 cases start of neoadjuvant treatment was only based on a radiologically highly suspicious lesion of the pancreas. To overcome this type of bias, future studies should focus on the effect of neoadjuvant strategies after histopathologic entity definition.

Considering the current literature and according to our observations, the ACC seems to be a tumoral entity, which may only take advantage from an aggressive surgical treatment. In fact, any additional systemic strategy failed to prevent the relapse after resection. In this sense, it is of great importance to do any possible effort to radically remove the tumoral mass.

Still, R1 resection did not represent a risk factor neither for OS nor for DFS. This might reflect the fact that the definition of R1 based on 1 mm clearance refers to ductal adenocarcinoma of the pancreas only. Indeed, there is no evidence for a clinical impact of this parameter when applying it for ACC, a tumour is known to have a less disperse and more expansive growth pattern with pushing-type margins.[33]

Limitations of this study include the retrospective design and the relative long observation time (2002–2020). Of utmost importance, different institutions applied different protocols approaching a very rare entity for which no guidelines exist. Still, similar therapeutic strategies were applied in very different contexts.

Together with a rather high number of patients lost to follow-up these aspects represent an important limiting factor when describing the real nature of pure ACC and its response to different therapies. On the other hand, the rigorous review of each specimen, as well as the exclusion of any histologic doubtful case gives to our series good data quality and high homogeneity of the selected cases. Also, the median follow-up time of this cohort was quite long (48 months), thus allowing us to be more precise in regard to the postoperative outcomes of this entity.

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Conclusion

The presented data of a homogeneous cohort of pure ACCs confirm those already published in previous multicentric and national databases-based studies, supporting the commitment towards aggressive surgery as the only curative treatment strategy, potentially even in the presence of oligometastatic disease.

Keeping in mind the limited case number, our results may support the use of neoadjuvant treatment protocols for upfront-unresectable ACC since in 9 patients neoadjuvant treatment resulted in conversion surgery achieving comparable long-term survival with those who were primarily resected. Similarly, there is still no consensus on which adjuvant protocols should be applied in the context of a multimodal treatment strategy. Further studies addressing the underlying tumor biology of ACC are urgently needed to refine treatment strategies in these patients.

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Conflict of Interest

The authors declare no Conflict of Interest for this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2023.07.897.

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