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Data Article

Data of 'Circulating tumor DNA correlates with tumor burden and predicts outcome in pancreatic cancer irrespective of tumor stage'

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ABSTRACT

This data article subsumes the data acquiration process, analysis and results of 'Circulating tumor DNA correlates with tumor burden and predicts outcome in pancreatic cancer irrespective of tumor stage' published in European Journal of Surgical Oncology (Eur J Surg Oncol. 2021 Dec 1:S0748-7983(21)00947-1. doi:10.1016/j.ejso.2021.11.138. PMID: 34876329) (Kirchweger et al., 2021). 28.5 mL of blood was obtained from 60 patients with localized pancreatic cancer directly prior to curative intended surgery as well as from 47 patients with metastasized pancreatic cancer (PDAC) directly prior to palliative intended systemic treatment initiation. Cell-free DNA preparation was done on the Chemagic

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360 (Perkin Elmer, Waltham, Massachusetts, USA) using the kits CMG-1304 and CMG-844 from the same provider and quantified using the Quantus fluorometer (Promega, Madison, Wisconsin, USA). Screening for most common KRAS alterations (KRAS G12/G13 screening kit and additionally for KRAS Q61 if screening was negative) was performed utilizing the QX200™ Droplet Digital™ PCR System from Bio-Rad (Bio-Rad Laboratories, Hercules, CA, USA). Volumetric analysis was performed on contrast enhanced dual-energy CT scans in the arterial and portal venous phase prior to treatment initiation using Syngo.via (Siemens Healthcare, Forchheim, Germany) on MM Oncology Workflow adhering to RECIST 1.1 criteria (Eisenhauer et al., 2009). CtDNA predicts outcome in localized and disseminated disease. Moreover, it correlates with distant metastasis volume and positive lymph nodes but not primary tumor volume and therefore could indicate subclinical synchronous distant metastases in localized PDAC undetectable by current gold standard (computed tomography).

Specifications Table

Subject	Oncology
Specific subject area	Circulating tumor DNA as novel biomarker for outcome prediction in pancreatic cancer
Type of data	Tables, Figures, Raw data
How the data were acquired	Blood collection via cell-free DNA tubes (Roche, Basel, Switzerland). Centrifugation for 10 min at 200 g and 10 min at 1500 g. Storage at -20 C. Preparation on Chemagic 360 (Perkin Elmer, Waltham, Massachusetts, USA) using the kits CMG-1304 and CMG-844 which resulted in a final DNA volume of 40–50 µL quantified using Quantus fluorometer (Promega, Madison, Wisconsin, USA). Screening for most common KRAS alterations was performed using QX200™ Droplet Digital™ PCR System from Bio-Rad (Bio-Rad Laboratories, Hercules, CA, USA). All samples were screened for KRAS G12/13. Negative Samples were further screened for alterations in KRAS Q61. Data analysis was performed using QuantaSoft™ Analysis Pro-software (version 1.0.596). A threshold of 3 mutant droplets was applied for the detection of ctDNA positivity. Volumetric data was assessed from contrast enhanced dual-energy CT scans in the arterial and portal venous phase prior to treatment initiation using Syngo.via (Siemens Healthcare, Forchheim, Germany) using MM Oncology Workflow adhering to RECIST 1.1 criteria [2].
Data format	Analyzed (Figures, Tables), raw (Excel)
Description of data collection	Blood collection and cfDNA preparation was performed at the Ordensklinikum Linz, Austria. Digital droplet PCR was performed at the Medical University of Innsbruck, Austria. Volumetric analysis was performed at the Ordensklinikum Linz, Austria.
Data source location	Mendeley Data: doi: 10.17632/5rzgwn8wv9.1
Data accessibility	Mendeley Data: doi: 10.17632/5rzgwn8wv9.1
Related research article	Kirchweger P, Kupferthaler A, Burghofer J, Webersinke G, Jukic E, Schwendinger S, Weitzendorfer M, Petzer A, Függer R, Rumpold H, Wundsam H. Circulating tumor DNA correlates with tumor burden and predicts outcome in pancreatic cancer irrespective of tumor stage. Eur J Surg Oncol. 2021 Dec 1:S0748-7983(21)00947-1. doi: 10.1016/j.ejso.2021.11.138. Epub ahead of print. PMID: 34876329.

Value of the Data

- Detection of circulating tumor DNA (ctDNA) prior to treatment initiation can predict outcome in pancreatic cancer irrespective of tumor stage. Moreover, ctDNA shows no correlation with primary tumor volume, but nodal positivity in localized disease and liver metastases volume in disseminated disease.
- For localized disease, detection of pretherapeutic ctDNA could indicate subclinical presence of synchronous distant metastases (e.g. in the liver) or locally advanced disease (nodal positivity) not detectable using computed tomography.
- For disseminated disease, detection of pretherapeutic ctDNA predicts significantly worse OS.
- Detectability of ctDNA ranges between 10 and 20% (stage I-III) and 50–60% (stage IV) in pancreatic cancer depending on the tumor stage when screening for KRAS G12/13 and KRAS Q61 in G12/13 negative samples (additional 15.2% detectability in metastatic disease). Nevertheless, additional screening for BRAF, SMAD4 or TP53 via NGS results only in a further 6.9% but may be not economical.

1. Data Description

- Tables 1 and 2 describe the patient demographics, volumetric data and liquid biopsy results for localized (Table 1) and disseminated (Table 2) pancreatic ductal adenocarcinoma with regard to their ctDNA detectability.
- Table 3 shows the Spearman correlation coefficients of ctDNA and conventional tumor markers with volumetric subsets of localized and metastatic pancreatic ductal adenocarcinoma. These results indicate ctDNA deriving mainly from liver metastases in disseminated disease and major nodal involvement in localized disease.
- Fig. 1 visualizes the correlation of ctDNA with tumor volume subsets (A-D) of metastatic pancreatic ductal adenocarcinoma that is mentioned in Table 3 in scatter diagrams.
- Fig. 2 outpoints a major impact on disease-free-survival of localized pancreatic ductal adenocarcinoma when ctDNA is detectable in patients' blood prior to treatment. Additionally, these results suggest that ctDNA positivity in localized PDAC may indicate subclinical disseminated disease culminating a median DFS of 3.3 compared to 18.1 months when not detectable in pre-treatment liquid biopsy.
- Fig. 3 outpoints a major impact of metastasis volume (A) on overall-survival in disseminated pancreatic ductal adenocarcinoma (median OS 6.8 vs. 11.7 months). Even greater influence could be shown for liver metastasis volume (B) in the same patient cohort (median OS 1.8 vs. 11.7 months).
- A cumulative raw data file for the entire analyses of 'Circulating tumor DNA correlates with tumor burden and predicts outcome in pancreatic cancer irrespective of tumor stage' is provided in Excel format in the supplementals.

Table 1
Patient demographics for localized pancreatic ductal cancer. Values are given as n (%) unless otherwise indicated.

Localized PDAC	Overall $n = 60$	ctDNA positive $n = 6$	ctDNA negative $n = 54$	p
Age Median (IQR)	69 (60–77)	76 (73–79)	54 (59–77)	0.039*
Male sex	39 (65)	3 (50)	36 (66.7)	0.421
ECOG PS				
0	40 (66.7)	4 (66.6)	36 (66.7)	1.000
1	18 (30)	2 (33.3)	16 (29.6)	0.852
≥2	2 (3.3)	0	2 (3.7)	0.634
ASA				
1	8 (13.3)	2 (33.3)	6 (11.1)	0.132
2	35 (58.3)	2 (33.3)	33 (61.1)	0.194
≥3	17 (28.3)	2 (33.3)	15 (27.8)	0.776
Tumor localization				
Head	52 (86.7)	4 (66.6)	48 (88.9)	0.089
Body	6 (10)	2 (33.3)	4 (7.4)	0.007*
Tail	2 (3.3)	0	2 (3.7)	0.631
Tumor stage				
UICC I	11 (18.3)	0	11 (20.4)	0.225
UICC II	23 (38.3)	2 (33.3)	21 (38.9)	0.792
UICC III	26 (43.3)	4 (66.6)	22 (40.7)	0.194
UICC IV	0	0	0	1.000
cT1	14 (23.3)	0	14 (25.9)	0.158
cT2	36 (60)	4 (66.6)	32 (59.3)	0.728
cT3	8 (13.3)	1 (16.7)	7 (12.9)	0.802
cT4	2 (3.3)	1 (16.7)	1 (1.9)	0.057
cN+	25 (41.7)	3 (50)	22 (40.7)	0.527
Neoadjuvant CTX	8 (13.3)	1 (16.7)	7 (12.9)	0.440
Adjuvant CTX	52 (86.7)	5 (83.3)	47 (87)	0.802
Resected	60 (100)	6 (100)	54 (100)	1.000
R0	48 (80)	6 (100)	42 (77.7)	0.200
R1	9 (15)	0	9 (16.7)	0.200
Rx, CRM+	3 (5)	0	3 (5.6)	0.557
Type of resection				
TP	18 (30)	0	18 (33.3)	0.094
DP	4 (6.7)	2 (33.3)	2 (3.7)	0.006*
PHR	38 (63.3)	4 (66.6)	34 (63)	0.859
Vascular involvement	26 (43.3)	6 (100)	20 (37)	0.621
Venous contact	18 (30.0)	1 (16.7)	17 (31.5)	0.321
Arterial contact	4 (6.7)	4 (66.7)	0	0.001**
Both	4 (6.7)	1 (16.7)	3 (5.6)	0.458
Vascular resection	20 (33.3)	0	20 (37)	0.070
Lymph nodes harvested	22 (17–29)	25 (18.75–32)	21 (16–29)	0.315
Positive lymph nodes	2 (0–7)	5 (0.75–15.75)	2 (0–7)	0.264
Node ratio	0.14 (0–0.24)	0.22 (0.05–0.49)	0.12 (0–0.24)	0.225
Blood loss (mL) Median (IQR)	300 (200–400)	200 (125–275)	335 (266–373)	0.027*
OP time (min.) Median (IQR)	335 (270–374)	347 (278–450)	335 (266–373)	0.775
Days at ICU Median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.353
Clavien Dindo ≥3b	6 (10)	1 (13.3)	5 (9.3)	0.569
POPF ≥*B*	5 (8.3)	0	5 (9.3)	0.436
Total tumor volume (mL) Median (IQR)	5.99 (3.23–13.2)	11.43 (5.04–14.55)	5.2 (3.16–13.06)	0.314

(*continued on next page*)

Table 1 (*continued*)

Localized PDAC	Overall $n = 60$	ctDNA positive $n = 6$	ctDNA negative $n = 54$	p
Primary tumor volume (mL)	5.99	11.43	5.2	0.314
Median (IQR)	(3.23–13.2)	(5.04–14.55)	(3.16–13.06)	
Histopathological size (mm)	31.5 (22.5–36.5)	29.5 (23.25–37)	34.5 (22–37.25)	0.800
Median (IQR)				
CEA (ng/mL)	3.2 (1.65–4.53)	3.8 (1.93–5.6)	3.05 (1.65–4.53)	0.653
Median (IQR)				
CA 19–9 (U/mL)	364.2	169.9	397.4	0.334
Median (IQR)	(48.1–1174.7)	(40.8–459.9)	(64.5–1357.6)	
cfDNA (ng/µL)	0.95 (0.61–1.6)	3.42	0.92 (0.61–1.51)	0.165
Median (IQR)		(0.58–12.93)		
ctDNA (ng/mL)	2.64	11.84	2.12	0.012*
Median (IQR)	(1.47–11.55)	(4.99–17.99)	(1.14–4.81)	
ctDNA (MAF%)	0 (0–0.11)	0.225	0 (0–0.08)	
Median (IQR)		(0.12–1.03)		0.000**

Abbreviations: ASA American Society of Anesthesiologists physical status classification system; cfDNA cell-free DNA; CRM circumferential resection margin; cT clinical Tumor site and size; cN clinical lymph node involvement; ctDNA circulating tumor DNA; CTX chemotherapy; DP distal pancreatectomy; ECOG PS Eastern Coopertive Oncology Group performance state; ICU intensive care unit; IQR interquartile range; MAF minor allele frequency; *p*-value ($p < 0.05$*, $p < 0.005$**); PHR pancreatic head resection; POPF postoperative pancreatic fistula; R residual tumor; TP total pancreatectomy; UICC Union internationale contre le cancer.

This table is provided by the authors of 'Circulating tumor DNA correlates with tumor burden and predicts outcome in pancreatic cancer irrespective of tumor stage' published in European Journal of Surgical Oncology (Eur J Surg Oncol. 2021 Dec 1:S0748-7983(21)00947-1. doi: 10.1016/j.ejso.2021.11.138. PMID: 34876329) [1].

Table 2
Patient demographics for metastatic pancreatic ductal cancer. Values are given as n (%) unless otherwise indicated.

Metastasized PDAC	Overall $n = 47$	ctDNA positive $n = 27$	ctDNA negative $n = 20$	p
Age	65 (58–73)	64 (57–71)	66 (59–73)	0.438
Median (IQR)				
Male sex	31 (66)	17 (63)	14 (70)	0.618
ECOG PS				
0	31 (66)	21 (77.8)	10 (50)	0.049*
1	12 (25.5)	3 (11.1)	9 (45)	0.009*
≥2	4 (8.5)	3 (11.1)	1 (5)	0.493
Chemotherapy Line				
1 Line	30 (63.8)	14 (51.9)	16 (80)	0.049*
2 Line	12 (25.6)	8 (29.6)	4 (20)	0.247
3 Line	5 (10.6)	5 (18.6)	0	0.044*
Primary localization				
Head	17 (37)	9 (34.6)	8 (40)	0.645
Body	10 (21.7)	6 (23.1)	4 (20)	0.845
Tail	6 (13)	4 (15.4)	2 (10)	0.508
Local relapse	13 (28.3)	7 (26.9)	6 (30)	0.217
Tumor stage				
cT1	3 (6.4)	2 (7.4)	1 (5)	0.741
cT2	26 (55.3)	16 (59.3)	10 (50)	0.532
cT3	10 (21.3)	5 (18.5)	5 (25)	0.595
cT4	8 (17)	4 (14.8)	4 (20)	0.644
cN+	25 (53.2)	15 (55.5)	10 (50)	0.936
Site of metastases				
Liver	34 (72.3)	24 (88.9)	10 (50)	0.028*
Lung	16 (34)	10 (37)	6 (30)	0.618
Lymph nodes	8 (17)	5 (18.5)	3 (15)	0.754

(*continued on next page*)

Table 2 (*continued*)

Metastasized PDAC	Overall $n = 47$	ctDNA positive $n = 27$	ctDNA negative $n = 20$	p
Peritoneum	12 (25.5)	7 (25.9)	5 (25)	0.943
Synchronous	28 (59.6)	16 (59.3)	12 (60)	0.196
Metachronous	19 (40.4)	11 (40.7)	8 (40)	0.732
Vascular involvement	23 (48.9)	12 (44.4)	11 (55)	0.528
Venous only	4 (17.4)	3 (11.1)	1 (5)	0.325
Arterial only	3 (13)	2 (7.4)	1 (5)	0.598
Both	16 (69.6)	7 (25.9)	9 (45)	0.232
Total tumor volume (mL)	28.25	40.68	11.26	0.073
Median (IQR)	(8.06–97.2)	(12.74–139.44)	(5.73–56.69)	
Primary tumor volume (mL)	9.67	11.54	8.31	0.614
Median (IQR)	(3.89–25.92)	(3.6–29)	(3.99–19.09)	
Liver met volume (mL)	19.99	30	3.66	0.025*
Median (IQR)	(3.95–25.92)	(9.34–87.41)	(1.4–22.23)	
Lung met volume (mL)	1.42	12.63	1.42	0.706
Median (IQR)	(0.17–39.98)	(0.16–156.22)	(0.33–34.21)	
Lymph node volume (mL)	15.51	3.75	101.7	0.228
Median (IQR)	(2.58–96.35)	(2.16–60.92)	($n = 1$)	
CEA (ng/mL)	5.9 (2.55–11.28)	8.6 (0.75–5.19)	5.35 (1.63–6.98)	0.052
Median (IQR)				
CA 19–9 (U/mL)	995.1	3074.7	267.2	
Median (IQR)	(228.4–5447.5)	(983.2–32,498.5)	(54.6–647)	0.000**
cfDNA (ng/µL)	0.97 (0.63–1.77)	0.99 (0.75–5.19)	0.79 (0.56–1.6)	0.155
Median (IQR)				
ctDNA (ng/µL)	5.33	16.04	1.11	
Median (IQR)	(1.3–38.74)	(3.96–741.78)	(0.7–1.54)	0.000**
ctDNA (MAF%)	0.15 (0.05–1.51)	1.47 (0.25–7.58)	0.05 (0.0025–0.07)	
Median (IQR)				0.000**

Abbreviations: cfDNA cell-free DNA; CRM circumferential resection margin; cT clinical Tumor site and size; cN clinical lymph node involvement; ctDNA circulating tumor DNA; ECOG PS Eastern Cooperative Oncology Group performance state; IQR interquartile range; MAF minor allele frequency; *p*-value ($p < 0.05^{*}$, $p < 0.005^{**}$).

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Table 3
Spearman correlation coefficients for cell-free-DNA, circulating-tumor-DNA and CA 19-9 and tumor volume.

Localized PDAC	Volume (total)	p	Volume (PRIM)	p	LN (pos)	p	LN (ratio)	p		
cfDNA (ng/µL)	.081	.619	.081	.619	.116	.391	.111	.413		
ctDNA MAF (%)	.077	.573	.077	.573	.331*	.030*	.393*	.009*		
CA 19-9 (U/mL)	.104	.488	.104	.488	.145	.320	.146	.318		
Metastasized PDAC	Volume (total)	p	Volume (PRIM)	p	Volume (HEP)	p	Volume (PUL)	p	Volume (OTH)	p
cfDNA (ng/µL)	.397*	.009*	.034	.841	.391*	.011*	.017	.918	.011	.945
ctDNA MAF (%)	.473*	.026*	−0.035	.878	.004*	.600**	.045	.784	.182	.254
CA 19-9 (U/mL)	.061	.709	.105	.543	.197	.391	.094	.574	.094	.574

Abbreviations: cfDNA: cell-free DNA; ctDNA: circulating tumor DNA; HEP: liver tumor volume; LN: lymph nodes; MAF: minor allele frequency; *p*-value ($p < 0.05^{*}$, $p < 0.005^{**}$); OTH: other tumor volume; PUL: lung tumor volume; PRIM: primary tumor volume.

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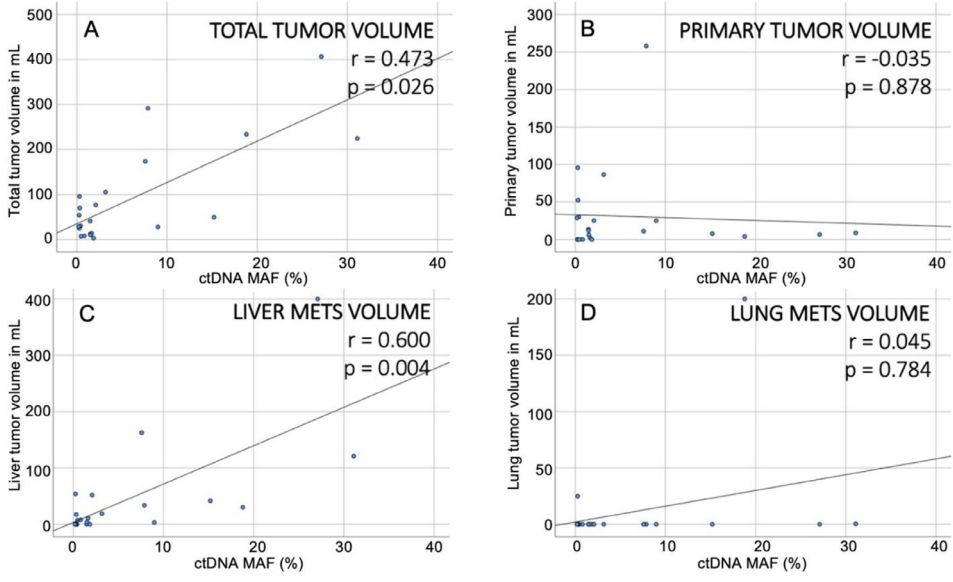
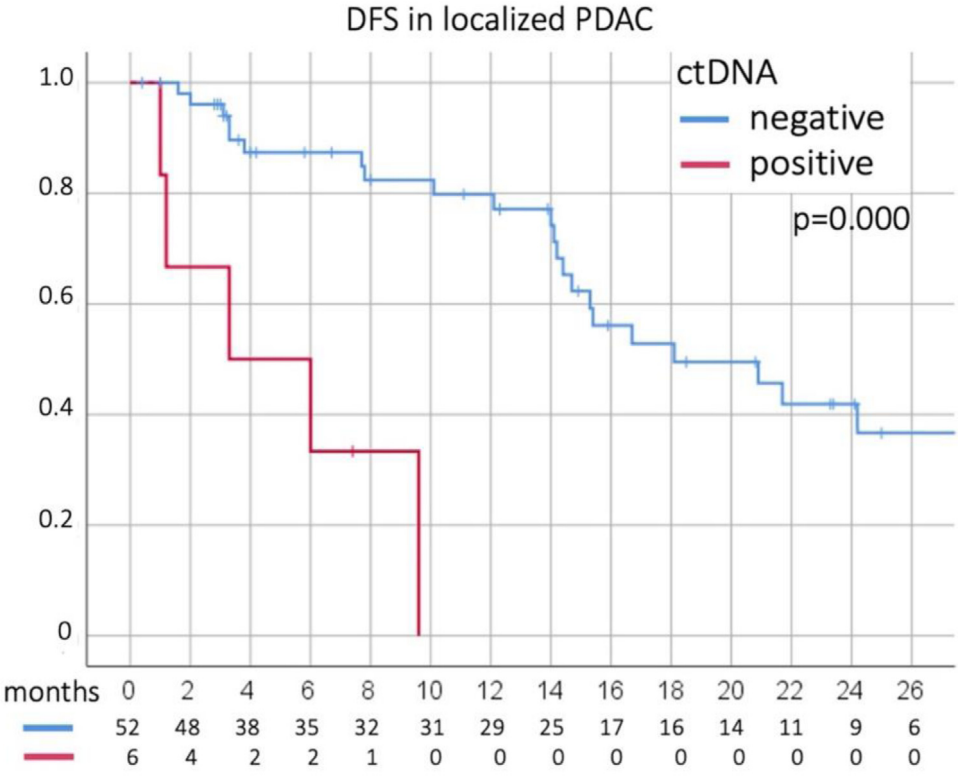


Fig. 1. Spearman correlation of ctDNA MAF with tumor volume subsets (A total tumor volume, B primary tumor volume, C liver metastases volume, D lung metastases volume). *Abbreviations:* *p*-value; r Spearman rho.
This figure is provided by the authors of 'Circulating tumor DNA correlates with tumor burden and predicts outcome in pancreatic cancer irrespective of tumor stage' published in European Journal of Surgical Oncology (Eur J Surg Oncol. 2021 Dec 1:S0748-7983(21)00947-1. doi: 10.1016/j.ejso.2021.11.138. PMID: 34876329) [1].



	Median DFS	IQR	95% CI	p
ctDNA pos.	3.3	1.2-9.6	0.0-9.1	0.000
ctDNA neg.	18.1	14-40	10.7-25.8	

Fig. 2. Disease free survival of patients with localized PDAC depending on ctDNA detection. *Abbreviations:* CI confidence interval; ctDNA circulating tumor DNA; DFS disease free survival; IQR interquartile range; *p*-value.
This figure is provided by the authors of 'Circulating tumor DNA correlates with tumor burden and predicts outcome in pancreatic cancer irrespective of tumor stage' published in European Journal of Surgical Oncology (Eur J Surg Oncol. 2021 Dec 1:S0748-7983(21)00947-1. doi: 10.1016/j.ejso.2021.11.138. PMID: 34876329) [1].

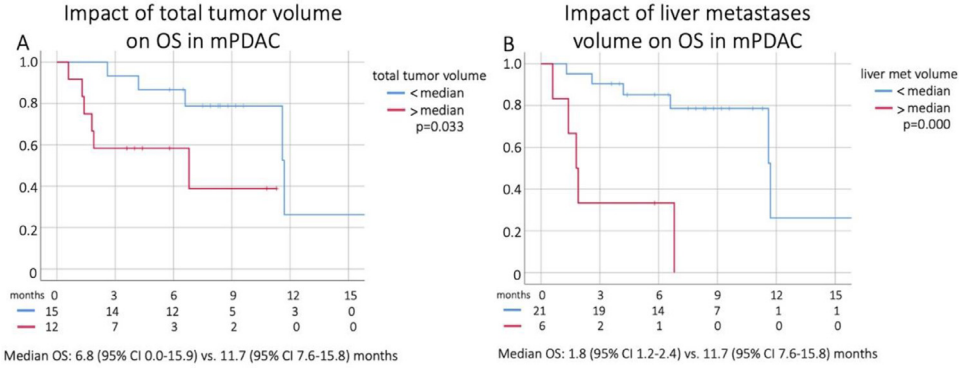


Fig. 3. Overall Survival of patients with stage IV PDAC depending on tumor (A) total tumor volume higher than the median value of the overall population and (B) liver metastasis volume higher than the median value of the overall study population. *Abbreviations:* CI confidence interval; ctDNA circulating tumor DNA; mPDAC metastasized pancreatic ductal adenocarcinoma; OS overall survival; *p*-value.
This figure is provided by the authors of 'Circulating tumor DNA correlates with tumor burden and predicts outcome in pancreatic cancer irrespective of tumor stage' published in European Journal of Surgical Oncology (Eur J Surg Oncol. 2021 Dec 1:S0748-7983(21)00947-1. doi: 10.1016/j.ejso.2021.11.138. PMID: 34876329) [1].

2. Experimental Design, Materials and Methods

2.1. Research issue

5-year-survival rates of 31.7% in stage IA and 11.8% in stage IB following upfront resection, compared to a mere 0.5% in stage IV tumors of a real-world cohort [3]. Moreover, about 60% of all patients are diagnosed at a metastasized stage and in a further 30% of patients, neoadjuvant chemotherapy is applied as they are regarded borderline resectable at the time of diagnosis; thus, only 10% of patients eligible for upfront resection that results in a very low 5-year-overall-survival of 4.2% [3–5]. Diagnostic laparoscopy identifies peritoneal or liver seeding, which was undetectable in prior high quality pancreas protocol staging CT scans in up to one-third of patients with locally advanced PDAC. Biomarkers for the early diagnosis and exact noninvasive assessment of resectability are urgently needed [6]. The detection of circulating tumor DNA (ctDNA) has emerged as a promising tool for the diagnosis, prognosis and treatment evaluation of several gastrointestinal malignancies through an easily reproducible, real-time assessment of the continual change of the disease in a minimally invasive way using liquid biopsy [7,8]. Few data have been published evaluating the association of ctDNA with tumor burden spanning localized and disseminated PDAC. Strijker et al. (2019) were the first to show a correlation of ctDNA and tumor volume in mPDAC, which was mainly driven by hepatic lesions [9]. Nevertheless, up to now data on localized pancreatic cancer concerning this topic are lacking.

2.2. Patient characteristics

A total of 107 patients with histologically confirmed PDAC were included. Of these, 60 patients had localized disease undergoing pancreatic surgery with curative intent and 47 patients had metastatic disease undergoing palliative chemotherapy. Eight patients (13.3%) with localized PDAC received neoadjuvant treatment and adjuvant chemotherapy was administered in 52 patients (86.7%). All stage IV patients ($n = 47$) received palliative chemotherapy (63.8% 1st line, 25.6% 2nd line, 10.6% 3rd line). Median follow up time was 441 days (IQR 205-743) for localized, 251 days (IQR 129-366.5) for metastasized and 329 days (IQR 173.75-625.25) for the overall patient cohort (Tables 1 and 2).

2.3. Detection rates

Obtaining cfDNA was successful for all patients ($n = 107$). Detection rates for KRAS G12/13 or Q61 was 10% (6/60) in localized and 57.4% (27/47) in metastasized patients. Initial screening for KRAS G12/13 mutation revealed positive results in 6.7% (4/60) in stage I-III and 51.1% (24/47) in stage IV patients. Further screening for KRAS Q61 in the remaining cohort revealed additional detectable ctDNA in 3.6% (2/56) of localized and 15% (3/20) of metastasized disease. Detection rates were highest in patients with liver metastases (88.9%) at stage IV or major vascular contact (100%, from which 83.3% of arterial contact) or higher tumor stage for localized disease. When detectable, there was a significant difference between localized and metastatic disease regarding ctDNA concentration (11.84 ng/mL IQR 4.99-17.99 vs. 16.04 ng/mL IQR 3.96-741.78, $p = 0.000$) and MAF (0.23% IQR 0.12-1.03 vs. (1.47% IQR 0.25-7.58, $p = 0.000$) respectively. There was no correlation between bilirubin levels with CEA, CA 19-9 or ctDNA levels in this study. Neither in the overall cohort, nor in the subpopulations (localized, metastasized PDAC).

2.4. Volumetric analysis and correlation of ctDNA with tumor volume subsets

Complete 3D volumetric assessment was possible in 57 (91.9%) patients with localized and 41 (87.2%) patients with metastasized disease.

A comparison of preoperative radiological measurements with the primary tumor lesion size in postoperative histological specimens resulted in a median difference of 6.6 mm (25.4 mm IQR 22.6-33.0 vs. 32.0 mm IQR 23.5-35.8; $n = 50$). Primary tumor volume did not correlate with ctDNA levels in either localized ($p = 0.573$) or metastatic disease ($p = 0.878$).

In localized disease, ctDNA showed a significant correlation with the number of positive lymph nodes ($r = 0.331$, $p = 0.030$) in histopathological specimens as well as with the lymph node ratio ($r = 0.393$, $p = 0.009$). In metastatic disease, total tumor volume (primary plus metastases, $r = 0.473$, $p = 0.026$) and liver metastases volume in particular, showed a strong correlation with ctDNA levels ($r = 0.600$, $p = 0.004$) with major differences of median liver metastases volume depending on the ctDNA detectability (30 mL IQR 9.34-87.41 vs. 3.66 mL IQR 1.4-22.23, $p = 0.025$). In contrast, lung ($p = 0.784$) or peritoneal and lymph node metastases ($p = 0.254$) did not correlate with tumor volume (Fig. 1 and Table 3).

In contrast to ctDNA, CA 19-9 showed no correlation to total tumor volume, primary tumor volume, liver metastasis volume, lung metastasis volume or lymph node involvement in either localized or metastasized PDAC (Table 3) in this study. However, this could have been due to the relatively high rate of missing CA 19-9 values in our patient cohort (as this was not the parameter of primary interest), in contrast to other studies who have shown the role of CA 19-9 in detecting lymph node metastases [10].

2.5. Prognostic impact of ctDNA and tumor volume

In locPDAC, patients with pretherapeutic detection of ctDNA had significantly shorter DFS than patients who were ctDNA negative (3.3 vs 18.1 months; 95% CI 0–9.1; $p = 0.000$; Fig. 2). In patients with mPDAC undergoing first line chemotherapy, detection of ctDNA showed a trend for OS with a median of 6.3 months (95% CI 3.5–9.1) compared to 10.4 months (95% CI 5.8–15.0). These results did not reach statistical significance ($p = 0.151$), which is likely due to the low number of observed events (52.6% in the ctDNA negative and 74% in the ctDNA positive group). In contrast, ctDNA levels above the median MAF had significant impact on OS in patients with metastatic disease undergoing first line treatment (5.7 vs. 7.8 months, 95% CI 0–12.9 vs. 4.2–12.8, $p = 0.036$).

A proportion of 83.3% ($n = 5$) of patients with locPDAC and preoperative detectable ctDNA had an early relapse within the first year and two thirds of them even within the first 6 months.

While higher volume of the primum (higher or lower than the median tumor volume) had no impact on survival data in locPDAC ($p = 0.695$), a significantly lower OS was observed in patients with total tumor volume higher than the median volume in mPDAC undergoing 1st line chemotherapy (6.8 months; 95% CI 0.0–15.9 vs. 11.7 months; 95% CI 7.6–15.8, $p = 0.033$). Liver metastases volume correlated significantly with OS (1.8 months 95% CI 1.2–2.4), whereas other locations did not (Fig. 3).

Ethics Statements

The study was approved by the local Ethics Committee (Upper Austria, EK 70/90).

Informed consent was obtained by all participants and this study was conducted adhering to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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