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Research article

Efficacy and safety of CT-guided high-dose-rate interstitial brachytherapy in primary and secondary malignancies of the pancreas

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ABSTRACT

Purpose: To evaluate efficacy and safety of CT-guided iBT in patients with primary and secondary malignancies of the pancreas.

Material and methods: 13 patients with 13 lesions of the pancreatic corpus and tail were included: 8 secondary malignancies (metastatic lesions = ML) and 5 primary malignancies, including 3 primary tumors (PT) and 2 isolated locoregional recurrences (ILR) after surgical resection were treated with image-guided iBT using a 192iridium source (single fraction irradiation). Every 3 months after treatment clinical and imaging follow-up were conducted to evaluate efficacy. Peri- and postinterventional complications were assessed descriptively.

Results: The median diameter of the gross tumor volume (GTV) was 3 cm (range 1–6.5 cm), treated with a median D100 (minimal enclosing tumor dose) of 15.3 Gy (range 9.2–25.4 Gy). Local tumor control (LTC) was 92.3% within a median follow-up period of 6.7 months (range 3.2–55.7 months). Cumulative median progression free survival (PFS) was 6.2 months (range 2.8–25.7 months; PFS of primary and secondary malignancies was 5.8 and 6.2 months, respectively). Cumulative median over all survival (OS) after iBT was 16.2 months (range 3.3–55.7 months; OS of primary and secondary malignancies was 7.4 months and 45.6 months, respectively). 1 patient developed mild acute pancreatits post iBT, spontanously resolved within 1 week. No severe adverse events (grade 3+) were recorded.

Conclusion: Image-guided iBT is a safe and particularly effective treatment in patients with primary and secondary malignancies of the pancreas and might provide a well-tolerated additional therapeutic option in the multidisciplinary management of selected patients.

1. Introduction

Treatment of advanced or metastatic disease is challenging and best approached by a multidisciplinary team with an increasing tendency towards an individually tailored anticancer therapy to achieve the best possible outcomes. In this context the significance of local ablative techniques is constantly rising. Out of the toolbox of local ablation techniques high-dose-rate interstitial Brachytherapy (HDR-iBT = iBT) is a well-tolerated catheter-based afterloading method and it has been shown to provide high tumor control rates in primary and secondary malignancies of the liver, such as hepatocellular carcinoma and particularly in metastatic colorectal carcinoma, demonstrating local tumor control (LTC) rates of 95% and 88.3% after 12 months, respectively [1–3].

Furthermore, favorable LTC rates have also been achieved in the ablation of primary and secondary lung malignancies with a LTC rate of 91% at 12 months [4,5].

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal disease with a varying 5-year survival rate of 0.5–9% [6]. Complete resections remains the only potential cure, however, more than 80% of the

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patients are diagnosed with locally advanced or metastatic PDAC and therefore are not suitable for resection [7]. Furthermore, despite advances in surgical techniques and postoperative management pancreatic resection is still associated with substantial morbidity and mortality [8,9]. Additionally, about one third of the patients undergoing pancreaticoduodenectomy develop isolated locoregional recurrence (ILR) [10]. However, despite many therapeutic developments only moderate achievements regarding outcome and survival have been made over the last decades and especially in patients with locally advanced/unresectable or recurrent disease treatment options are scarce [11–13].

Apart from numerous studies considering therapy of PDAC little data exists regarding secondary malignancies of the pancreas; the estimated incidence of clinical occurrence of isolated metastatic lesions (ML) to the pancreas is about 2–5 % of all pancreatic neoplasm and in the majority of cases the represented primary tumor are renal, lung, colorectal or breast cancer and sarcoma [14,15]. Therapeutic options including resection depend on the type of primary tumor, location and number/volume of metastatic lesions and the patient's performance status.

In contrast, local ablative techniques, such as iBT provide a safe and minimal invasive approach and might offer an additional therapeutic option in the management of pancreatic neoplasms. To our knowledge no data has been published so far evaluating safety and efficacy of iBT in the ablation of primary and secondary malignancies of the pancreas. In this study we retrospectively analyzed a cohort of 13 patients with 13 inoperable lesions of the pancreas who underwent image-guided iBT.

2. Material and methods

2.1. Eligibility criteria and patients characteristics

Patient recruitment took place in a German university clinic, between October 2009 and February 2018. Indication for iBT was determined in an interdisciplinary tumor conference.

Principal inclusion criteria were: (a) unresectable neoplastic lesion of the pancreatic corpus or tail (including primary tumor = PT, ILR and ML), assessed by a surgeon with expertise in pancreatic malignancies, who considered them unresectable either due to tumor extent or medical comorbidities, (b) refusal of surgery, (c) East Coast Oncology Group (ECOG) performance status below 2. An upper limit was neither placed upon the number of lesions nor on the maximum tumor diameter. Contraindications to local ablation were (a) peritoneal carcinomatosis (b) prognosis limiting, widespread systemic disease (c) uncorrectable coagulation defects (target values: platelet count > 50,000/nl, Quick > 50%, partial thromboplastin time > 5 s) (d) lack of consent. The study was approved by the ethics committee of XXXXX (BLINDED).

In consideration of these criteria we included 13 patients (5 female and 8 male; median age 70 range 44–81) with one inoperable pancreatic lesion per patient (10 lesions of the pancreatic body and 3 lesions of the pancreatic tail). In detail: 3 PT (1 PDAC, 2 neuroendocrine tumors = NET), 2 ILR (PDAC) and 8 ML were treated, the latter comprised of 1 metastasis of gastric cancer, 1 breast cancer lesion and 6 renal cancer metastases. Out of these 8 patients with secondary malignancies 7 were presented with metachrone metastases. 11/13 patients had resection of the primary tumor, including 2 pylorus-preserving pancreaticoduodenectomy, followed by ILRs. 9/13 patients received palliative chemotherapy before iBT, including immune-checkpoint-inhibitors. Furthermore, 8/13 patients had additionally local ablative treatments of extrapancreatic metastases or the primary tumor prior to iBT; in detail: 1 iBT of lymphnode metastasis, 2 iBT of adrenal gland lesions, ablation of renal lesions (1 radiofrequency ablation, 3 iBTs) and 1 radioembolisation of the liver (for detailed patient characteristics see Table 1).

Prior to iBT all patients received a full clinical status evaluation with

Table 1
Patient characteristics.

Patient	Gender	Age	Location and Type of pancreatic neoplasm	Primary Tumor	Pathologic Subtypes	Maximum Diameter of the GTV (cm)	Administered D100 (Gy)	Local Recurrence (months after iBT)
1	m	75	ML of the corpus	gastric cancer	squamous cell carcinoma	4.3	12.0	6.7
2	m	77	ILR of the Corpus	pancreatic cancer	ductal adenocarcinoma	3	15.3	–
3	m	76	ILR of the Corpus	pancreatic cancer	ductal adenocarcinoma	3	9.2	–
4	m	69	PT of the cauda	pancreatic cancer	ductal adenocarcinoma	3	25.4	–
5	m	81	PT of the corpus	pancreatic cancer	neuroendocrine tumor	6.5	11.3	–
6	f	52	ML of the corpus	breast cancer	neuroendocrine tumor	4.5	17.4	–
7	f	44	PT of the corpus	pancreatic cancer	neuroendocrine tumor	2.5	10.3	–
8	f	73	ML of the corpus	renal cancer	clear cell renal cell carcinoma	1.3	15.8	–
9	m	73	ML of the caput	renal cancer	clear cell renal cell carcinoma	2.3	16.0	–
10	m	64	ML of the cauda	renal cancer	clear cell renal cell carcinoma	6.5	15.7	–
11	m	54	ML of the cauda	renal cancer	clear cell renal cell carcinoma	2.5	14.8	–
12	f	54	ML of the corpus	renal cancer	clear cell renal cell carcinoma	2.3	15.2	–
13	f	70	ML of the corpus	renal cancer	clear cell renal cell carcinoma	1	15.4	–

ML metastatic lesion, ILR isolated locoregional recurrence PT primary tumor.

a physical examination, laboratory assessment, whole body contrast-enhanced CT and Gb-EOB-DTPA-enhanced MRI (Primovist ®, Bayer, Pharma, Leverkusen, Germany) of the liver. Every 3 months after iBT clinical, laboratory and image-based follow-up (contrast-enhanced whole body CT) were performed.

2.2. Interventional procedure

The applied technique has been described elsewhere in detail [1,16,17]. Under guidance of a fluoroscopy-CT (Toshiba, Aquilion, Japan) an 18-gauge trocar puncture needle was inserted into the target lesions and a stiff angiography guide wire was exchanged for a flexible 6-F catheter sheath (Radifocus, Terumo™, Tokyo, Japan) using Seldinger's-technique followed by the placement of a 6-F afterloading catheter (Afterloadingkatheter, Primed® Medizintechnik GmbH, Halberstadt, Germany). The described intervention was performed under analgosedation (midazolam and fentanyl) and local anesthesia (lidocaine). The number and arrangement of the catheters was determined by the size, shape and anatomic location of the target. After catheter positioning a contrast-enhanced CT scan in breath-holding technique was acquired to document catheter positioning and for the purpose of irradiation planning. On these images the target lesion was carefully outlined as gross tumor volume (GTV), additionally, clinical target volume (CTV) and organs at risk (= OAR; e.g. stomach, duodenum) were marked by the interventional radiologist and the radiooncologist. Dose calculation was performed using the acquired dataset and Oncentra Masterplan (Oncentra® Brachy treatment planning system, Elekta AB, Stockholm, Sweden). The calculated isodose lines -relative to margins of the CTV- were controlled and adapted slice by slice. All irradiations were administered as single fraction irradiations using an iridium-192 source with a nominal activity of 10 Ci. A reference dose of 15 Gy was prescribed in our patients, which was defined as the minimum dose enclosing the complete CTV (D100). Inside the tumor higher doses were permitted and not limited. Additionally, dose limitations were taken into account due to adjacent OAR, i.e. gastric or duodenal wall (< 15 Gy/ml). After irradiation the catheters were removed and the puncture channels were sealed using gelfoam or fibrin tissue glue (Fig. 1 A–C illustrates the interventional method) [18].

2.3. Study design and statistical analysis

We retrospectively collected the data from our internally database ASENA® (LoeScap Technology GmbH). Primary endpoints were local tumor control (LTC) and safety; secondary endpoints were over all survival (OS) and progression free survival (PFS). The results were analyzed in a non-randomized and retrospective approach. Response Evaluation Criteria In Solid Tumors (RECIST vs1.1) were used to assess LTC and PFS. OS was calculated from the day of ablation to death. LTC, OS and PFS were evaluated employing the Kaplan-Meier method with SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp). Adverse events were defined according to Common Terminology Criteria for Adverse Events (CTCAE vs 4.03).

Safety was evaluated descriptively. Diagnosis of acute pancreatitis (AP) was made on the base of the Revised Atlanta Classification: requiring 2 of the following features: (a) characteristic abdominal pain (acute onset, severe character, epigastric pain often radiating to the back), (b) elevated enzyme activity (lipase or amylase) at least 3 times > than the upper limit of normal and (c) characteristic findings on contrast-enhanced CT scan.

3. Results

3.1. Treatment characteristics

We treated a total of 13 pancreatic lesions, comprised of 8 secondary malignancies/ML (61.5%) and 5 primary malignancies: 3 PT (23.1%) and 2 ILR (15.4%). Median diameter of the target lesions was 3 cm (range 1.0–6.5 cm). All lesions were irradiated in a total of 13 sessions with an employed mean of 1.5 catheters (range 1–4). The median administered D100 was 15.3 Gy (range 9.2–25.4 Gy). No OAR were irradiated in excess of critical value during treatment. The median irradiation time was 10.1 min (range 4–33 min).

3.2. Local tumor control, progression free survival and overall survival

Within the median follow up of 6.7 months (range 3.2–55.6 months) 1 patient displayed local recurrence of the GTV, resulting in a LTC of 92.3% in the Kaplan-Meier analysis (Fig. 2). The treated lesion was a ML of gastric squamous cell carcinoma to the pancreatic corpus and was covered with a minimum tumor dose of 12 Gy at time of treatment. Additionally, this patient displayed needle track tumor seeding. Cumulative median PFS was 6.2 months and ranged from 2.8 to 25.7 months, for patients with primary and secondary malignancies PFS was 5.8 (2.9–6.7 months) and 6.2 months (range 2.8–25.7 months), respectively (Fig. 3). Within the follow up period 12/13 patients displayed a systemic progressive disease and out of these 12 patients 7 received specific tumor therapy in the timespan between iBT and systemic progression: in detail, palliative chemotherapy (5/7) and radioembolisation of the liver (2/7). The cumulative median OS was 16.2 months (range 3.3–55.7 months) for patients with primary and secondary malignancies OS was 7.4 (5.8–19.1 months) and 45.6 months (range 3.3–55.7 months), respectively (Fig. 4). At time of censoring 6 patients were still alive (5/8 secondary malignancies). Patient No.4 was

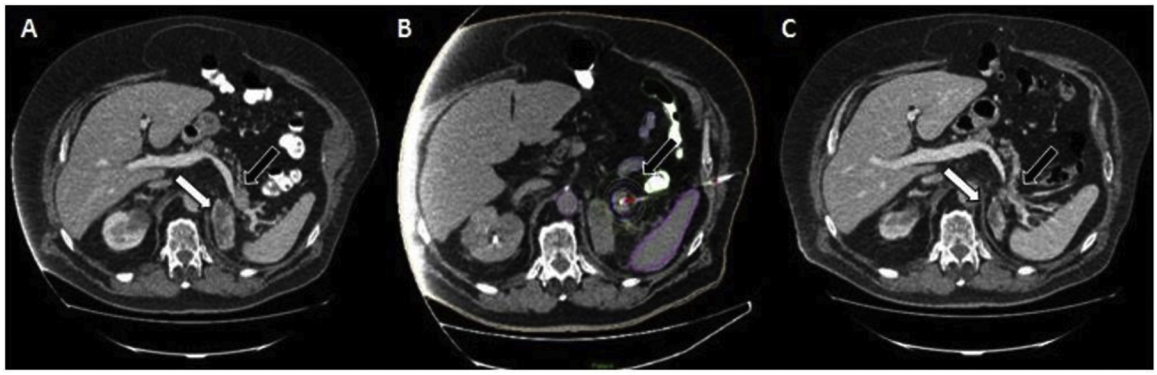

Fig. 1. (A): Pre-interventional contrast-enhanced CT slice showing a metastasis of NCC (black arrow) in the pancreatic tail. White arrow shows a metastasis of NCC of the left adrenal gland, previously treated with high dose rate brachytherapy (HDRBT). (B): Planning CT with indicated CTV (red line), catheter (marked in red) and isodose lines. (C): Follow up after 18 months: local control of treated lesion in the pancreatic tail (black arrow). Size reduction of the previously treated lesion in the left adrenal gland (white arrow).

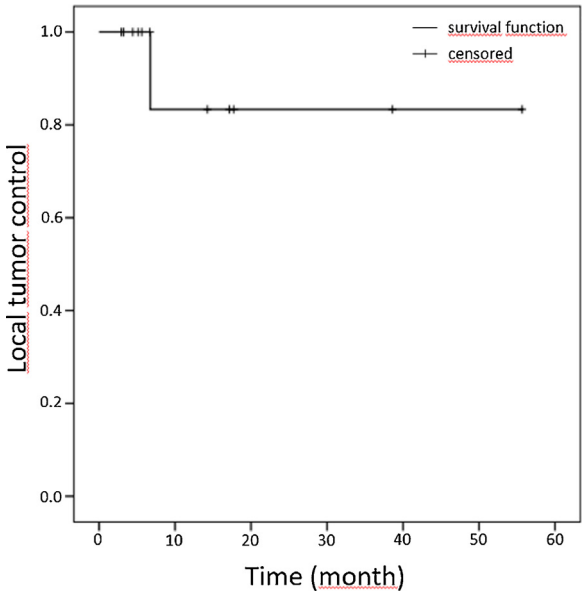

Fig. 2. Local tumor control after iBT of all treated pancreatic neoplasms.

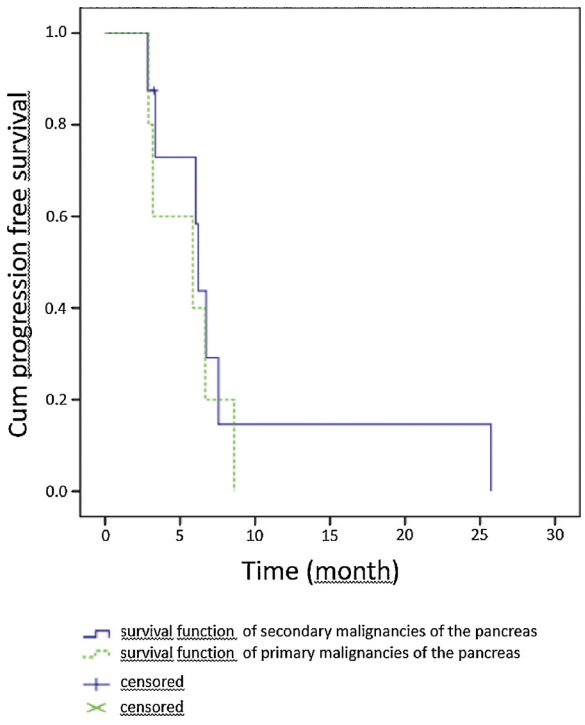

Fig. 3. Progression free survival of patients with primary (green line) and secondary malignancies (blue line) of the pancreas after iBT.

excluded from OS analysis due to lack of detailed information regarding the time point of death.

3.3. Safety and peri-and postinterventional complications

Median hospital stay was 4 days (range 4–11 days), whereby 1 patient underwent catheter positioning twice due to incorrect catheter placement in the first session. Patient No.6 was treated with iBT of the liver in the same hospital stay.

In 1 patient we observed increased level of systemic inflammation markers (C-reactive protein, leukocytosis) without fever or additional symptoms, administration of intravenous antibiotics (Ciproflaxacin and

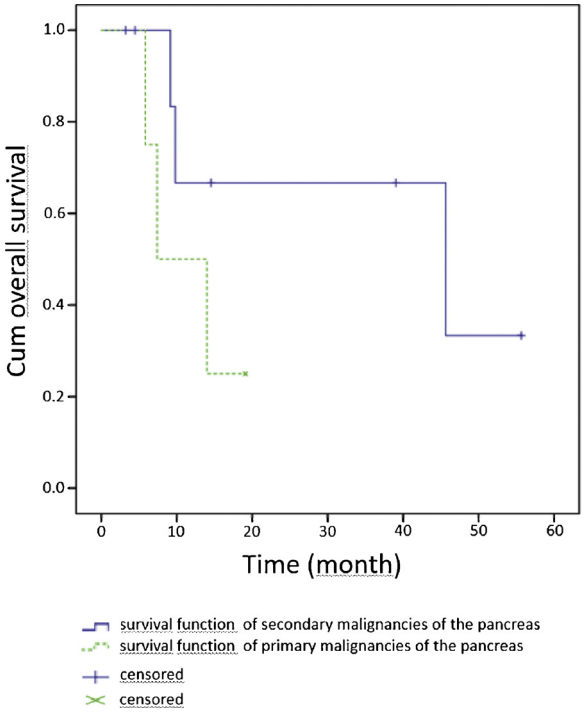

Fig. 4. Overall survival for patients with primary (green line) and secondary malignancies (blue line) of the pancreas after iBT. At the date of censoring 6 patients were still alive.

Metronidazole) led to rapid normalization. 1 patients reported unspecific nausea. With regard to the diagnosis of acute pancreatitis, 2 patients showed biochemical sign of a local injury of the pancreas, i.e. lipase elevated > 3times the upper limit of normal. Patient No.8 additionally experienced characteristic abdominal pain, an ultrasound and CT-scan did not show any sign of bleeding or early phase pancreatitis. The symptoms spontaneously resolved within the hospital stay (7days). However, this event was classified as mild acute pancreatitis, categorized as adverse event grade2. In patient No.9 we also observed critical enzyme elevation, but without any pain and therefore this patient did not received further radiologic examination. In conclusion, after iBT 12/13 patients did not show sufficient clinical features required for the diagnosis of acute pancreatitis on the base of the Revised Atlanta Classification. Furthermore, on the follow-up imaging no morphological features of acute pancreatitis, local complications (in terms of late toxicities) or following structural changes, including pancreatic strictures were observed.

4. Discussion

In selected patients with primary or secondary malignancies of the pancreas surgical resection remains the only possible cure or might achieve long-term survival, respectively [19]. In the literature pancreaticoduodenectomy is described to be associated with a substantial postoperative morbidity of 30–60% and in-hospital mortality rate of fewer than 5% [8,9]. However, Nimptsch et al. analyzed 58,003 inpatient episodes of pancreatic surgery between 2009 and 2013 in Germany and found a overall in-hospital mortality rate of 10.1%, including all surgical procedures of the pancreas; severe surgical complications occurred in 12.2–20.2% (i.e. peritonitis, sepsis, re-laparotomy, and > 6 blood transfusions) [20]. These findings suggest an underestimation of the mortality and morbidity rate due to publication bias, given the fact that low complication rates are mostly reported by single- and multiinstitutional studies of rather experienced hospitals with high caseloads.

However, only a minority of patients diagnosed with pancreatic

neoplasms are candidates for surgery, i.e. less than 20% of the patients diagnosed with PDAC are eligible for resection, likely a result of the tumor's invasiveness and propensity towards metastases [21]. Additionally, even after curative-intent surgery over 60% of patients will develop disease recurrence within 2 years resulting in a dismal prognosis [22], for instance after curative resection plus adjuvant chemotherapy median OS is reported to be 18.7–25 months for PDAC [23,24]. However, after complete pancreatic head resections for PDAC the surgical margin status has significant impact on further treatment an prognosis, with positive microscopic margin status (R1 resection) described to be as high as up to 76% [25]. This fact might explain that ILRs in the remnant pancreas or the locoregional structures are reported to occur in up to 30% after curative pancreatic surgery for PDAC [23,26].

Data is scarce for resection of secondary malignancies, however, Hung et al. found a 5-year survival rate of 61.1% after resection of 241 ML of the pancreas (73.9% renal cell carcinoma), suggesting that pancreatic resection should not be ruled out for ML [27].

In contrast, the presented study provides evidence that iBT achieves a high LTC rate of 92.3% in the ablation of primary and secondary pancreatic neoplasm. Within the median follow-up of 6.7 months 1 patient displayed local recurrence and needle track seeding after iBT of a ML of gastric squamous cell carcinoma, possibly caused by a relatively low administered D100 of 12 Gy regarding the pathologic subtype of the primary tumor.

However, in contrast to the reported surgery associated complication rates our findings demonstrate that iBT is a well-tolerated and safe procedure with no recorded severe adverse events (grade 3+). We report 1 case with mild acute pancreatitis post iBT that spontaneously resolved within 1 week (categorized as adverse event grade2). In the follow-up (including CT or MRI scans) no signs of acute pancreatitis (early or late phase), obstructive pancreatitis due to strictures or other late toxicities to adjacent organs were recorded.

About 30–40% of patients with PDAC are presented with borderline resectable or locally advanced unresectable disease and are -according to the current standard of care- treated with (neoadjuvant/palliative) chemotherapy depending on the patient's performance status [28]. Additionally, for this patient population subsequent local therapies, such as radiofrequency ablation (RFA), microwave ablation (MWA), irreversible electroporation (IRE) and cryoablation are available. These treatments are less evidence based and moreover seen in a palliative context with an emphasis on local tumor control and symptom relief. In general the techniques are delivered via laparotomy, again associated with surgical complications. Furthermore, to our knowledge no data regarding percutaneous ablation of secondary malignancies of the pancreas exists and even literature regarding percutaneous ablation of PDAC or NET is scarce.

RFA is a thermal ablative technique that uses heat generated from high frequency alternating current. The associated risk of thermal injuries to adjacent structures is relatively high, in surgical settings initially resulting in substantial morbidity (up to 40%) and mortality rates (up to 25%) due to massive gastrointestinal bleeding or duodenal injury, after technical adjustments the rates could be lowered to 24–28% and 1.8–3%, respectively [29–31]. To our knowledge, data regarding CT-guided RFA is only reported in cases studies. There are two studies concerning percutaneous, ultrasound-guided RFA, mainly focused on feasibility and safety: D'Onofrio et al treated 18 patients with PDAC with no described postprocedural complications, but efficacy regarding LTC was not assessed [32]; in the second study 7 patients with pancreatic NET were treated with a high complication rate of 3 grade3 adverse events [33]. IBT, in contrast, is independent of technical limitations concerning a potential cooling effect arising from large tumor masses (> 5 cm), resulting in a possible incomplete ablation, and even more importantly implies no potential thermal injury to adjacent OAR.

IRE is a non-thermal technique that uses short pulses of high voltage electrical current to create nanopores in the cell membrane causing apoptosis. In contrast to RFA IRE is thought to be able to destroy tumor tissue without the risk of thermal injuries to adjacent structures. Leen et al included 75 preteated patients with unresectable PDAC, median OS and PFS after CT-guided IRE was 27 and 15 months, respectively; local recurrence was reported to be 3% after 2–3 months [34]. Associated morbidity was 25%, mortality was nil. Although, one of the greatest technical restrictions of IRE is the need for general anesthesia with complete muscular paralysis, which provides additional risk and is a limiting factor for patient selection and procedural setting. IBT in contrast is performed under local anesthesia with analgosedation.

Data regarding percutaneous MWA and cryoablation is scarce and mainly concerning feasibility and safety in small case series [35–37].

Besides resection and percutaneous ablation of pancreatic neoplasms radiotherapy (including conventional radiotherapy and stereotactic bodyradiation = SBRT) provides another non-invasive approach. For patients treated with chemoradiation (gemcitabine plus radiotherapy: 1.8 Gy/fraction for a total of 50.4 Gy) for locally advanced PDAC early grade4 and 5 toxicities are described to occur in 41% and 9%, respectively [38]. SBRT has been studied with varying techniques and radiation doses applied, inducing morbidity rates up to 25% and especially late toxicities (grade2-4) up to 44% [39,40], i.e. adverse effects occurring at least 6 months post radiation of the pancreas, such as gastric/duodenal ulcer or perforation, gastrointestinal bleed, enteritis, colitis, intrapancreatic bile duct stricture. A phase-2-trail showed a LTC rate of 90% over a median follow-up of 13.5 months for 45 patients treated with SBRT for locally advanced PDAC (application of 45 Gy in 6 fractions); median PFS and OS was 8 and 13 months, respectively [41]. 49% of the population experienced grade1-2 toxicities, no grade 3+ events were reported, although, late toxicities occurred in 4% [41]. These results propose that SBRT permits precise irradiation, however, the varying rates for early and late toxicities suggest a significant exposure of normal surrounding tissue, resulting in gastrointestinal complications. Due to its percutaneous delivery iBT in contrast, allows the application of an effective, precise ablative dose in the CTV while saving adjacent OAR from potentially harmful exposure resulting in a low complication rate. Therefore iBT is not limited to the size or restrictions due to anatomic localization of the target. Moreover, in the presented study we did not report any early or late severe toxicities related to iBT.

From an oncological perspective our findings of a median PFS of 6.2 months (range 2.8–25.7 months) and an OS of 45.6 months (range 3.3–55.7 months) after iBT for patients with ML go in line with published outcome after resection. Hung et al, report a median OS of 20.0 months after resection of 241 ML, without the evaluation of LTC and PFS [27], and also Dar et al described a varying survival of 6–56 months for a case series of 5 patients [42]. Since, surgical risk is always one of the major concerns in consideration of any metastasectomy, iBT provides a particularly safe and effective alternative method.

For the patients presented with primary malignancies we found a median PFS of 5.8 months (2.9–6.7 months) and an OS of 7.4 months (5.8–19.1 months), however, our heterogeneous and rather small cohort is not comparable to the existing literature without restrictions, but for patients with locally advanced/unresectable or metastatic PDAC OS is reported to be similar with a median of 4–11 months under 1 st line chemotherapy [43,44]. Therefore, our findings might also suggest a potential additional survival benefit of selected patients treated with iBT, since the oncological impact of any local treatment is far from being answered.

Nevertheless, our study has several limitations: its retrospective nature and the low case number; moreover, the treated cohort was heterogeneous with respect to primary tumor, disease stage and previous treatment, resulting in a PFS and OS that is not beneficial from an oncological perspective. Therefore, a prospective trial with a higher caseload would be needed to investigate the effect of iBT with respect to the primary tumor and the previous treatment and also to possibly establish iBT in the toolbox of local ablative techniques for pancreatic

neoplasms located in the pancreatic body or tail.

However, despite these limitations our study demonstrates that iBT is a feasible alternative to resection of secondary malignancies and also provides a promising treatment for locally advanced/unresectable or recurrent primary malignancies of the pancreas. It offers treatment- and primary-tumor-independent effective LTC rates and accordingly, might offer a well-tolerated therapeutic option in the multidisciplinary management of selected patients.

In conclusion, for patients presented with primary or secondary malignancies of the pancreas located in the pancreatic body or tail iBT is a safe and particularly effective ablative technique that provides a promising alternative to surgery, SBRT and existing percutaneous ablation methods.

Conflicts of interest

The authors have no conflicts of interest to declare.

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