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Original article

Isolated pulmonary metastases define a favorable subgroup in metastatic pancreatic cancer

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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

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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.

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