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Surgical and local therapeutic concepts of oligometastatic pancreatic cancer in the era of effective chemotherapy

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Summary
Background Pancreatic cancer (PC) remains a disease characterized by an extremely poor prognosis, which is often limited by advanced tumor stage at diagnosis. As surgery remains the only option for long-term survival, indications for resection to achieve a complete tumor removal have been extended in recent years, including locally advanced as well as metastatic disease.
Methods Here, we provide a literature overview of modern multimodal treatment concepts of metastatic PC focused on surgery and local interventions including neoadjuvant concepts, stratification of patients, prognostic parameters, and oncological outcomes.
Results The current literature lacks level I evidence studies on surgery in stage IV PC. The available observational studies show that resection for liver metastasis has been increasingly performed in recent years, outcomes improve after neoadjuvant therapy, and certain prognostic parameters can identify patients who benefit from this approach. In addition, interventional or radio-oncological liver-directed therapies have been evaluated showing the possibility of some disease control. Resection of pulmonary metastases is rarely performed, although this patient subgroup may have a more favorable prognosis than patients with stage IV liver cancer. Surgery in the setting of peritoneal carcinomatosis remains experimental without any valid supporting data.
Conclusions There are promising data to support resection of metastatic PC, presuming this approach is embedded in a multimodal oncological concept with modern and effective multi-agent chemotherapies and proper patient selection. Based on this, future studies should specify distinct groups of patients who benefit from extended surgical approaches including synchronous or staged metastasectomy.

Keywords Metastatic pancreatic cancer · Resection · Liver surgery · Interventional therapies · Patient selection

Novel aspects

- This review summarizes the available literature on surgical and interventional treatment of metastatic pancreatic cancer in the light of modern, effective chemotherapies.
- Risk factors derived from studies are highlighted and a possible clinical algorithm is proposed.
- An outlook on future perspectives regarding multimodal treatment of metastatic pancreatic cancer is provided.

Introduction

Despite enormous efforts and improvements in terms of effective chemotherapy regimens as well as the perioperative and surgical management of patients with pancreatic cancer (PC; [1–4]), the prognosis for the whole cohort suffering from this disease remains poor, with a 5-year overall survival (OS) of approximately 10% in central European countries such as Germany or Austria according to national statistics

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[5]. Since most patients present with metastatic disease or with locally unresectable, advanced tumors, only a small proportion of patients of around 20% are primarily classified amendable for surgical resection according to accepted guidelines [6, 7]. Therefore, palliative systemic chemotherapy represents the therapeutic mainstay in most cases. However, in some patients with PC, the metastatic spread at the time of the first diagnosis is limited in terms of number of nodules and organs involved, commonly defined as oligometastatic cancer [6, 8, 9]. This subset of cancers potentially depicts a transitional state between localized and widespread systemic involvement and also exhibits specific biological behavior, e. g., by expression of typical micro Ribonucleid acid (mi-RNA) patterns. Insights from oligometastatic situations in other cancer types such as colorectal malignancies with improved outcomes achieved by aggressive surgical resection in an environment of modern perioperative chemotherapies [10, 11] have triggered a spark of hope also in PC. Several single-center reports showed potentially beneficial outcomes when progressive surgery for extra-regional lymph node or liver metastases (LM) was performed in PC [12–14]. This has also been suggested by a retrospective European multicenter study [15] and a recent analysis of the surveillance, epidemiology and end results (SEER) database in the United States, showing a potentially improved survival in a subset of patients with isolated liver and lung metastases [16]. Furthermore, successes reported for poly-chemotherapy combined with progressive surgery in locally advanced or borderline-resectable PC [1, 17–19] as well as adjuvant treatment [20, 21] have once more inspired interdisciplinary discussions on the selection criteria and usefulness of curative-intent surgical resection for oligometastatic PC in the era of effective, modern chemotherapies [22]. However, no high-level evidence via prospective trials or meta-analyses has been generated on this topic to date, as studies are ongoing [23]. Also, biomarkers or clinical factors guiding treatment algorithms are not well defined [24]. The present narrative literature review summarizes available oncosurgical reports on potentially resectable oligometastatic PC and compares these outcomes with other local treatments such as liver-directed stereotactic body radiotherapy (SBRT), selective internal radiation therapy (SIRT), or radiofrequency ablation (RFA; [25, 26]) to propose a treatment algo-

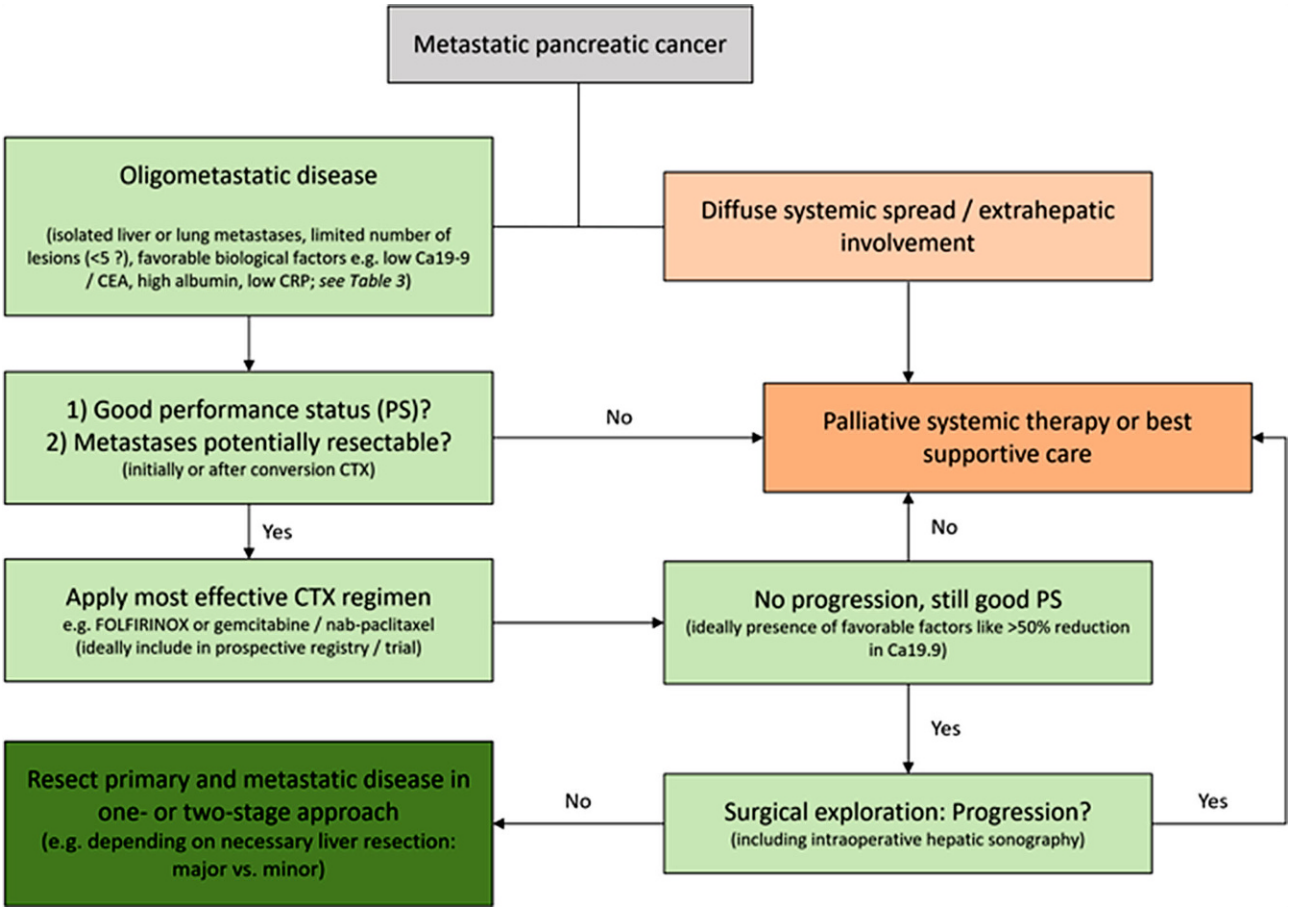

Fig. 1 Proposed algorithm for decision-making and risk stratification in metastatic pancreatic cancer patients evaluated for potential resection. *CA 19-9* Carbohydrate Antigen 19-9, *CEA* carcinoembryonic antigen, *CRP* C-reactive protein, *CTX* chemotherapy, *FOLFIRINOX* 5-FU, folinic acid, irinotecan and oxaliplatin, *PS* performance status

rithm (Fig. 1) and also gives an outlook on potential factors and biomarkers for stratification.

The age of effective chemotherapies in pancreatic cancer

Influence of chemotherapy on resectable, borderline-resectable and unresectable PC

Presently, the use of neoadjuvant chemotherapy alone or in combination with radiotherapy in patients with resectable, borderline-resectable, and locally advanced PC is a field of intense studies. Before considering neoadjuvant therapy and surgery, the general and performance status of the patient has to be evaluated after accurate staging to assess the presence and volume of any metastatic disease as well as the local resectability status [27]. Contrast-enhanced computed tomography (CE-CT) is the most commonly used imaging modality for the basic examination, which may be supplemented by magnetic resonance imaging (MRI) if LM are suspected as well as ^{18}fluorine-2-fluoro-2-deoxy-d-glucose positron emission tomography with computed tomography (^{18}FDG-PET–CT) scanning, which is more sensitive for the detection of widespread metastatic disease [28, 29].

The consideration of neoadjuvant treatment in primary resectable PC is to treat micro-metastatic disease at an early stage and to increase the rate of complete microscopic tumor clearance. To date, there is no high-level evidence for this concept; however, a number of randomized controlled trials on this topic are ongoing. Among others these include the PANACHE01-PRODIGE48 trial (four cycles of modified 5-FU, FA, irinotecan, and oxaliplatin [mFOLFIRINOX] or 5-FU, FA, and oxaliplatin [FOLFOX] to upfront surgery followed by adjuvant chemotherapy; [30]) and the NEONAX trial (gemcitabine/nab-paclitaxel pre- and postoperatively vs. upfront resection and only adjuvant therapy; [31]).

Neoadjuvant therapy for borderline-resectable PC is currently practiced in many centers, although—similar to resectable PC—sufficient evidence is lacking. The most recent PREOPANC trial included borderline patients randomized to neoadjuvant therapy ($n=63$) vs. upfront resection ($n=58$; [32]). Regarding the results, there was a significant benefit for neoadjuvant therapy of 29.9 months vs. 16.8 months after upfront resection plus adjuvant chemotherapy. However, when compared with the results of the ESPAC 4 study (28.4 months median survival with upfront resection + adjuvant treatment; [21]), survival was not strikingly improved in the neoadjuvant PREOPANC arm, therefore raising the question regarding the true advantages of this concept. A multicenter randomized controlled phase II/III trial from Korea investigated neoadjuvant chemoradiotherapy and chemotherapy (with adjuvant chemoradiotherapy and chemotherapy) compared with adjuvant chemoradiotherapy and chemotherapy alone [33]. After 58 patients had been enrolled, an interim analysis was performed to show a statistically significant treatment efficacy for the neoadjuvant arm and the trial was terminated. Finally, there were only eight and six patients, respectively, who actually completed the per-protocol treatment, rendering the data highly unstable and no conclusion possible.

In contrast to resectable and borderline-resectable PC, locally advanced PC certainly represents a tumor stage requiring neoadjuvant therapy, although no high-quality randomized trials are published. However, there is considerable interest in this approach given remarkable findings in large single-center reports. A series of 575 consecutive patients with unresectable PC who had undergone neoadjuvant therapy found that 292 (50.8%) patients could undergo resection using advanced surgical techniques [1]. Neoadjuvant treatment protocols included FOLFIRINOX ($n=125$), gemcitabine and radiotherapy ($n=322$), and other regimens ($n=128$). The highest resection rates were achieved after FOLFIRINOX (60.8%) and median OS and 3-year survival rates were 15.3 months and 23.0% after resection compared with 8.5 months and 2.4% after exploration alone ($p<0.0001$). With regard to metastatic PC (mPC) in this study, metastases were still present at the time of resection in 38% of patients in the FOLFIRINOX group, in 7% in the gemcitabine and radiotherapy group, and in 17% of patients receiving other regimens ($p<0.0001$). Median survival after resection in the three groups was 16.0, 16.5, and 14.5 months, respectively. Multivariable analysis suggested that FOLFIRINOX was an independent prognostic factor compared with the other regimens. As survival after resection was not different, this underlines that resection itself is the crucial prognostic factor and that a stage of resectability can most effectively be achieved by FOLFIRINOX even in the metastatic setting. This is consistent with a recent individual patient data meta-analysis showing that patients with locally advanced PC treated with FOLFIRINOX had a median OS of 24.2 months that is far superior to previously reported median OS with gemcitabine in these patients [34].

Palliative setting studies

The history of palliative chemotherapy treatment for locally advanced and metastatic disease changed fundamentally in 1997 when Burris et al. published their randomized trial comparing gemcitabine with 5-FU [35]. In this study of 126 patients, gemcitabine was the first agent demonstrating a significant survival benefit over 5-FU, increasing the median survival from 4.4 to 5.7 months ($p=0.0025$) and the dismal 1-year survival of 2% after 5-FU to 18% after gemcitabine. Furthermore, the generally good tolerability in patients resulted in gemcitabine becoming the standard agent of care in palliative treatment for almost 20 years. Mean-

Table 1 Studies of patients undergoing resection for metastatic pancreatic cancer

Author	Year	Inclusion period	Center	*N*	Type of metastases	Mortality (%)/ morbidity (%)	Max. size (cm)	Lesions (*n*)	Primary tumor resected?	Median follow-up (mo)	Median OS (mo) after resection	Median RFS (mo)	Recurrence (%)	(Independent) factors for poor survival
Zanini N et al. [14]	2015	2003–2014	Bologna	15	Liver	0/60	3.5	1–3	All	12.6	9.1	5.2	93	Timing (synchronous), >1LM
Crippa S et al. [42]	2016	2003–2013	Milan and Ancona	11	Liver	0/27	n.a.	1–5+	All	n.a.	39 (from diagnosis)	n.a.	91	>5LM, <50% CA 19-9 reduction, Gem monotherapy
Wright P et al. [44]	2016	2008–2013	Pittsburgh and Baltimore	23	Liver, Lung, Peritoneum	0/13 (major)	n.a.	1–5+	All	30	18.2	8.6	74	n.a.
Tachezy M et al. [15]	2016	1994–2014	European Multicenter	69	Liver	1/68	n.a.	1–11	All	n.a.	15	n.a.	n.a.	Tumor located in pancreatic tail
Frigerio I et al. [43]	2017	2007–2015	Verona	24	Liver (all complete hep. response)	No liver resection	n.a.	1–2+	All	31	13 (after resection) 56 (after diagnosis)	11 (after surgery) 21 (after diagnosis)	75	None
Hackert T et al. [17]	2017	2001–2014	Heidelberg	128	Liver (85), ILN (43)	2.9/45 4.3/22 (syn./met.)	75% ≤2 cm	1–3+	All	n.a.	12.3	n.a.	n.a.	None

CA 19-9 Carbohydrate Antigen 19-9, *Gem* gemcitabine, *hep* hepatic, *ILN* inter-aortocaval lymph nodes, *LM* liver metastases, *N* number of patients included in (sub)analysis, *n.a.* data not available, *met.* metachronous disease, *mo* months, *OS* overall survival, *RFS* recurrence-free survival, *syn.* synchronous disease

while combining different agents like platinum-based therapies with gemcitabine did not show any superiority compared with gemcitabine mono use, although meta-analyses on that topic showed slightly improved survival for gemcitabine combined with platin-based agents [36–38].

It was not until 2011 that the results of the ACCORD11/PRODIGE4 trial changed the general treatment for metastatic disease entirely. Conroy et al. recruited 342 patients with either irresectable or mPC, comparing FOLFIRINOX and gemcitabine. The median survival in the gemcitabine group was 6.8 months and thus comparable to the data of Burris et al. [35], whereas the use of FOLFIRINOX resulted in an increased survival of 11 months ($p<0.001$). The superiority of FOLFIRINOX over gemcitabine was also seen in the response rate increase of 9.4% for gemcitabine to 31.6% for FOLFIRINOX. The study population, however, represented a (highly) selected fit of patients, i. e., only patients with limited cardiac comorbidities, age 76 or younger, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were included. The price for the higher survival rates of FOLFIRINOX was increased toxicities, i. e., grade III/IV effects.

Several attempts to decrease the toxicities of FOLFIRINOX were made since Conroy's trial was published. Therefore, the use of a modified FOLFIRINOX (mFOLFIRINOX) has been analyzed by various groups yielding similar results with regard to survival [39]. Nevertheless, there are no data available comparing the initially proposed regimen with the modified scheme, which is why FOLFIRINOX is still the standard of care for patients in a good health state who are competent to undergo an aggressive, yet potent therapy.

Besides FOLFIRINOX, the use of nanoparticle albumin-bound paclitaxel (Nab-paclitaxel) in combination with gemcitabine was compared with gemcitabine monotherapy in 861 patients with mPC in 2015 [40]. Combining Nab-paclitaxel with gemcitabine increased the OS from 6.7 months for gemcitabine monotherapy to 8.5 months ($p<0.001$). The response rate was also increased from 7% for gemcitabine to 23% in the gemcitabine with Nab-paclitaxel group giving two potent options for mPC.

Surgery for oligometastatic pancreatic cancer

Liver metastases

Current guidelines do not recommend surgery for metastatic disease. This recommendation is derived from the generally poor prognosis and especially the lack of randomized controlled trials. Thus, the available data are limited to retrospective analyses, case series, and case reports [14]. However, high-volume centers tend to push boundaries and perform partial hepatectomy combined with pancreatic resections

or metachronous liver resections in cases of isolated hepatic recurrence. A systematic review published in 2008 [41] included three case reports, and 21 retrospective case series, and studies that included up to 22 patients with heterogeneous results, showing that this approach was applied only in a very small number of patients.

However, a recently published European multicenter retrospective analysis included 69 patients who underwent pancreatic and simultaneous hepatic resection for mPC in six European pancreas centers [15]. These 69 patients were matched to patients who did not receive curative resection with regard to several factors, e. g., number of hepatic metastases, age, sex, and tumor stage. Unsurprisingly, the OS in the resection group was significantly better than in the control group with a median survival of 14.5 months for curative surgery while the control group had a median survival of 7.5 months ($p < 0.001$). The 5-year survival rate was 0% for palliative patients and 5.8% for resected patients. Of note, 65% ($n = 35$) of patients underwent adjuvant treatment with gemcitabine, a regimen inferior to modern treatments such as (m)FOLFIRINOX. It can be assumed that the age of modern and more effective chemotherapy protocols will have a further effect on survival in the very near future.

A series published in 2016 analyzed 127 patients with PC LM treated with palliative chemotherapy [42]. A subgroup of 11 of those patients eventually showed a good response after neoadjuvant treatment making them eligible for curative resection. The chemotherapy protocols used varied, including FOLFIRINOX, GEMOX, and others. The OS of these 11 patients was 39 months while the palliative control group had a median OS of 11 months ($p < 0.0001$).

The largest monocenter analysis from Heidelberg published in 2017 included 85 patients with either synchronous or metachronous LM [12]. Resection types varied from atypical to extended hepatectomies with acceptable morbidity and mortality. The median survival for patients with synchronous LM was 10.6 months, for patients undergoing liver surgery for metachronous LM it was 14.8 months ($p = 0.210$). For all patients combined ($n = 85$), the median survival was 12.3 months, comparable to the above multicenter analysis. Although median survival data do not seem too encouraging at first glance, long-term survival was observed after metastasectomy with 8.1% 5-year OS. By contrast, even modern chemotherapy treatment cannot achieve long-term survival in mPC.

A common feature of both the Heidelberg study and the European registry is that only a minority of patients underwent neoadjuvant therapy before LM resection was performed. By contrast, three other reports showed much longer survival rates when all of the analyzed patients received neoadjuvant therapy prior to undergoing resection [42–44]. This observation is certainly explained by the selection effect of neoadjuvant treatment, which is exemplarily shown in the study by Crippa et al. [42]. Although only 11 patients eventually underwent metastasectomy in this collective, survival was impressively high when multiagent chemotherapy was used, the number of resected metastases did not exceed five lesions, and CA 19-9 levels showed a reduction of >50% during neoadjuvant therapy. Interestingly, in one study from Verona, patients with hepatic metastases had exploration laparotomy after preoperative chemotherapy and underwent isolated primary tumor resection only in cases with complete intraoperatively vanished liver lesions, and therefore did never receive hepatectomy [43]. Still, the resulting median OS in these 24 patients was 13 months after pancreatic resection and 56 months after the initial diagnosis of metastases. Table 1 summarizes the most recent studies on hepatic metastasectomy together with pancreatic resection in a synchronous or metachronous setting.

Pulmonary and peritoneal metastases

The available data on pulmonary metastases and surgical treatment are even more limited than those for LM. However, the few available studies suggest that patients who develop isolated pulmonary metastases represent a favorable subgroup in mPC over patients with distant metastases in the liver or peritoneum [45].

A recently published trial [46] analyzed 12 patients with isolated pulmonary metastases. While one patient underwent pulmonary resection despite local inoperable primary disease, the other 11 patient's curative intent procedures varied from atypical wedge resections up to lobectomy. The median survival after diagnosis of pulmonary metastases was 47 months (6–66 months) with reported 3-year and 5-year survival rates of 62.3 and 31.2%, respectively. Taking the time span between primary pancreatic resection and survival after metastasectomy into consideration, the estimated 5-year OS was 82.5%. Although these data are very limited with a small number of patients who are both biologically and medically selected, no similar data are available for palliative chemotherapy treatment.

Patients who develop peritoneal spread generally have a very dismal prognosis with survival rates ranging between weeks and several months. Furthermore, local complications such as jaundice, ascites, malnutrition, and eventually cachexia often obviate the administration of palliative chemotherapy. The location itself inside the peritoneum results in low chemotherapy effectiveness. The group of Satoi et al. conducted a multicenter trial including 33 patients with either macroscopic peritoneal spread or positive wash cytology in PC [47]. The chemotherapy agent administered intravenously was S-1 while the protocol included intraperitoneal application of paclitaxel every 3 weeks for a median observational time of 8.8 months. Considering the devastating prognosis of peritoneal metastases in PC patients, the

Table 2 Studies of patients undergoing locoregional treatment for pancreatic cancer metastases

Author	Year	Inclusion period	Centre	*N*	Type of intervention	Mortality (%)/ morbidity (%)	Max. size (cm)	Lesions (*n*)	Primary tumor resected?	Median follow-up (mo/ range)	Median OS (mo)	Median RFS (mo)	Recurrence (%)	(Independent) factors for poor survival
Park JB et al. [26]	2012	2002–2009	Seoul	34	RFA (liver)	0/12 (all mild)	3.2	1–4	Always	15 (3–65)	14	n.a.	>91	G3, >1LM, ≥2 cm LM
Hua Y-Q et al. [54]	2017	2012–2015	Shanghai	102	RFA (liver)	0/10 (all mild)	5.0	1–3+	Never	21 (4–43.8)	11.4	n.a.	82.4	Primary tumor location (head), ≥3 cm LM, NLR ≥2.5
Sun J-H et al. [55]	2017	2009–2015	Hangzhou	18	TACE (liver)	0/>85 (all mild)	n.a.	n.a.	<50% of cases	n.a.	9.2	n.a.	n.a.	Extrahepatic disease
Azizi et al. [52]	2011	2002–2007	Frankfurt	32	TACE (liver)	0/n.a.	n.a.	60% >5	Some (% n.a.)	n.a.	16 (10% 5y)	n.a. (10% 5y)	~90	Progressive disease during TACE, >5 LM
Huang Z-M et al. [56]	2013	1998–2011	Guangzhou	71	TACE + RFA + seeds (pancreas + liver)	0/n.a.	n.a.	54% >3	Never	n.a.	11 (6% 3y)	n.a. (no CR)	n.a. (no CR)	>3 LM
Michl M et al. [57]	2014	2004–2011	Munich	19	SIRT (liver)	11/74	n.a.	n.a.	>70%	n.a.	9	2.6 mo systemic PFS	n.a. (no CR)	Increased CA 19-9, CRP, extrahepatic disease
Kim A et al. [53]	2016	2012–2015	Washington	16	SIRT (liver)	0/13 (all < grade 4)	n.a.	n.a.	1 patient	n.a.	20 after LM 12.5 after SIRT	3.4 mo systemic PFS	n.a.	n.a.
Gibbs P et al. [58]	2015	2006–2009	Melbourne	14	SIRT (liver)	7/57 (grade 3/4)	n.a.	1–5	29%	n.a.	5.5	4.4 mo systemic PFS	n.a. (no CR)	Primary tumor in situ
Mahadevan A et al. [25]	2018	2005–2017	25 centers (LM registry)	20	SBRT (liver)	0/n.a. (no severe)	n.a.	n.a.	n.a.	n.a.	6	n.a.	All had local progress	Tumor volume <40 cm^3
Wieners G et al. [59]	2015	n.a.	Berlin	20	HDRBT	0/15 (severe)	7.3	1–3+	n.a.	14 (mean)	8.6	4.9 mo systemic PFS	10% local recurrence	No chemotherapy received after HDRBT

CA 19-9 Carbohydrate Antigen 19-9, *CR* complete response, *CRP* C-reactive protein, *HDBRT* high-dose-rate brachy-radiotherapy, *LM* liver metastases, *N* number of patients included in (sub)analysis, *n.a.* data not available, *NLR* neutrophil-to-lymphocyte ratio, *mo* months, *OS* overall survival, *PFS* progression-free survival, *RFA* radiofrequency ablation, *RFS* recurrence-free survival, *TACE* transarterial chemoembolization, *SIRT* selective internal radiation therapy

results of this trial were extremely encouraging with 16.3 months median survival and 62% 1-year survival rate. The response rates were 36% partial response, 46% stable disease, 6% progressive disease, and in 12% response was not available. It has to be added that the efficacy of S-1 is different between the Asian and Caucasian population due to differences in the cytochrome P-450 2A6 activity eventually resulting in higher toxicity in Caucasians. Therefore, adjustments in the S-1 protocol are needed for other ethnicities to evaluate the promising effects.

Nonsurgical, local treatment of oligometastases

Experience with nonsurgical, local treatment is limited in mPC compared with other malignancies such as metastatic colorectal cancer or primary liver cancers, where techniques like RFA, microwave ablation (MWA), or transarterial chemoembolization (TACE) have become widely accepted modalities in treatment algorithms [48–50]. Furthermore, studies of stage IV PC have to be interpreted with caution, since most of these publications are single-arm, proof-of-principle studies and no randomized controlled trial exists comparing nonsurgical hepatic treatment vs. liver resection or systemic therapy alone. Also, in the majority of cases the primary tumor has not been surgically removed [6]. An early series from Johns Hopkins and the Mayo Clinic (USA) published in 2010 gives an overview of the utilization of different liver-directed treatments as an adjunct to pancreatic resection in mPC and other malignancies necessitating pancreatic head resections [51]. The authors state that pancreaticoduodenectomies plus liver-directed therapies are associated with considerable morbidity of >34% (more than 50% major complications) with an overall mortality of 2.4%. Intriguingly, hepatic abscesses are especially common after two-stage resection and local therapy (14.5% vs. 7%).

Table 2 gives a summary of studies evaluating specific locoregional treatments for mPC including data on postinterventional complications and oncological survival. In summary, most series are retrospective reports of far less than 100 patients with inhomogeneous inclusion criteria with details on hepatic tumor number and size often missing. Most commonly, median OS ranges from 5.5 to 14 months, only rarely surpassing 16–20 months in selected cohorts [52, 53], as principally all patients either experience local or distant recurrence after RFA/TACE or do not reach complete response after SIRT or local radiotherapy.

Liver-directed therapies

Radiofrequency ablation In a Korean series published 2012, a total of 34 patients underwent ultrasound-guided hepatic RFA either intraoperatively with simultaneous primary tumor resection or in a two-stage approach after pancreatic surgery [26]. The number of lesions treated ranged from one to four with a maximum diameter of 3.2 cm, resulting in a median survival after diagnosis of LM of 14 months. About half of the patients underwent re-ablation of recurring LM. Intriguingly, at the time of analysis, one patient was alive and free from recurrence for 44 months after RFA, showing that long-term survival is possibly in exceptional cases of mPC. This study identified the presence of a single <2-cm-diameter LM and good or moderate differentiation (G1 or G2) as factors associated with favorable OS. The major limitation in the study besides the single-arm design was the low number of pathological confirmations of LM of only 27% of patients. However, the authors state that concurrent CA 19-9 increment and post-ablational metastatic recurrence in almost all patients proves the presence of mPC.

The second, recently published study on RFA for hepatic oligometastatic PC comes from the Fudan University Shanghai Cancer Center in China including patients with synchronous LM between 2012 and 2015 [54]. In the study period a total of 469 patients with LM from mPC presented to the department, of whom 102 (22%) were amenable for treatment with RFA, showing that less than one fourth of LM patients do indeed have oligometastatic disease. The main endpoint in this study was analysis of safety and efficacy, through CT or MRI imaging after 1 month of treatment. In a total of 145 ultrasound-guided RFA sessions, in 95% of cases a radiologically complete tumor ablation was achieved. The overall morbidity rate reported was 10%, all manageable with conservative treatment, with no severe complications. After a median follow-up of 21 months, the median OS from diagnosis of LM was 11.4 months. Factors associated with poor survival analyzed with multivariable regression were a location of the primary tumor in the pancreatic head, a maximum diameter of LM of ≥3 cm, and a neutrophil-to-lymphocyte ratio (NLR) of ≥2.5. In this series, no patient underwent primary tumor resection, limiting comparability with the aforementioned publication from Korea.

Transarterial chemoembolization

In a study of 27 patients (18 with LM from PC and 9 cases with neuroendocrine tumors [NET]), authors from Hangzhou, China examined the efficacy and survival outcome after TACE [55]. In summary, 52 TACE sessions (1–7) were applied, including eight treatments with drug-eluting beads (DEB) after an average time of 4.5 months after diagnosis of LM. In less than half of the patients, the primary tumor was resected, 14 patients had extrahepatic lesions, and three patients had undergone partial liver resection before, four had previous RFA or HIFU (high intensity focused ultrasound). Only 12 patients did not receive any other treatment than TACE. Almost all patients experienced mild complications such as bone marrow suppression, epigastric pain, or lack of appetite. No severe complications or mortality occurred related

to the procedures. The OS in the mPC group was 9.2 months (vs. 50.1 months in NET patients). The main risk factor for poor survival was extrahepatic involvement.

Another series from Frankfurt, Germany suggested that repetitive TACE may result in a relevant response in PC-LM [52]. In summary, 32 patients who had not undergone any other ablative therapies previously and had no extrahepatic disease, received a mean of 3.2 TACE sessions (range 2–4) and underwent retrospective evaluation. No major complications occurred, the treatment response according to RECIST criteria was stable disease (SD) in 72% and partial response (PR) in 9.4%, and no patient experienced complete response. The median OS calculated from the first TACE session was 16 months, and was significantly better for patients with SD or PR (20 months) during TACE treatment compared with those with progressive disease (5 months). Also, median OS was better in patients with oligonodular disease (≤5 LM; 20 months) compared with multinodular mPC (11 months).

In another study from Guangzhou, China, 71 patients with unresectable PC primary tumor with ($n=51$) or without ($n=20$) LM underwent primarily TACE (mean 3 sessions, range 2–6; [56]). In the case of residual lesions in the primary tumor site, the liver, or metastatic lymph nodes, this was followed by RFA (24 patients) or radioactive seed implantation ($n=24$) or both ($n=31$). The resulting median OS was 11 months after diagnosis of LM, and was significantly better for patients with oligonodular (≤3 LM) metastases (18 months) compared with multinodular disease.

Selective internal radiation therapy

In 2014, radioembolization with Yttrium-90 microspheres in PC-LM was evaluated regarding efficacy, safety, and prognostic factors in 19 patients by a German group [57]. Most patients had previously undergone systemic therapy with gemcitabine-based regimens. Objective response in the liver was 47%, the median local progression-free survival (PFS) in the liver was 3.4 months and median OS was 9.0 months. No severe adverse short-term events occurred; however, in the long-term, liver abscesses, gastroduodenal ulceration, cholangitis, ascites, and spleen infraction were observed. In particular, two patients later died due to liver abscess and radioembolization-induced liver disease, necessitating careful long-term observation. Increased CA 19-9 and CRP were associated with shorter OS.

Another retrospective single-center series from Washington, DC analyzed 16 patients with liver-dominant mPC (>50% had extrahepatic disease) undergoing SIRT, 15 of whom also had received systemic chemotherapy, while only one patient underwent primary tumor resection [53]. Of these patients, 69%had SD or PR in the liver. No treatment-related grade 4 or 5 toxicities were observed, and the resulting median OS was 22 months since diagnosis of LM and 12.5 months after SIRT therapy.

Most recently, a phase II study from Melbourne, Australia was published with 14 patients, of whom ten had a primary tumor in situ and eight had liver-limited metastases [58]. Median PFS in the liver was 5.2 months and 4.4 at any site, and was prolonged in those with resected primary tumor (7.8 months vs. 3.4 months). Median OS was 5.5 months in all patients (13.6 months with resected primary tumor). Grade 3/4 adverse events occurred in 57% of patients within 60 days, and there was one death related to posttreatment liver failure and another one with unclear underlying cause.

Table 3 Factors associated with worse overall survival or time-to-progression in metastatic pancreatic cancer patients

	Examples of cutoffs evaluated in studies
Blood markers	
CA 19-9	≥200 or ≥626 or ≥1000 U/ml
CEA	≥2.9 or ≥4.5 ng/ml
CYFRA 21-1	≥2.7 ng/ml
Neutrophil–lymphocyte ratio	≥3.75 or >5
CRP	≥1 mg/dl
Bilirubin	>1 mg/dl
Albumin	<35 g/L
Patient or tumor factors	
Poor performance index	ECOG >0 or ECOG ≥2, Karnofsky index ≤80%
Metastatic spread	Hepatic involvement compared with isolated extrahepatic

CA 19-9 Carbohydrate Antigen 19-9, *CEA* carcinoembryonic antigen, *CRP* C-reactive protein, *CYFRA 21-1* cytokeratin 19-fragments, *ECOG* Eastern Cooperative Oncology Group performance status

SBRT or CT-guided brachytherapy

In a recently published international, multi-institutional registry of SBRT for 427 patients with LM of a number of different entities, 20 patients with mPC were also included [25]. Median OS was 6 months in these patients compared to, for example, 27 months in colorectal or 21 months in breast cancer ($p<0.0001$). Although local control after 12 months in mPC was comparable to other entities with an encouraging 70%, it rapidly decreased thereafter with all patients experiencing recurrence in the study period. In the whole cohort, small tumors (<40 cm^3) had improved local control rates compared with larger-volume tumors. Although toxicity data were not available from all participating studies, there was no grade 3 or higher adverse event reported from any institution.

Computed tomography-guided high-dose-rate brachytherapy (CT-HDRBT) is an interventional technique applying radiation through a percutaneous brachycatheter into targeted lesions. A study with

20 consecutive patients with 49 PC-LM retrospectively evaluated local tumor control, safety, and efficacy of this technique applied with a single-fraction high dose (15–20 Gy; [59]). With a mean diameter of 29 mm (10–73) and mean radiation time of 20 min (7–42), a mean coverage of 98% of the clinical target volume was reached. Three major complications (20%) occurred in terms of abscesses, all in patients with biliodigestive anastomosis. After a mean follow-up of 13.7 months, the median PFS was 4.9 months, with a local recurrence in 10% of 49 metastases. The median OS was 8.6 months after treatment.

Other nonsurgical local treatments

Other techniques currently evaluated for non-resectable mPC include electrochemotherapy [60], high-intensity ultrasound [61], and irreversible electroporation [62]. So far, only small series exist with very heterogeneous inclusion criteria and varying utilization of concomitant surgical resection, resulting in a median OS between 13 and 16 months for these therapies in mPC.

Prognostic factors for patient selection

Clinical factors and blood markers in mPC patients

In an attempt to evaluate established classic blood parameters as prognostic factors for survival compared to classic tumor markers like CA 19-9 (carbohydrate antigen 19-9), a German multicenter analysis pooled data from two phase II chemotherapy trials and one prospective high-volume center registry [63]. In a total of 291 patients with locally advanced and metastatic PC, the authors confirmed high baseline CA 19-9 to be associated with time-to-progression (TTP) and increased bilirubin as well as pretreatment CRP with poor OS in multivariable analysis. In this study, advanced age (>64 years) and decreased performance index (Karnofsky index ≤80%) were also linked to shortened TTP and OS, respectively. The participating high-volume center in a separate publication also reported increased pretreatment cytokeratin 19-fragments (CYFRA 21-1) to be associated with poor OS and TTP in 78 prospectively recorded, advanced PC patients [64]. In a multivariable Cox model, CYFRA 21-1 was shown to be an independent prognostic factor in addition to CA 19-9 and Karnofsky index, also providing prognostic information in Lewis antigen-negative (about 5–10%) or cholestatic individuals, cases that are both associated with unreliable CA 19-9 results.

Markers of inflammation have been shown to be predictors of poor survival in many cancer types. In mPC, NLR (cutoff: ≥3.75) was confirmed to be associated with decreased OS and may serve as a useful combination marker to enhance the prognostic value of CA 19-9 (cutoff: ≥626 U/ml) alone, with an Area under the Curve (AUC) of 0.843 when these two values were combined [65]. The prognostic value of NLR has also been confirmed in a recent Italian study, with an NLR cutoff of >5 [66]. Regarding the prognostic value of preoperative C-reactive protein (CRP), evidence for some time has been less clear since studies on resectable PC reported conflicting results, as summarized in a previous systematic review [67]. However, it was shown in a recent report from Shanghai of 386 patients with PC of whom 258 had TNM stage III or IV cancers, that a CRP/albumin ratio of ≥0.180 was significantly associated with poor OS in these advanced stages, whereas there was no difference in early-tumor stage patients. Also, in an earlier study from the year 2000, a prognostic index including CRP ≥5 mg/dl was associated with poor median OS [68].

In a large Chinese multicenter trial, a nomogram including decreased performance status, presence of LM, increased CA 19-9, high absolute neutrophil count, and decreased albumin was created to predict OS in mPC patients and validated in two cohorts of external Caucasian patient populations [69]. According to the nomogram score, the three resulting subgroups (high-, intermediate- and low-risk) showed significantly different median OS of approximately 4 vs. 7 vs. 11 months ($p<0.001$) in both the training and validation set.

All of the aforementioned non-tumor marker factors (performance index ECOG ≥2, albumin <35 g/l, CRP >10 mg/l, or NLR >5) were also confirmed as prognostic for OS in a large Korean study of 343 patients with stage IV disease [70]. The authors furthermore found that the initial metastatic site was prognostic: While extrahepatic-limited disease had a median OS of 7.5 months, isolated LM showed inferior OS of 4.8 and simultaneous extrahepatic and hepatic involvement had the worst prognosis of 2.4 median OS.

Table 3 summarizes blood markers as well as patient and tumor factors associated with poor survival in mPC.

New biomarkers

Future diagnostic tools such as circulating tumor cells and serum micro-RNAs to predict resectability, prognosis, and response to chemotherapy are continuously evaluated in ongoing studies [71–74]. Another review on "Molecular biology in pancreatic ductal adenocarcinoma" by Søreide K et al. in this journal gives further insight into this promising new field [75].

Conclusion

In conclusion, PC therapy has undergone substantial changes during the past decade with regard to the use of effective chemotherapy regimens in the neoadjuvant as well as the adjuvant setting. These approaches have been shown to improve patients' prognosis in all

situations. However, surgery still remains the key to long-term survival in PC, and with the standardization and centralization of pancreatic surgery, surgical outcomes have also improved. These developments have led to more extended surgical indications in PC, and patients with tumor stages that were historically defined as palliative are increasingly regarded as potential candidates for surgery in a multimodal therapy setting. Especially for locally advanced PC and oligometastatic disease, there are promising survival results if these patients undergo surgery after proper stratification and selection. Regarding the latter, this seems to be an essential task for future studies and research since currently available markers and imaging modalities still fail to predict tumor biology accurately and are therefore of only limited reliability in identifying patients who will benefit from extended surgical approaches with possible long-term survival.

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