Pancreatology 16 (2016) 593–598

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Isolated pulmonary metastases define a favorable subgroup in metastatic pancreatic cancer

Stephan Kruger [a], Michael Haas [a], Philipp Johannes Burger [a], Steffen Ormanns [b], Dominik Paul Modest [a], Christoph Benedikt Westphalen [a], Marlies Michl [a], Axel Kleespies [c], Martin Kurt Angele [c], Werner Hartwig [c], Christiane Josephine Bruns [d], Maximilian Niyazi [e], Falk Roeder [e, f], Thomas Kirchner [b], Jens Werner [c], Volker Heinemann [a], Stefan Boeck [a, *]

[a] Department of Internal Medicine III and Comprehensive Cancer Center, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, D-81377 Munich, Germany
[b] Institute of Pathology, Ludwig-Maximilians-University of Munich, D-81377 Munich, Germany
[c] Department of General, Visceral, Transplantation, Vascular and Thoracic Surgery, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, D-81377 Munich, Germany
[d] Department of General, Abdominal and Vascular Surgery, Otto-von-Guericke-University, D-39120 Magdeburg, Germany
[e] Department of Radiation Oncology, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, D-81377 Munich, Germany
[f] Department of Molecular Radiation Oncology, Deutsches Krebsforschungszentrum (DKFZ), D-69120 Heidelberg, Germany

ARTICLE INFO

Article history:
Available online 30 March 2016

Keywords:
Ductal adenocarcinoma
Lung
Pancreatic cancer
Pulmonary metastases
Isolated
Lung recurrence

ABSTRACT

Purpose: Liver metastasis represents the first site of dissemination in >80% of metastatic pancreatic cancer (PC) patients. Pulmonary metastasis as first site of dissemination in PC is a rare event and might define a biologically distinct subgroup in metastatic PC.
Methods: Consecutive PC patients who were diagnosed or treated with isolated pulmonary metastases at our high-volume comprehensive cancer center were included in a prospectively maintained database between 2002 and 2015. Medical records and correlating computed tomography findings (CT) were retrospectively analyzed.
Results: A total of 40 PC patients with isolated pulmonary metastases were identified. Pulmonary metastases represented disease recurrence after initial resection of PC in 22 patients and disease progression of locally advanced pancreatic cancer in 5 patients. 14 out of 27 PC patients (56%) had received chemoradiotherapy for localized disease prior to pulmonary metastasis. Data on 1st-line treatment for pulmonary metastases was available for 38 patients: most patients (71%) received a gemcitabine-based chemotherapy regimen, 5 patients (13%) received best supportive care. After a median follow-up of 37.3 months, median survival after diagnosis of pulmonary metastasis was estimated with 25.5 months (95% CI 19.1–31.8); a significantly improved survival after diagnosis of pulmonary metastasis was observed for patients with less than 10 lung metastases (31.3 vs 18.7 months, $p = 0.003$) and for an unilateral localization of lung involvement (31.3 vs 21.8 months, $p = 0.03$).
Conclusions: Our results suggest a favorable outcome of PC patients with isolated pulmonary metastases. Further research is warranted to elucidate the specific molecular characteristics of this rare subgroup.

Introduction

Despite a declining overall cancer mortality, pancreatic cancer (PC) related mortality has been on the rise in recent years, ranking fourth and fifth in terms of organ specific cancer mortality in the US and Europe respectively [1,2]. A further increase in incidence is

* Corresponding author. Department of Internal Medicine III and Comprehensive Cancer Center, Klinikum Grosshadern, Ludwig-Maximilians-University of Munich, Marchioninistr. 15, D-81377 Munich, Germany. Tel.: +49 89 4400 72208; fax: +49 89 4400 75256.
E-mail address: stefan.boeck@med.uni-muenchen.de (S. Boeck).

http://dx.doi.org/10.1016/j.pan.2016.03.016
1424-3903/

predicted to make PC the second leading cause of cancer related mortality by 2030 [3]. At initial diagnosis of PC, approximately 80% of patients present with advanced disease [4]. Notwithstanding decades of research aiming on improving the dire prognosis of advanced PC, five-year survival rate remains low at around 5–10% [1].

A significant improvement in overall survival has been achieved for advanced PC patients with good performance status, using the intensive chemotherapy regimens 5-fluorouracil, folinic acid, irinotecan and oxaliplatin (FOLFIRINOX) or by adding nab-paclitaxel to standard-of-care gemcitabine [5,6]. Erlotinib, the only FDA and EMA approved targeted agent for advanced PC, provides only a modest clinical benefit in an unselected metastatic PC population [7]. Many other targeted treatment approaches that have substantially improved the prognosis in a variety of solid malignancies have similarly failed to provide a significant benefit for PC patients [8,9]. Recent advances in genomic sequencing have improved the understanding of cancer initiation and progression of PC. PC is driven by mutations in a small subset of genes that are almost ubiquitously mutated in PC patients (KRAS, TP53, SMAD4, CDKN2A) [10]. Mutations in other genes – particularly druggable mutations – occur at a low frequency making PC a genetically heterogeneous disease [10]. This provides a likely explanation why unselected targeted treatment approaches in PC have been doomed to fail so far. Identification of genetically and clinically unique PC subgroups thus might pave the way for successful targeted treatment approaches.

Dissemination is a late step during the evolution of PC – occurring approximately seven years after primary tumor formation [11]. Genetic alterations present in metastatic lesions reflect the mutational landscape in the founder clone and might determine metastatic pattern of PC [11]. Metastatic pattern of PC could therefore indicate distinct clinical and genetic subgroups. A majority of patients with disseminated PC present with liver metastases. Pulmonary metastases as first site of dissemination are a rare event [11,12]. We hypothesized that patients with isolated pulmonary metastases might define a clinically distinct subgroup of PC and sought to determine outcome and prognostic factors of these patients.

Patients and methods

Patient selection

From 2002 until 2015, patients who were diagnosed and/or treated with PC at our high-volume comprehensive cancer center were prospectively included in a patient database. Follow-Up visits and chest CTs' were performed routinely according to the local guidelines at our cancer center. For the current study, medical records and correlating computed tomography findings (CT) were retrospectively analyzed for all patients with isolated lung metastases. The following data were evaluated: patient and tumor characteristics including age; sex; tumor-, node-, metastases- (TNM) stage; grading; date of initial diagnosis of PC; date of first appearance of pulmonary metastases; treatment of PC (surgery, radiotherapy, 1st to 3rd-line chemotherapeutic regimens); size, number and site of pulmonary metastases upon initial diagnosis and follow-up. Occurrence of pulmonary metastases had to be confirmed by histology or retrospective review of serial computed tomography (CT) scans, showing enlarging pulmonary nodules over time. To rule out synchronous extrapulmonary dissemination, abdominal CT scans were reviewed for the presence of extrapulmonary metastases. Survival status was determined by (a) review of medical records at our institution, (b) consultation of patient's primary care physician or (c) consultation of patient's civil registrar office. All living patients were followed up for survival status between June and August 2015. The study was approved by the local ethics committee of Ludwig-Maximilians-University of Munich (approval number 134-15).

Statistical analyses

Overall survival from the time of first appearance of pulmonary metastases to the time of death was selected as primary study endpoint. Patients that did not die were censored at their last follow-up. Median overall survival was calculated using the Kaplan–Meier method; differences in overall survival according to size, number and site of pulmonary metastases were calculated using the log-rank test. Median follow-up time was calculated using the reversed Kaplan–Meier method as described previously [13]. SPSS PASW 23.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analyses. For this study, a p-value of ≤ 0.05 was considered to be statistically significant.

Results

Patient characteristics

Between 2002 and 2015, 42 patients with pulmonary metastases of PC were diagnosed and/or treated at our comprehensive cancer center and included in a prospectively maintained database. Upon careful retrospective review of chest and abdominal CT scans at time of diagnosis of pulmonary metastasized PC, two patients had to be excluded from the current analysis due to synchronous appearance of liver metastases. Median age at diagnosis of pulmonary metastasized PC for the remaining 40 patients was 69 years. A majority of patients were female (70%; n = 28); had a good performance status (ECOG 0 – 1: 75% or n = 34) and had initially presented with resectable disease (55%; n = 22) (Table 1). 12 of the included patients were treated within different prospective clinical trials at our institution. Diagnosis of pulmonary metastasized PC

Table 1
Patient characteristics (n = 40) at diagnosis of isolated pulmonary metastases.

	n	%
Age (years)		
Median	69	
Range	41–84	
Gender		
Male	12	30
Female	28	70
Initial stage of disease		
Resectable	22	55
Metastatic	13	32.5
Locally advanced	5	12.5
Primary tumor site		
Head of pancreas	28	70
Body of pancreas	7	17.5
Tail of pancreas	5	12.5
Performance status		
ECOG 0	19	47.5
ECOG 1	15	37.5
ECOG 2	2	5
Missing	4	10
Diagnosis of pulmonary metastases		
Radiographic	27	67.5
Histologically	13	32.5
Histology		
Ductal adenocarcinoma	36	90.0
Acinar cell carcinoma	1	2.5
Adenosquamous carcinoma	1	2.5
Mucinous adenocarcinoma	1	2.5
Cytology only	1	2.5

Abbreviations: ECOG = Eastern Cooperative Oncology Group.

was based upon serial CT scans showing enlarging pulmonary metastases in 27 patients. A histological confirmation of pulmonary metastases from PC was obtained in 13 patients (32.5%) (Table 1).

Therapy for localized disease prior to pulmonary dissemination

Most PC patients who developed isolated pulmonary metastases had initially received chemotherapy for localized disease (i. e. neoadjuvant or palliative treatment for locally advanced PC [LAPC] or adjuvant treatment after resection with curative intent for PC; Table 2). Interestingly, all 5 patients with LAPC had received chemoradiotherapy which resulted in a secondary tumor resection of the pancreatic primary in one patient. Adjuvant treatment in patients with resectable disease consisted of single-agent gemcitabine in 11 patients (50%) and chemoradiotherapy in 9 patients (41%). Two patients did not receive adjuvant treatment (Table 2).

Treatment after diagnosis of isolated pulmonary metastases

Data on 1st-line treatment was available for 95% of patients (n = 38) (Table 3): a majority received chemotherapy in palliative intent (84%; n = 32). One patient received stereotactic radiation of a pulmonary metastasis in palliative intent. Five patients did receive best supportive care only. Among patients who received chemotherapy, 56% (n = 18) received a single-agent regimen while the remaining 43% (n = 14) received different combinational regimens. Among monotherapy regimens, gemcitabine was the most frequently applied agent (n = 13). Combination regimens consisted of 5-fluorouracil, folinic acid, irinotecan and oxaliplatin (FOLFIRINOX) (n = 3); gemcitabine plus a second chemotherapeutic agent (n = 5) or gemcitabine in combination with different targeted agents (n = 6) (Table 3).

Median time from localized disease to pulmonary dissemination

For patients with LAPC, the median time to pulmonary dissemination was 5.0 months. Patients with resectable PC developed metastatic lung lesions after a median of 10.5 months. Of note, the observed time range for pulmonary recurrence after surgical resection of PC was widely scattered (1.7–65.7 months) (Table 4).

Survival analyses

To characterize the prognostic relevance of isolated pulmonary metastases, we estimated the survival time from first appearance of pulmonary metastases to death from any cause. Median overall survival in the whole analyzed population (n = 40) was 25.5 months (95% confidence interval [CI]: 19.1–31.8 months) (Fig. 1 and Table 5) with a median follow-up estimated to be 37.3 months, (95% CI: 24.6–50.1 months).

Table 2
Therapy for localized disease prior to pulmonary dissemination.

	n	%
Locally advanced pancreatic cancer	**5**	
Primary treatment		
Chemoradiotherapy	5	100
Subsequent resection of primary tumor		
Yes	1	20
No	4	80
Resectable pancreatic cancer	**22**	
Adjuvant treatment		
Gemcitabine	11	50
Chemoradiotherapy	9	41
No adjuvant treatment	2	9

Table 3
Palliative first-line therapy after diagnosis of isolated pulmonary metastases.

	n	%
Single-agent Chemotherapy	**18**	
Gemcitabine	13	
Capecitabine	4	
Pemetrexed	1[a]	
Combination Chemotherapy	**14**	
FOLFIRINOX	3	
Gemcitabine + nab-Paclitaxel	1	
Gemcitabine + Erlotinib	2	
Gemcitabine + Rapamycin	2[a]	
Gemcitabine + Carboplatin	1	
Gemcitabine + Cisplatin	2[b]	
Gemcitabine + Oxaliplatin	1	
Gemcitabine + Brivudin	1[a]	
Gemcitabine + Erlotinib + Bevacizumab/Placebo	1[a]	
Radiotherapy	**1**[c]	
BSC	**5**	
Missing	**2**	

Abbreviations: BSC = Best supportive care.
[a] Patients were treated within clinical trials at our institution.
[b] One patient received concurrent radiation therapy of primary tumor.
[c] Radiotherapy was applied to the largest of three pulmonary metastases.

This observation compares favorably to survival data from unselected metastatic PC patients (independent of the site of dissemination) who had been treated between 2002 and 2015 at our institution: data to calculate overall survival was available for 277 patients with resectable, locally advanced or metastatic PC. Of those, 186 patients had been treated in palliative intent for metastatic disease of any site. Median overall survival in these patients was estimated with 9.4 months (95% CI: 7.6–11.1 months).

For patients with isolated pulmonary recurrence after initial resectable disease (n = 22) median survival from time of diagnosis of lung metastases was 31.3 months, whereas survival for patients initially diagnosed with LAPC (n = 5) was 10.7 months, respectively. Total overall survival from time of initial diagnosis of resectable or locally advanced PC was 46.4 months (95% CI: 34.6–58.2 months) and 23.9 months (95% CI: 10.6–37.2 months), respectively. Patients with synchronous isolated lung metastasis at first diagnosis of PC (n = 13) had a median overall survival of 22.8 months (Table 5).

For the 32 patients who had received chemotherapy in palliative intent, only a slight difference in overall survival was observed between patients who received single agent chemotherapy (n = 18) versus patients who received combinational chemotherapy regimens (n = 14), (21.8 vs 28.6 months, respectively).

An additional analysis comparing overall survival between patients who had been diagnosed histologically (n = 13, median OS: 25.5 months, 95% CI: 20.1–30.8 months) versus patients who had been diagnosed radiographically (n = 27, median OS: 25.3 months, 95% CI: 16.4–34.3 months) showed no survival difference between those two groups (p = 0.765).

Data from retrospective series suggests that time to recurrence after resection of PC greater 9 or greater than 20 months, respectively, may serve as a predictor of improved overall survival after diagnosis of recurrent disease [20–22]. We therefore also calculated survival for patients according to time to pulmonary recurrence: no statistical significant difference in overall survival was seen for patients with time to recurrence ≤9 months or ≤20 months versus patients with time to recurrence >9 months or >20 months, respectively (see Table 5).

We further calculated median overall survival times according to number, size and largest diameter of pulmonary metastases at initial diagnosis (Fig. 2 and Table 5): a majority of patients had less than 10 pulmonary metastases (63%) and at least one pulmonary metastasis of more than 5 mm in diameter (58%) upon initial

Table 4
Median time from localized disease to pulmonary dissemination.

	Median time to pulmonary dissemination (months)	Range (months)
Locally advanced pancreatic cancer (n = 5)	5.0	3.4–8.0
Resectable pancreatic cancer (n = 21[a])	10.5	1.7–65.7

[a] One patient was excluded, because he underwent resection of pancreatic cancer despite presence of pulmonary metastasis.

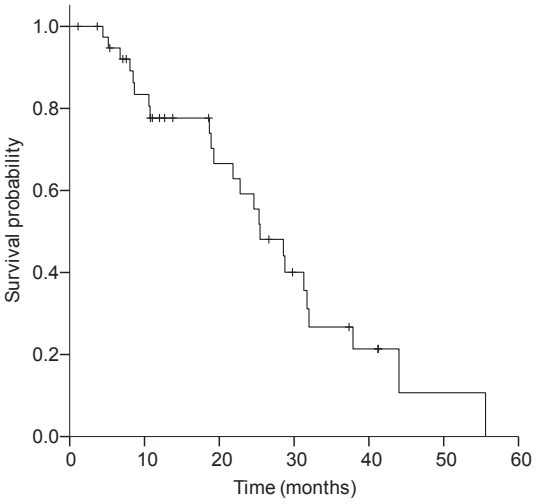

Fig. 1. Overall survival of pancreatic cancer patients with isolated pulmonary metastases. Median overall survival was calculated from date of initial diagnosis of pulmonary metastases to death from any cause (n = 40, median overall survival 25.5 months).

Table 5
Survival analyses for PC patients with isolated lung metastases (OS calculated from date of initial diagnosis of pulmonary metastases to death from any cause).

Subgroup	n	Median OS (months)	95% CI (months)	
All patients	40	25.5	19.1–31.8	
Stage of disease at initial diagnosis of PC				
Resectable	22	31.3	23.8–38.8	
LAPC	5	10.7	0.0–24.9	
Metastatic	13	22.8	17.3–28.3	
Time to pulmonary recurrence[a]				
≤9 months	8	37.9	7.4–68.4	p = 0.755
>9 months	13	28.8	20.7–36.8	
≤20 months	15	25.4	23.4–27.5	p = 0.495
>20 months	6	31.3	26.0–36.6	
Number of pulmonary metastases				
≤10	25	31.3	23.8–38.8	p = 0.003
>10	15	18.7	0.0–46.0	
Size of pulmonary metastases				
≤5 mm	17	24.6	10.8–38.4	p = 0.97
>5 mm	23	25.5	19.6–31.3	
Location of pulmonary metastases				
Unilateral	21	31.3	26.5–36.1	p = 0.03
Bilateral	19	21.8	15.2–28.5	

Abbreviations: OS = Overall survival, CI = Confidence interval.
PC = Pancreatic cancer.
LAPC = Locally advanced pancreatic cancer.
[a] One patient was excluded, because he underwent resection of pancreatic cancer despite presence of pulmonary metastasis.

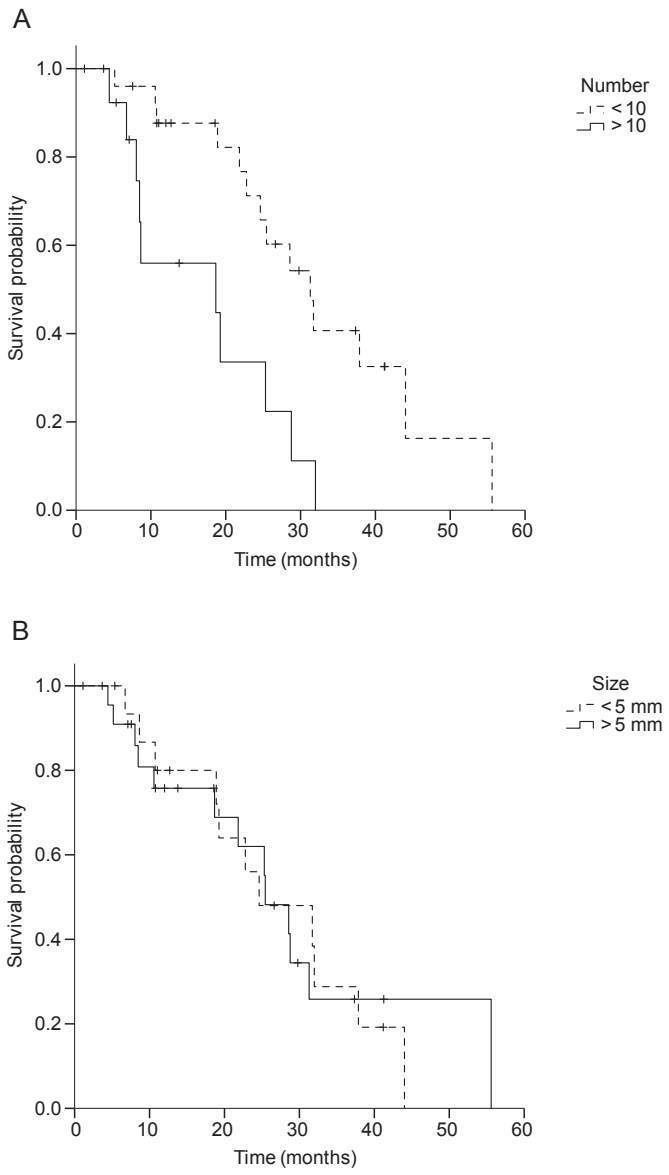

Fig. 2. A Overall survival for patients with more than 10 pulmonary metastases at initial diagnosis of pulmonary metastases (n = 15, median overall survival 18.7 months) vs. patients with 10 or less pulmonary metastases (n = 25, median overall survival 31.3 months) (calculated from date of initial diagnosis of pulmonary metastases to death from any cause). B Overall survival for patients with at least one pulmonary metastasis larger than 5 mm in diameter at initial diagnosis of pulmonary metastases (n = 23, median overall survival 25.5 months) vs. patients without pulmonary metastases larger than 5 mm (n = 17, median overall survival 24.6 months) (calculated from date of initial diagnosis of pulmonary metastases to death from any cause).

diagnosis. Range of maximum diameter of the largest pulmonary metastasis was less than 5 mm up to 32 mm.

Bilateral lung involvement and a high number of pulmonary metastases were correlated to an adverse outcome (median survival: 31.3 vs 21.8 months, p = 0.03; and 31.3 vs 18.7 months, p = 0.003, respectively) (Fig. 2a and Table 5). Interestingly, survival was not influenced by size of individual metastatic lesions (24.6 vs 25.5 months for diameter ≤ 5 mm vs. > 5 mm of largest metastatic lesion) (Fig. 2b).

Discussion

The present single-center study reports a highly favorable outcome of PC patients with isolated pulmonary metastases. During 13 years of observation at our high-volume comprehensive cancer center, 40 cases were identified. Hence, PC patients with isolated pulmonary metastases represent a rare PC subgroup. For patients with recurrence after resection of PC in curative intent, two previous studies reported an isolated recurrence to the lung in 9.8% and 16.1% of all cases, respectively [14,15]. Regarding the 22 patients with isolated lung recurrence after PC resection in our patient population, we calculated a median time to relapse of 10.5 months; 90% of these patients had received adjuvant gemcitabine or adjuvant chemoradiotherapy. Adjuvant chemotherapy with gemcitabine after PC resection was established as one standard of care by the landmark CONKO-001: this German multicenter phase III study reported a median time to recurrence of 13.4 months in patients receiving adjuvant chemotherapy with gemcitabine versus 6.7 months in patients who underwent observation only [16]. Comparable disease free survival times of about one year have also been reported for adjuvant chemoradiation in PC [17]. Interestingly, time to pulmonary recurrence in our study did not differ – besides the markedly improved overall survival – from time to recurrence of any site (local, regional or distant) reported in aforementioned studies. This observation is in line with a recent study investigating recurrence patterns after resection of PC in 174 patients: Wangjam and co-workers reported a median time of 12.7 months to isolated pulmonary recurrence ($n = 28$) and a median time to recurrence of 10.1 months in the overall population [15]. Thus, the favorable survival seen in patients with isolated pulmonary metastases after PC surgery interestingly is not reflected by a prolonged disease free interval after surgery, but may be attributed to the benign course of the disease after diagnosis of an isolated pulmonary relapse.

Even with intensive treatment regimens, median overall survival for metastatic PC patients with good performance status has been reported to be less than one year [6,7]. Median overall survival in the small subgroup of PC patients with isolated pulmonary metastases in our study was estimated with 25.5 months (from first diagnosis of pulmonary metastasis). This is in line with a recent finding by Downs-Canner et al. who reported an overall survival of 23.1 months for PC patients with isolated pulmonary metastases and a recently published case series of six PC patients with isolated pulmonary metastases after initially resectable PC or LAPC who responded favorably to treatment of metastatic disease [18,19]. Moreover, very recently, Wangjam et al. reported a median overall survival in 28 patients with isolated pulmonary recurrence after PC surgery of 8.5 months. While this interval is remarkably shorter than the survival times reported by Downs-Canner et al. and our study, it was found to be significantly longer than overall survival from time of recurrence for patients with sites of recurrence other than the lung (liver: $n = 73$, overall survival: 5.1 months; local recurrence: $n = 28$, overall survival: 5.1 months; peritoneal: $n = 25$, overall survival: 2.3 months) [15].

As hypothesized previously, patients with solitary lung recurrence after resection of PC might also benefit from surgical intervention or stereotactic radiosurgery [18,20]. Up to date, these interventions remain a non-standard and individual treatment approach for highly selected patients with limited pulmonary metastases and indolent tumor biology [20]. Independent of surgical resection, we show that limited disease (defined as metastatic disease of less than 10 metastases) confined to one lung might predict favorable outcome among patients with isolated pulmonary metastases, while size of individual pulmonary metastases appears to be of minor importance. Thus, PC patients with less than 10 metastases confined to one lung might have exceptional indolent tumor biology and could potentially also represent candidates for surgical intervention or stereotactic radiosurgery.

Furthermore, data from retrospective series suggests that time to recurrence after resection of pancreatic cancer greater 9, 18.9 and 20 months, respectively might be a predictor of improved overall survival after diagnosis of recurrent disease [20–22]. We observed no (statistically significant) difference in overall survival according to time of pulmonary recurrence. While these results should be interpreted with caution given the small number of patients, one might at least hypothesize that isolated pulmonary recurrence represents a favorable prognostic factor independent of time to recurrence.

When analyzing patterns of previous treatment in patients who develop pulmonary metastases after resection of PC or treatment for localized disease in LAPC, we noted that 14 out of 27 patients had received chemoradiation for localized disease. A possible explanation for this phenomenon can be derived from recent findings in translational and preclinical studies investigating the mechanism of pulmonary dissemination and effects of radiation therapy in PC respectively. Song and colleagues reported higher levels of phosphorylated SMAD3 as an indicator for increased TGF-β signaling in resected primary tumor specimens of PC patients with pulmonary metastases. Subsequent in vitro studies confirmed the potential role of TGF-β signaling in pulmonary dissemination [23,24]. Interestingly, radiation therapy was recently shown to induce TGF-β signaling migratory capacities of pancreatic carcinoma cells [23,24]. Radiation therapy thus might induce TGF-β, eventually leading to a distinct metastatic pattern in a subset of PC patients.

The main methodological limitations of the present study arise from the limited number of patients from a single center and the explorative nature of the statistical analyses. To minimize selection bias, consecutive patients had been included in a prospectively maintained database. Up to now, there is only very limited evidence describing the (rare but potentially important) subgroup of PC patients with isolated lung metastases; to our best knowledge only three small case series and/or single-center studies were reported very recently [15,18,19]: in those studies most of the included patients underwent surgical resection before the occurrence of a pulmonary relapse. Of note, based on our data, the improved survival of this distinct patient population may also hold true – at a somewhat lower extent - for patients with synchronous lung metastasis at presentation.

In conclusion our single center study is one of the first investigations showing that a clinically defined subgroup of PC patients (namely those with isolated lung metastasis) may represent a very distinct PC population with regard to its clinical features and prognosis. A multicenter re-evaluation of this hypothesis is strongly recommended; such an approach should also be combined with a profound translational research program in order to define the molecular basics of this novel and unique observation.

Acknowledgments

This work is part of the doctoral thesis of Johannes Philipp Burger.

The work of Steffen Ormanns was supported by a grant from the Friedrich-Baur-Stiftung, Munich.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J Clin 2015;2015(65):5–29.

[2] Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in europe: estimates for 40 countries in 2012. Eur J Cancer 2013;49:1374–403.

[3] Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the united states. Cancer Res 2014;74:2913–21.
[4] Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011;378:607–20.
[5] Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. Folfirinox versus gemcitabine for metastatic pancreatic cancer. N Engl J Med 2011;364:1817–25.
[6] Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med 2013;369:1691–703.
[7] Heinemann V, Haas M, Boeck S. Systemic treatment of advanced pancreatic cancer. Cancer Treat Rev 2012;38:843–53.
[8] Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. N Engl J Med 2014;371:1039–49.
[9] Kruger S, Haas M, Ormanns S, Bachmann S, Siveke JT, Kirchner T, et al. Translational research in pancreatic ductal adenocarcinoma: current evidence and future concepts. World J Gastroenterol 2014;20:10769–77.
[10] Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. Nature 2015;518:495–501.
[11] Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 2010;467:1114–7.
[12] Yachida S, Iacobuzio-Donahue CA. The pathology and genetics of metastatic pancreatic cancer. Arch Pathol Lab Med 2009;133:413–22.
[13] Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343–6.
[14] Chen K Tzung-Kai, Singla S, Papavasiliou P, Arrangoiz R, Gaughan JP, Hoffman JP. Patterns of recurrence and outcomes in pancreatic cancer. In: Gastrointestinal cancers symposium 2013; 2013. p. 234.
[15] Wangjam T, Zhang Z, Zhou XC, Lyer L, Faisal F, Soares KC, et al. Resected pancreatic ductal adenocarcinomas with recurrence limited in lung have a significantly better prognosis than those with other recurrence patterns. Oncotarget 2015;6:36903–10.
[16] Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the conko- 001 randomized trial. Jama 2013;310:1473–81.
[17] Van Laethem JL, Hammel P, Mornex F, Azria D, Van Tienhoven G, Vergauwe P, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: a randomized eortc-40013-22012/ffcd-9203/gercor phase ii study. J Clin Oncol 2010;28:4450–6.
[18] Downs-Canner S, Zenati M, Boone BA, Varley PR, Steve J, Hogg ME, et al. The indolent nature of pulmonary metastases from ductal adenocarcinoma of the pancreas. J Surg Oncol 2015;112:80–5.
[19] Deeb A, Haque SU, Olowokure O. Pulmonary metastases in pancreatic cancer, is there a survival influence? J Gastrointest Oncol 2015;6:E48–51.
[20] Thomas RM, Truty MJ, Nogueras-Gonzalez GM, Fleming JB, Vauthey JN, Pisters PW, et al. Selective reoperation for locally recurrent or metastatic pancreatic ductal adenocarcinoma following primary pancreatic resection. J Gastrointest Surg 2012;16:1696–704.
[21] Kleeff J, Reiser C, Hinz U, Bachmann J, Debus J, Jaeger D, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. Ann Surg 2007;245:566–72.
[22] Nakamura A, Itasaka S, Takaori K, Kawaguchi Y, Shibuya K, Yoshimura M, et al. Radiotherapy for patients with isolated local recurrence of primary resected pancreatic cancer. Prolonged disease-free interval associated with favorable prognosis. Strahlenther Onkol Organ Dtsch Rontgengesellschaft 2014;190:485–90.
[23] Song L, Wang P, Tian Y, Chang D, Li K, Fan Y, et al. Lung metastasis of pancreatic carcinoma is regulated by tgfbeta signaling. Tumour Biol 2015;36:2271–6.
[24] Carl C, Flindt A, Hartmann J, Dahlke M, Rades D, Dunst J, et al. Ionizing radiation induces a motile phenotype in human carcinoma cells in vitro through hyperactivation of the tgf-beta signaling pathway. Cell Mol Life Sci 2016;73:427–43.