Oligometastatic pulmonary metastasis in pancreatic cancer patients: Safety and outcome of resection

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ABSTRACT

Objective: To assess the perioperative and long-term outcome following pulmonary resection in patients with metachronous metastasis of pancreatic ductal adenocarcinoma (PDAC).

Background: Most patients with PDAC relapse or develop tumor spread to secondary organs. Currently, it remains unclear how to proceed with pulmonary metastasis in the metachronous setting. In particular, the role of surgery remains controversial.

Methods: Data of patients with pulmonary metachronous metastasis after PDAC collected from 2003 to 2015 in databases of two high-volume pancreatic cancer centers were retrospectively analyzed. Clinical and pathological aspects of primary PDAC as well as the perioperative and long-term outcome following pulmonary metastasectomy (PM) was evaluated, respectively. Patients with synchronous liver metastasis or metastasis to other secondary organs were excluded. Univariate survival analysis was performed.

Results: We identified 15 patients undergoing pulmonary resection for suspected metastasis after primary pancreatic resection. Operative and histopathologic evaluation revealed resectable pancreatic pulmonary metastasis in 11 patients (73.3%). The median disease-free survival (DFS) and overall survival (OS) after PM diagnosis was 18 months and 26 months, respectively. The median time to metachronous metastasis (TMM) was 17 months [3–64 months]. Perioperative morbidity was low with only one readmission (8.3%). There was no perioperative mortality. Patients who developed pulmonary metastasis later than 17 months after primary surgery showed better OS compared to those who did earlier (32.2 vs. 14.75 months, p = 0.025). In addition, patients with high-grade tumors had worse survival (12.4 vs. 31 months, p = 0.02). Elevated serum CEA levels or CA 19-9 levels were also not associated with shortened OS.

Conclusions: This study suggests that pulmonary metastasectomy after PDAC is safe and effective. Patients with extended DFS after primary pancreatic surgery as well as favorable tumor grading seem to particularly benefit from pulmonary surgery.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes for cancer-related death and ranks fourth in Europe and fifth in the US [1,2]. Local resection of the primary tumor offers the only prospect of survival beyond 5 years and is feasible in about 15–20% of patients at first time presentation [3]. However, with its high propensity for local recurrence and distant metastasis, the overall 5-year

survival is still less than 5% [4]. Despite increasing research efforts and the development of novel chemotherapeutic treatment strategies, most patients with distant metastasis [2] and locoregional or distant recurring disease will face a dismal 2-year survival rate of less than 5% [5].

The most frequent sites for distant metastases in metachronous settings are the liver (47%) followed by the lung (22%), regional lymph nodes (17%), and the peritoneum (13%) with pulmonary metastasis being the leading organ of metastatic recurrence 3 years after primary surgery [6]. Another report from 2011 confirmed the lung as the most frequent organ of metachronous metastasis in long-term survivors of pancreatic adenocarcinoma [7]. Paradigm shifts towards a more aggressive surgical approach for pulmonary metastasectomy (PM) with encouraging outcomes in colorectal adenocarcinoma, soft tissue sarcoma or renal cell carcinoma have been reported [8–10].

Resection of solitary pulmonary nodules as well as adjacent lymphadenectomy has been well established and is a safe procedure. Especially, the introduction of video-assisted thoracoscopic surgeries helped to reduce the length of hospital stay and improve postoperative outcomes [11].

While hepatic metastasectomy is widely considered prohibitive in PDAC patients, it is intriguing as to whether PM in patients with metachronous metastasis to the lungs after initial curative surgical therapy of PDAC is beneficial [12]. With no clear recommendations for or against PM in PDAC being currently existent [13–18], it is of great importance to clarify this critical issue for PDAC patients with pulmonary metastasis. Describing the outcome of these patients and identifying risk factors of worsened outcomes may provide insights into how patient selection in this rare population could be improved.

Thus, this study aimed to describe the histopathologic parameters and postoperative clinical outcomes of patients undergoing complete PM at two German high-volume pancreatic cancer centers after primary surgery for PDAC to better define prognostic criteria.

2. Patients and methods

2.1. Study design and patients

The present study was approved by the ethics committee of each of the participating institutions. From the clinical databases of two high-volume pancreatic cancer centers in Munich, Germany, we retrospectively identified 15 patients that underwent pulmonary nodule resection suggestive of pulmonary metastasis after primary pancreatic cancer surgery between 2003 and 2015. Two patients had to be excluded from the study due to non-malignant histologic findings. In 13 patients, histopathologic results confirmed pulmonary metastatic disease. However, only 11 of these patients underwent complete pulmonary metastasectomy and we therefore excluded the other two patients that were surgically explored and biopsied, but didn't undergo complete PM. From those 11 patients, clinicopathologic data and survival was analyzed after anonymization of the data set. The median follow-up was 31 [IQR 28–61] months.

2.2. Data collection

Co-morbidities were assessed by the patient's medical history, and stratified applying the ASA classification according to the American Association of Anesthesiologists' as well as the Charlson co-morbidity score [19]. Furthermore, surgical procedures, perioperative course and histopathological results such as tumor stage were assessed. Postoperative complications were assessed according to the Clavien-Dindo classification [20,21]. Accordingly, grade 3–5 complications were classified as major complications. In addition, specific surgical and non-surgical complications, stay on the intensive care unit (ICU), and total length of hospital stay were documented. Thirty-day- and 90-day-mortality were defined as death within 30 and 90 days after surgery, respectively.

Table 1
Patients' clinical characteristics..

	Pulmonary metastasis, n (%)
No. Patients	11 (100)
Demographics	
Sex, male	6 (55)
Age, y[a]	66 [49–75]
ASA score	
≥2	8 (72.7)
T-stage (primary tumor) [b]	
pT1/2	0
pT3/4	11 (100)
Nodal involvement, pN + [b]	9 (81.8)
Margins involved, R1/2	1 (9.0)
Grading [b]	
Low grade, G1/G2	8 (72.7)
High grade, G3/G4	3 (27.3)
Primary tumor	
Pancreatic head	9 (81.8)
Pancreatic corpus	1 (9.0)
Pancreatic tail	1 (9.0)
Duration of stay [a]	
ICU stay	4 (36.4)
ICU duration of stay, d	1.8 [1–3]
HLOS, d	17 [10–26]
Tumor marker[a]	
CA19-9[b]	259 [0–960]
CA19-9[c]	29.1 [5.4–50.0]
CEA[b]	4.5 [0.8–18.8]
CEA[c]	3.0 [1.1–10.4]

ASA, American Society of Anesthesiologists.
HLOS, hospital duration of stay, ICU, intensive care unit.
  [a] Numbers are median [range].
  [b] At time of primary surgery.
  [c] At time of metastasectomy.

2.3. Statistical analyses

Continuous variables are given as median and range and categorical variables as number and percentage. Univariate survival analysis was estimated applying Kaplan-Meier statistics. Statistical differences were assessed by the log-rank test. For statistical analyses, SPSS (version 23.0, IBM, Chicago, IL) or GraphPad Prism (version 7, San Diego, CA) were used.

3. Results

3.1. Demographic and clinical characteristics

Patients' clinical characteristics are presented in Table 1. The mean age of the patients was 66 years with a range from 49 to 75 years. Gender distribution was comparable with 55% male and 45% female patients. Due to the high impact of metastatic disease on the score, the calculated Charlson-Comorbidity Index (CCI) and age-factored CCIs tended to be high with a median of 6.54 and 8.91, respectively (Table 2). Regarding primary PDAC resection, advanced pT-stages 3 were observed in all patients, and 73% of these showed lymph node involvement (pN +). Furthermore, primary PDACs tended to be low grade (72% were G1/G2) and mostly located in the head of the pancreas (82%).

Pulmonary metastasis in patients after PDAC removal was detected after a median disease-free survival (DFS) time of 18 months (Fig. 1A) with most patients (91%) undergoing routine CT scans, which also ruled out local recurrence, whereas PET-CT scan was used in one patient.

Four patients (36.4%) had a single nodule after histopathological evaluation of the resected lung tissue, whereas 7 (63.6%) revealed

Table 2
Postoperative complications..

	Pulmonary metastasis, n (%)
No. Patients	11 (100)
Postoperative morbidity	
90 days	1 (9)
Clavien-Dindo-Classification (CD)	
Grade II	1 (9)
Charleson-Comorbidity Index (CCI)[a]	6.54 [6–8]
Age-factored CCI[a]	8.91 [8–10]

[a] Numbers are median [range].

Table 3
Characteristics of Metastasis..

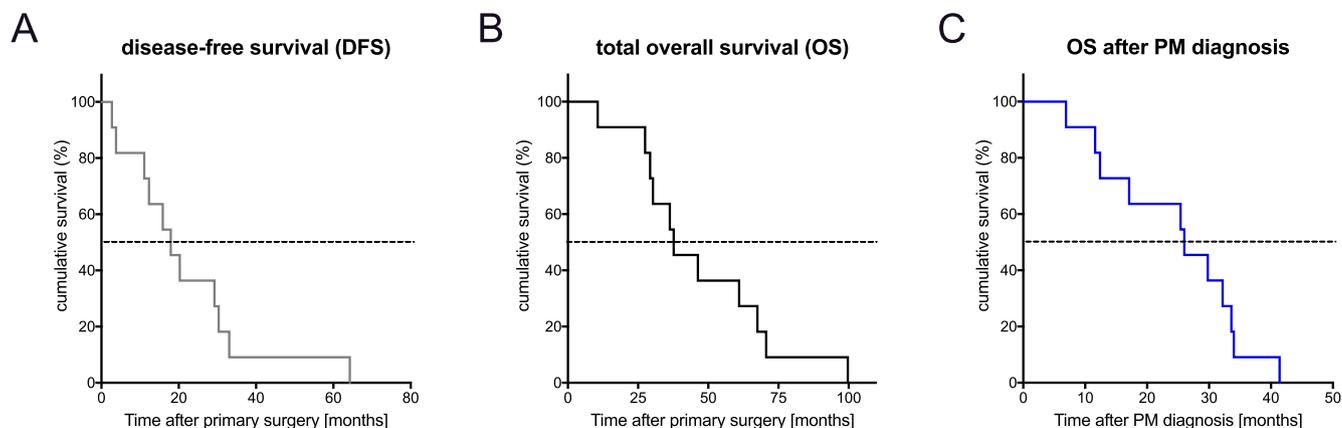|	Pulmonary metastasis, n (%)
No. Patients	11 (100)
No. Nodules	
1	4 (36.4)
> 1	7 (63.6)
Lung	
Left	4 (36.4)
Right	4 (36.4)
Both	3 (27.2)
Lobes	
Upper	2 (18.2)
Middle	1 (9.0)
Lower	4 (36.4)
Multiple	4 (36.4)

* Numbers are median [range].

multiple nodes (Table 3). Pulmonary metastasis occurred to both lungs with no preference in our investigated patient group. Four patients could be identified with metastatic nodules to both lungs. In terms of lobe distribution, we found 2 upper lobe, 1 middle lobe, and 4 lower lobe involvements with the rest of the patients presenting with pulmonary metastasis in multiple lobes (Table 3).

All patients were recommended adjuvant chemotherapy after primary resection of the pancreatic tumor, however, one patient refused therapy. After complete PM, all 11 patients in our cohort received additive chemotherapy with two patients subjected to FOLFIRINOX and the other 9 patients to therapies based on gemcitabine regimens.

3.2. Morbidity and mortality

Within hospital stay, there was no morbidity. Overall, postoperative morbidity occurred in one patient after discharge that required re-admission to the hospital (Clavien-Dindo (CD) Classification grade II, Table 2). Four patients (36.4%) were routinely admitted to the ICU immediately after PM for a median of 1.8 days due to their co-morbidities, such as cardiovascular diseases or thromboembolic events in one patient's history (Table 1). There was no re-admission to the ICU and no mortality at thirty and ninety days after PM.

3.3. Overall survival and univariate survival analysis

The median overall survival (OS) of our examined cohort after primary pancreatic surgery was 37.7 months (Figs. 1B) and 26 months after pulmonary resection (Fig. 1C) with one out of 11 patients alive after three years. Documented cause of death in most cases was progression of PDAC of the metastatic site or both local and metastatic recurrence.

Univariate analysis of risk factors is presented in Fig. 2. When clustered into patient groups with early occurrence of pulmonary nodules (less than 17 months, black curve) and late occurrence (later than 17 months after primary surgery, green curve), OS was better in the latter group (32.2 months) as compared to the first (14.75 months, $P = 0.025$; Fig. 2A). Also, high grade tumors were associated with worse outcome (12.4 vs. 31 months, p = 0.02, Fig. 2B). Elevated serum CA19-9 levels, CEA levels or number of metastatic pulmonary nodules were found to be of no relevant difference (Fig. 2C–E).

4. Discussion

In the present work, we aimed to evaluate potentially beneficial effects of metastasectomy of metachronous pulmonary nodules suggestive for metastatic disease after primary curative surgery for PDAC. Eleven out of 15 patients (73.3%) whose findings had been found to be suspicious, clinically and histologically proved to have resectable pulmonary metastases and, hence, underwent complete PM. Two patients revealed to have a benign histology and two further patients were not resectable due to the relation of the tumor to major thoracic vessels or extensive metastatic burden upon thoracic exploration.

It is well established that most patients with pancreatic cancer show recurrence within five years after initial surgical resection plus adjuvant therapies and this fact contributes to the dismal outcome of this disease despite recent interventions with intensified combination chemotherapies [22,23]. However, recent evidence shows that recurrence only to the lung occurs significantly later after surgery compared to metastasis to other organs such as the liver [14]. This was also associated with a longer median survival from recurrence to death of the

Fig. 1. Survival analysis. (A) Disease-free survival of all patients included in the study after primary pancreatic surgery. (B) Total overall survival after pancreatic surgery and (C) overall survival after diagnosis of pulmonary metastasis is shown.
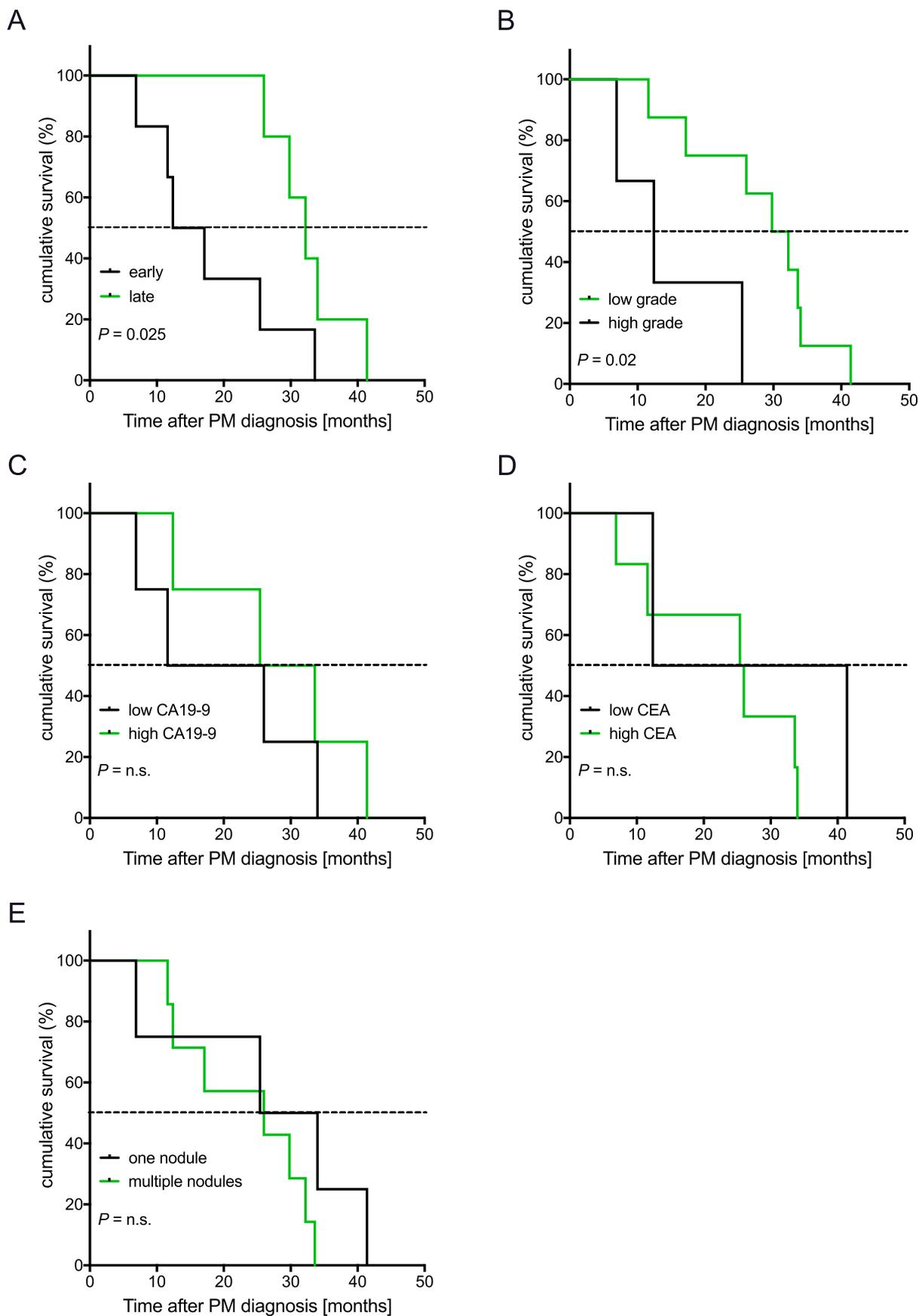
Fig. 2. Univariate survival analysis. (A) Cumulative survival of patients detected with pulmonary metastasis more than 17 months after primary pancreatic cancer surgery (green curve) compared to patients that recurred earlier than 17 months (black curve) ($P = 0.025$, Gehan-Breslow-Wilcoxon test). (B) Univariate analysis of tumor grade and OS in all patients (low grade (G1/G2) green curve, high grade (G3) black curve) ($P = 0.02$, Mantel-Cox test). (C–E) Cumulative survival with respect to CA19-9 levels (C), CEA levels (D) or number of nodules detected after PM (E).

patient in our study. Interestingly, Poruk et al. could also show that there is no statistically significant difference in survival between patients with primary pulmonary metastasis of pancreatic cancer compared to no lung metastasis [24]. These data suggest that pancreatic cancer that spreads to the lung only might have biological properties that favor longer survival of the patient.

In our cohort, OS after primary surgery and PM were 37.7 and 26 months, respectively. We found that resection of pulmonary nodules is associated with a low perioperative as well as 90-days' morbidity and mortality. Therefore, it might be recommendable for this highly selected group of patients as it seems safe and effective. This positive postoperative course is also in line with previously reported outcomes [7,25].

Intriguingly, we couldn't detect a correlation of the number of metastatic nodules and OS ($P = 0.57$), suggesting that in this highly-selected group of patients, PM might have been beneficial regardless of tumor involvement. Hence, one could postulate here that the technical resectability of metastatic nodules to the lung might determine the decision to operate rather than the tumor burden of the patient.

Compared to Wangjam et al., recurrence to the lung in our cohort (17 months vs. 12.7 months) occurred later and the median OS after pulmonary resection was longer (26 months vs. 8.5 months [14]. Moreover, in our cohort, we found that patients had a significantly better survival, if recurrences to the lung were detected later than 17 months after primary PDAC resection (32.2 vs. 14.75 months, $P = 0.025$) suggesting that PM might be especially beneficial to patients with late pulmonary metastasis of PDAC.

One fact that might explain the good overall survival apart from genetic properties in our study population is that the majority of the primary PDACs were well-differentiated with two thirds graded as low grade (G1/G2, Table 1). One might speculate here that these tumors belong to a distinctive subgroup in an earlier stage of genetic evolution rendering more time for the patient to develop distant metastasis [26].

However, this study is limited by some factors. First, the retrospective design leads to inherited selection bias of a particularly fortunate/unique group of long-term survivors. This is also due to the fact that, as reported above, only roughly about 22% of all metachronous metastatic events appear in the lungs, a group that is further reduced by the fact that not all patients will be amenable to PM [6]. Second, it might not be feasible to draw general conclusions for treatment consequences due to the limited number of patients evaluated. Nevertheless, it is one of the largest trials assessing pulmonary metastasis resection in pancreatic cancer today.

A minimum of 50 patients per group is needed for an 80% power to detect significant survival differences [7]. Such studies, although desirable in order to identify parameters which could help to select patients that might benefit the most from surgical treatment of pulmonary metastasis, will be difficult to perform secondary to one rare event.

On the basis of the present data, it is warranted that patients might benefit from surgical approaches of metachronous pulmonary metastasis. In addition, the question of whether palliative, neoadjuvant or adjuvant chemotherapy should be applied in these patients and when to proceed to PM needs to be evaluated.

5. Conclusion

In summary, we report minimal perioperative morbidity and mortality and successful positive outcomes in a selected cohort of patients undergoing pulmonary metastasectomy who had previously undergone pancreatic surgery due to pancreatic adenocarcinoma. The benefits seem most obvious in patients with late occurrences of metachronous disease. In addition, primary tumor biology indicated by tumor grading seems to be of importance. We acknowledge the limitations of the retrospective nature and the limited number of cases of this series. Future prospective trials will be necessary to validate our findings.

Conflicts of interest

None to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2019.08.010.

References

[1] T. Seufferlein, J.B. Bachet, E. Van Cutsem, P. RougierO.B.O.T.E.G.W. Group, Pancreatic adenocarcinoma: ESMO–ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Ann. Oncol. 23 (2012) vii33–vii40, https://doi.org/10.1093/annonc/mds224.

[2] T. Conroy, F. Desseigne, M. Ychou, O. Bouché, R. Guimbaud, Y. Bécouarn, et al., FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, N. Engl. J. Med. 364 (2011) 1817–1825, https://doi.org/10.1056/NEJMoa1011923.

[3] C.-T. Hsueh, Pancreatic cancer: current standards, research updates and future directions, J. Gastrointest. Oncol.. 2 (n.d.) 123–125. doi:10.3978/j.issn.2078-6891.2011.037.

[4] W. Hartwig, J. Werner, D. Jäger, J. Debus, M.W. Büchler, Improvement of surgical results for pancreatic cancer, Lancet Oncol. 14 (2013) e476–e485, https://doi.org/10.1016/S1470-2045(13)70172-4.

[5] Y. Zhang, A.E. Frampton, C. Kyriakides, J.J. Bong, N. Habib, R. Ahmad, et al., Locorecurrence after resection for ductal adenocarcinoma of the pancreas: predictors and implications for adjuvant chemoradiotherapy, J. Cancer Res. Clin. Oncol. 138 (2012) 1063–1071, https://doi.org/10.1007/s00432-012-1165-7.

[6] M.H.G. Katz, H. Wang, J.B. Fleming, C.C. Sun, R.F. Hwang, R.A. Wolff, et al., Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma, Ann. Surg. Oncol. 16 (2009) 836–847, https://doi.org/10.1245/s10434-008-0295-2.

[7] G.J. Arnaoutakis, D. Rangachari, D.A. Laheru, C.A. Iacobuzio-Donahue, R.H. Hruban, J.M. Herman, et al., Pulmonary resection for isolated pancreatic adenocarcinoma metastasis: an analysis of outcomes and survival, J. Gastrointest. Surg. 15 (2011) 1611–1617, https://doi.org/10.1007/s11605-011-1605-8.

[8] A. Kawashima, M. Nakayama, D. Oka, M. Sato, K. Hatano, M. Mukai, et al., Pulmonary metastasectomy in patients with renal cell carcinoma: a single-institution experience, Int. J. Clin. Oncol. 16 (2011) 660–665, https://doi.org/10.1007/s10147-011-0244-0.

[9] T. Treasure, F. Fiorentino, M. Scarci, H. Møller, M. Utley, Pulmonary metastasectomy for sarcoma: a systematic review of reported outcomes in the context of Thames Cancer Registry data, BMJ Open 2 (2012), https://doi.org/10.1136/bmjopen-2012-001736 e001736–e001736.

[10] R.N. Younes, F. Abrao, J. Gross, Pulmonary metastasectomy for colorectal cancer: long-term survival and prognostic factors, Int. J. Surg. 11 (2013) 244–248, https://doi.org/10.1016/j.ijsu.2013.01.003.

[11] H. Winter, G. Meimarakis, M. Pirker, F. Spelsberg, R. Kopp, D. Rüttinger, et al., Predictors of general complications after video-assisted thoracoscopic surgical procedures, Surg. Endosc. 22 (2008) 640–645, https://doi.org/10.1007/s00464-007-9428-0.

[12] B.W. Renz, S. Boeck, F. Roeder, C. Trumm, Oligometastatic Disease in Pancreatic Cancer-How to Proceed, Visceral, 2017.

[13] S.D. Canner, M. Zenati, B.A. Boone, The indolent nature of pulmonary metastases from ductal adenocarcinoma of the pancreas, Journal of Surgical (2015), https://doi.org/10.1002/jso.23943/pdf.

[14] T. Wangjam, Z. Zhang, X.C. Zhou, L. Lyer, F. Faisal, M.P. Paronetto, et al., Resected pancreatic ductal adenocarcinomas with recurrence limited in lung have a significantly better prognosis than those with other recurrence patterns, Oncotarget 5 (2015), https://doi.org/10.18632/oncotarget.5054.

[15] L.A. Robinson, T. Tanvetyanon, G. Springett, J. Fontaine, E. Toloza, P. Hodul, et al., Pulmonary metastasectomy for suspected pancreaticobiliary cancer, J. Thorac. Cardiovasc. Surg. 152 (2016) 75–82, https://doi.org/10.1016/j.jtcvs.2016.02.066.

[16] M. Nakajima, T. Ueno, N. Suzuki, H. Matsui, Y. Shindo, K. Sakamoto, et al., Novel indications for surgical resection of metachronous lung metastases from pancreatic cancer after curative resection, J. Clin. Gastroenterol. (2016), https://doi.org/10.1097/MCG.0000000000000551.

[17] R.F. Falkenstern-Ge, M. Wohlleber, M. Kimmich, K. Huettl, G. Friedel, G. Ott, et al., Pulmonary adenocarcinoma occurring 5 Years after resection of a primary pancreatic adenocarcinoma, A Relevant Differential Diagnosis, Case Reports in Oncological Medicine (2014) 1–4, https://doi.org/10.1155/2014/841907 2014.

[18] A. Deeb, S.-U. Haque, O. Olowokure, Pulmonary metastases in pancreatic cancer, is there a survival influence? J. Gastrointest. Oncol. 6 (2015) E48–E51, https://doi.

org/10.3978/j.issn.2078-6891.2014.114.

[19] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (1987) 373–383.

[20] P.A. Clavien, J. Barkun, M.L. de Oliveira, J.-N. Vauthey, D. Dindo, R.D. Schulick, et al., The Clavien-Dindo classification of surgical complications: five-year experience, Ann. Surg. 250 (2009) 187–196, https://doi.org/10.1097/SLA.0b013e3181b13ca2.

[21] D. Dindo, N. Demartines, P.A. Clavien, Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey, Ann. Surg. (2004), https://doi.org/10.1097/01.sla.0000133083.54934.ae.

[22] J. Kleeff, C. Reiser, U. Hinz, J. Bachmann, J. Debus, D. Jaeger, et al., Surgery for recurrent pancreatic ductal adenocarcinoma, Ann. Surg. 245 (2007) 566–572, https://doi.org/10.1097/01.sla.0000245845.06772.7d.

[23] J.P. Neoptolemos, D.H. Palmer, P. Ghaneh, E.E. Psarelli, J.W. Valle, C.M. Halloran, et al., Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial, Lancet 389 (2017) 1011–1024, https://doi.org/10.1016/S0140-6736(16)32409-6.

[24] K.E. Poruk, Y. Kim, J.L. Cameron, J. He, F.E. Eckhauser, N. Rezaee, et al., What is the significance of indeterminate pulmonary nodules in patients undergoing resection for pancreatic adenocarcinoma? - PubMed - NCBI, J. Gastrointest. Surg. 19 (2015) 841–847, https://doi.org/10.1007/s11605-014-2740-9.

[25] B. Brieau, M. Barret, A. Rouquette, J. Dréanic, C. Brezault, J.F. Regnard, et al., Resection of late pulmonary metastases from pancreatic adenocarcinoma: is surgery an option? Canc. Invest. (2015), https://doi.org/10.3109/07357907.2015.1080831.

[26] S. Yachida, S. Jones, I. Bozic, T. Antal, R. Leary, B. Fu, et al., Distant metastasis occurs late during the genetic evolution of pancreatic cancer, Nature 467 (2010) 1114–1117, https://doi.org/10.1038/nature09515.