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Short Report

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The impact of adjuvant therapy on outcome in UICC stage I pancreatic cancer

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Abstract

Adjuvant chemotherapy has become standard of care for pancreatic ductal adenocarcinoma (PDAC) as it improves patient outcome. However, its clinical meaning in early-stage, UICC I tumors remains uncertain. We examined the effect of adjuvant therapy on disease-free survival (DFS) and overall survival (OS) of UICC stage I PDAC patients treated at an academic tertiary care center between 2000 and 2016. Among 124 patients (69 male, 55 female; median age 68 years, range 41-84 years) with UICC stage I disease, adjuvant therapy improved both DFS (19.8 vs 12.8 months, HR 0.59, 95% CI: 0.37-0.94, $P = .03$) and OS (40.9 vs 20.3 months, HR 0.54, 95% CI: 0.35-0.84, $P = .005$). Multivariate analyses and propensity score matching confirmed the prognostic impact of adjuvant therapy independent of localization, differentiation and R-status. Thus, every patient with UICC I PDAC should receive adjuvant chemotherapy as it may improve outcome significantly. Our findings support the concept of PDAC as systemic disease from early stages on.

KEYWORDS
adjuvant therapy, early-stage pancreatic cancer, outcome

What's new?

The incidence of early-stage pancreatic ductal adenocarcinoma (PDAC) is on the rise, casting new light on pre-existing therapeutic challenges. Overcoming these challenges may be possible with adjuvant chemotherapy, though little is known about its clinical relevance for early-stage disease. The present study examined the impact of adjuvant chemotherapy on survival specifically among stage I PDAC patients. Analyses show that the approach significantly improves disease-free and overall survival, with 5-year survival rate about 26.6% among adjuvant therapy-treated patients and 10.5% for nonadjuvant patients. The findings suggest that adjuvant chemotherapy should be offered to all PDAC patients after resection.

Abbreviations: 95% CI, 95% confidence interval; DFS, disease free survival; HR, hazard ratio; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; UICC, Union Internationale Contre le Cancer.

1 | INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) has a dismal prognosis, also in the minority of primarily resectable patients.[1] Adjuvant systemic chemotherapy has become standard-of-care in this situation, as it increases both disease-free survival (DFS) and overall survival (OS) significantly.[2] Since the CONKO-001 study,[3,4] adjuvant gemcitabine therapy is widely employed although other regimens showed similar[5] or higher efficacy, at the cost of higher toxicity rates.[6] The clinical meaning of adjuvant therapy in early-stage PDAC, that is, UICC stage I (pT1/2, pN0-tumors), however, remains a matter of debate[7] as data on this subgroup cannot be readily extracted from the trials on adjuvant treatment. In the CONKO-001 trial, 49 patients had pT1- or pT2-tumors, but no information on UICC stage or pN-status was published although these patients had comparable OS hazard ratios in the adjuvant gemcitabine arm as higher pT-stage patients (HR 0.58; 95% CI: 0.30-1.10 vs HR 0.78; 95% CI: 0.61-0.99).[3,4] Despite the large group of 104 patients with stage I disease (UICC fifth edition, 1997) in the ESPAC-3 trial, no analysis of this subgroup was published to date.[5] In PRODIGE-24, only 26 patients had stage I disease (UICC 7th edition, 2010), rendering a comparative analysis of this subgroup impossible.[6] Scarce retrospective data, relying on OS as surrogate marker only, indicated a beneficial effect of adjuvant therapy also in stage I PDAC.[8] In all of these studies the tumor extent was assessed according to categories published before the introduction of the current UICC tumor classification, which introduced a novel definition of pT-stage based on tumor diameter.[9] This resulted not only in more accurate prognostication by

TABLE 1 Baseline clinicopathological variables and their differences (Pearson χ^2 test) in each study cohort

	No adjuvant treatment (n = 44) n (%)	Adjuvant treatment (n = 80) n (%)	*P*-value (χ^2-test)
Sex			
Male	28 (63.6)	41 (51.3)	.18
Female	16 (36.4)	39 (48.7)	
Age, years			
≤68	17 (38.6)	44 (55.0)	.08
>68	27 (61.4)	36 (45.0)	
Tumor site			
Head	37 (84.0)	62 (77.5)	.38
Body or tail	7 (16.0)	18 (22.5)	
pT (UICC 2017)			
pT1a	2 (4.5)	1 (1.3)	.15
pT1b	0 (0)	3 (3.8)	
pT1c	11 (25.0)	11 (13.8)	
pT2	31 (70.5)	65 (81.3)	
UICC stage (2017)			
IA	13 (29.5)	15 (18.8)	.17
IB	31 (70.5)	65 (81.2)	
Resection status			
R0	32 (72.7)	62 (77.5)	.55
R1	12 (27.3)	18 (22.5)	
Tumor differentiation			
G1-G2	23 (52.3)	25 (31.3)	.02
G3-G4	21 (47.7)	55 (68.7)	
5-year-survival			
Deceased	34 (89.5)	47 (73.4)	.05
Alive	4 (10.5)	17 (26.6)	
Adjuvant treatment rates			
Year 2000-2005	22 (56.4)	17 (43.5)	.003
Year 2006-2010	11 (30.6)	25 (69.4)	
Year 2011-2016	11 (22.5)	38 (77.5)	
Smoking	5 (11.4)	17 (21.3)	.31
Diabetes	11 (25.0)	16 (20.0)	.25

disease stage but also in downstaging of a significant proportion of previous pT3-tumors to pT2- or even pT1-stage.[10] Although the definition of stage I disease did not change over time, which can thus be considered a consistent entity, with the current staging system and generally increasing incidences of stage I PDAC,[11] significantly more tumors fall into this category. Consequently, more early-stage patients will be diagnosed, confronting the treating physicians with the question whether to recommend adjuvant treatment or not.

2 | MATERIALS AND METHODS

Clinicopathological information and data on patient outcome and treatment were derived from the databases of the Institute of Pathology, the Munich Cancer Registry and the University Hospital of Ludwig-Maximilians-University. Each cases' TNM classification was updated to the current UICC staging system.[9] Survival analyses were conducted using univariate and multivariate Cox regression models to evaluate the association of adjuvant therapy with DFS and OS independent of other clinicopathologic factors. DFS times were calculated from the date of surgery to radiologically or clinically apparent disease relapse. OS times were calculated from surgery to death by disease. Only patients with histologically confirmed pancreatic ductal adenocarcinoma, curative intent resection and no neoadjuvant therapy were included. Patients resected for other pancreatic neoplasia such as neuroendocrine tumors or acinar cell carcinoma, patients receiving antineoplastic agents for neoadjuvant therapy or other reasons and patients which deceased due to perioperative mortality within 30 days postsurgery or other causes than pancreatic cancer were excluded. Five-year survival rates were calculated for patients with follow-up data only, excluding patients lost to follow-up. Statistical significance was indicated by a P value <.05. Propensity score matching was conducted using Python software (version 3.7, https://www.anaconda.com; Anaconda Inc., Austin, Texas) and the pymatch package (version 0.3.4; https://github.com/benmiroglio/pymatch).

3 | RESULTS

The study cohort consisted of 69 men and 55 women (median age [range] 68 years, [41-84 years]), resected between 2000 and 2016 for histologically confirmed PDAC of which 80 patients (64.5%)

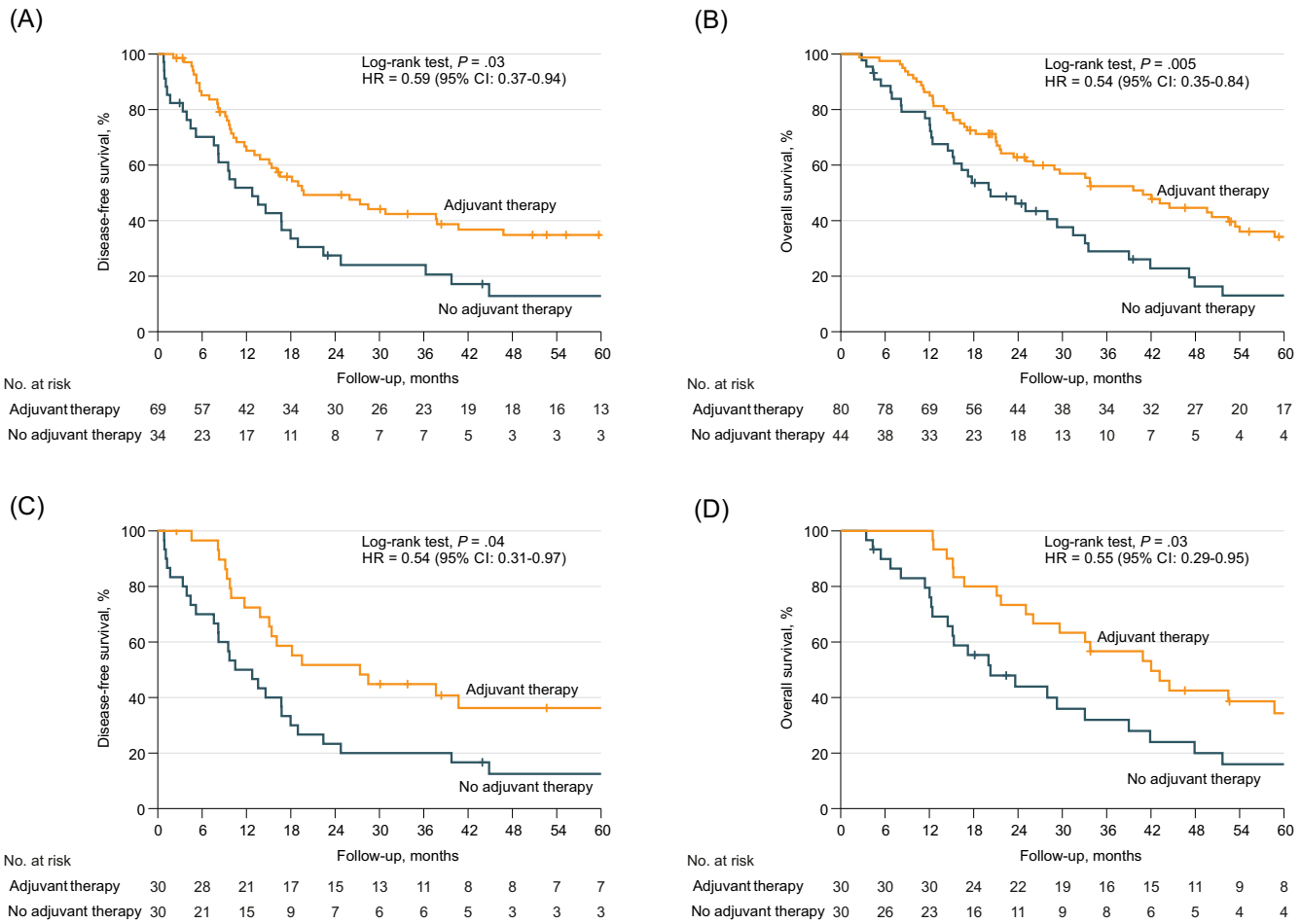

FIGURE 1 Kaplan-Meier curves illustrating the association of adjuvant therapy with disease-free survival and overall survival according to the application of adjuvant therapy in the entire study cohort (A,B) and the propensity-score matched cohort (C,D) [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Disease-free survival and overall survival times in the entire study cohort and the stage IA and stage IB subgroups

	Adjuvant treatment	n	%	DFS (months)	95% CI	*P* (log-rank)	HR	95% CI	n	OS (months)	95% CI	*P* (log-rank)	HR	95% CI
Total	+	69	64.5	19.8	7.2-32.3	.03	0.59	0.37-0.94	80	40.9	28.7-53.1	.005	0.54	0.35-0.84
	−	34	35.5	12.8	7.1-18.4				44	20.3	10.9-29.6			
Stage IA	+	13	53.6	30.8	13.4-48.3	.07	0.39	0.14-1.13	15	52.5	38.1-66.8	.002	0.25	0.09-0.64
	−	8	46.4	13.6	8.1-19.1				13	29.3	7.8-50.7			
Stage IB	+	56	67.7	19.0	5.6-32.4	.06	0.60	0.35-1.02	65	33.7	14.6-52.8	.07	0.63	0.38-1.04
	−	26	32.3	9.7	6.0-13.4				31	20.0	9.6-30.4			

received adjuvant therapy (Table 1). The median follow-up time was 63.8 months (95% CI: 53.7-73.9) for DFS and 76.7 months (95% CI: 56.5-96.9) for OS. Upon data cut-off (May 2021), 72.8% of patients had a radiologically and/or clinically confirmed relapse event and 27.2% were censored for progression; 70.2% had deceased by disease and 29.8% of patients were censored for OS. After reclassification of the disease stages according to the current system,[9] 96 tumors (77.4%) were classified as pT2-stage and 28 (22.6%) as pT1-stage (Table 1). In the patient subgroup treated with adjuvant therapy, the following regimens were administered: single-agent gemcitabine or gemcitabine-based chemotherapy (n = 56; 70.0%), gemcitabine-based chemoradiotherapy (n = 18, 22.5%), 5-fluorouracil-based chemotherapy or chemoradiotherapy (n = 2, 2.5%) and adjuvant chemotherapy or chemoradiotherapy not otherwise specified (n = 4, 5.0%). The application of adjuvant therapy increased with the time period in which the patients underwent surgery, with adjuvant treatment rates of 43.5% in the years 2000 to 2005, over 69.4% between 2006 and 2010 to 77.5% from 2011 to 2016 (Table 1). In univariate analyses, the use of adjuvant therapy was associated with superior DFS and OS in the entire study cohort (DFS 19.8 vs 12.8 months, HR 0.59, $P = .003$; OS 40.9 vs 20.3 months, HR 0.54, $P = .005$, Figure 1A,B) as well as in the UICC stage IA and stage IB subgroups (Table 2).

Multivariate Cox regression analyses adjusting for age, tumor differentiation grade and R-status confirmed adjuvant therapy as independent prognosticator for DFS ($P = .01$; HR 0.51) and OS ($P = .001$; HR 0.45, Table S1). The impact of adjuvant therapy on OS was also reflected in 5-year-survival rates, with 26.6% in the adjuvant treatment group and 10.5% in the group without adjuvant therapy (Table S2). After propensity score matching for 60 patients to reduce the imbalances between both study cohorts (Table S3), univariate analyses verified the prognostic impact of adjuvant therapy (Figure 1C,D) and were confirmed in additional multivariate analyses (Table S4).

4 | DISCUSSION

As recently outlined by Gervaso et al,[7] an evidence-based decision making process regarding adjuvant treatment for stage I PDAC patients remains a challenge and there is an unmet need for more data on these patients. They were included in all large adjuvant (chemo-) therapy trials, but represented a small subgroup within the overall population.[3-6] Only the CONKO-001 trial had an observation-only arm, which would allow to conclude on the value of adjuvant chemotherapy in stage I patients. Practice-changing studies conducted later on[5,6] did not include a chemotherapy-free control arm—thus the meaning of adjuvant treatment for stage I patients compared to surgery alone cannot be derived.

This retrospective study from our single high-volume cancer center is among the first reports to address the question if adjuvant treatment is beneficial in stage I PDAC and we found evidence that adjuvant treatment improves DFS and OS in this subgroup. All patients included

underwent a TNM-stage reclassification based on the current UICC staging system.[9] We know that retrospective, single-center data may be limited and biased. As expected in a nonrandomized setting, we observed a higher number of younger patients in the adjuvant cohort (55% vs 39%), and more patients with G3/4 tumors (69% vs 48%). We tried to overcome these limitations by a propensity score matching approach which confirmed the results of the entire cohort. Due to the long observation period from 2000 to 2016, the applied regimens were heterogeneous. However, of 80 patients in the adjuvant cohort, the majority (n = 74) received single-agent gemcitabine or gemcitabine-based chemotherapy. Although no patient received adjuvant mFOLFIRINOX, even stronger survival differences compared to observation only can be expected with this much more active regimen.

PDAC is considered a systemic disease upon diagnosis[12] and our data clearly support this hypothesis: even in stage IB PDAC, the median DFS without adjuvant treatment was estimated as 9.7 months and median OS 20.0 months only, whereas with adjuvant treatment these survival times increased to 19.0 months for DFS and 33.7 months for OS (Table 2).

In this retrospective cohort study, the use of adjuvant treatment in UICC stage I PDAC significantly improved patient outcome regarding both DFS and OS. With the advent of ever more sophisticated diagnostic approaches for early disease detection such as circulating tumor DNA sequencing[13] and artificial intelligence based integration of complex patient data including biomarkers, health records and imaging,[14,15] more early stage patients will be diagnosed in the future. Due to the lack of evidence for this relevant patient population, our data support the use of established adjuvant treatment options in these patients. A prospective confirmation of our findings within a randomized trial is desirable.

AUTHOR CONTRIBUTIONS

Michael Guenther, Volker Heinemann, Stefan Boeck, Jens Werner, Jutta Engel and Steffen Ormanns provided data. Michael Guenther and Steffen Ormanns analyzed data, drafted figures and tables. Michael Guenther, Stefan Boeck and Steffen Ormanns drafted the article. The work reported in the article has been performed by the authors, unless clearly specified in the text. All authors reviewed and approved the final version of the article.

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CONFLICT OF INTEREST

SB received honoraria for scientific presentations, consultation and travel support unrelated to the present study from Celgene, Servier, MSD, Janssen-Cilag, Astra-Zeneca, Incyte and Fresenius. VH received honoraria for talks and advisory board role or research funding unrelated to the present study from Merck, Amgen, Roche, Sanofi, Sirtex, Servier, Pfizer, Pierre-Fabre, Astra-Zeneca, BMS, MSD, Novartis, Boehringer Ingelheim, Celgene, Oncosil, Terumo and Seagen. All other authors declare no conflict of interested related to the present study.

DATA AVAILABILITY STATEMENT

Anonymized raw data on the study can be obtained from the corresponding author on request.

ETHICS STATEMENT

Due to the observation period of our study (2000 to 2016) and the poor prognosis of the disease, patient informed consent could not be obtained. Considering these circumstances, the ethics committee of the medical faculty of Ludwig-Maximilians-University approved the use of anonymized patient data without obtaining the patients' informed consent (project 20-081 to SO).

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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