Strahlenther Onkol (2018) 194:185–195
https://doi.org/10.1007/s00066-017-1227-5

REVIEW ARTICLE

Essential role of radiation therapy for the treatment of pancreatic cancer

Novel study concepts and established treatment recommendations

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Received: 14 March 2017 / Accepted: 9 October 2017 / Published online: 1 November 2017

Abstract
Background Pancreatic cancer is one of the most aggressive human tumors and the incidence has increased over the last 6 years. In the majority of cases the disease is already in an advanced stage at the time of diagnosis where surgery, the only curative treatment, is no longer an option and explains the still abysmal overall survival. The role of radiation therapy as treatment option for patients with pancreatic cancer is controversially discussed although radiation oncology has emerged as a central pillar in the combined oncological treatment.
Purpose The present manuscript gives an overview of advanced radiotherapeutic strategies in the context of chemotherapy and surgery according to the current American Society of Clinical Oncology (ASCO) guidelines in comparison with the German guidelines and to elucidate the role of radiation therapy for the treatment of pancreatic cancer.
Conclusion Advanced modern radiotherapeutic techniques in combination with individualized high-precision radiation concepts are new therapeutic approaches for pancreatic cancer in a multimodal setting with tolerable side effects. Several clinical studies together with experimental approaches are in process, to deliver further evidence and ultimately allow true personalized medicine.

Keywords Intensity modulated radiotherapy · Disease-free survival · Stereotactic radiosurgery · Clinical studies · Interdisciplinary treatment

Essenzielle Rolle der Strahlentherapie in der Behandlung des Pankreaskarzinoms

Neuartige Studienmodelle und etablierte Therapieempfehlungen

Zusammenfassung
Hintergrund Das Pankreaskarzinom gehört zu den aggressivsten menschlichen Tumoren und verzeichnete in den letzten 6 Jahren eine steigende Inzidenz. Die Diagnose wird meist erst im fortgeschrittenen Stadium gestellt; dies schließt häufig eine primär kurative Intervention mithilfe der chirurgischen Resektion aus und bedingt die hohe Mortalität. Obwohl die Strahlentherapie im multimodalen Therapieansatz des Pankreaskarzinoms eine zentrale Säule darstellt, wird die Rolle der Strahlentherapie in der Literatur kontrovers diskutiert.
Zielsetzung Der vorliegende Beitrag bietet eine Übersicht moderner Bestrahlungsstrategien im interdisziplinären Konzept gemäß der Leitlinien der American Society of Clinical Oncology (ASCO) im Vergleich zu den deutschen Leitlinien für Patienten mit Pankreaskarzinom und verdeutlicht dabei die Rolle der Strahlentherapie.
Schlussfolgerung Innovative Bestrahlungstechniken in Kombination mit individualisierten Hochpräzisionsbestrah-

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lungskonzepten stellen neue Behandlungsansätze des Pankreaskarzinoms im multimodalen Therapieansatz mit einem tolerablen Nebenwirkungsprofil dar. Verschiedene klinische Studien und experimentelle Ansätze werden derzeit evaluiert, um weitere Evidenz zu schaffen und eine echte personalisierte Medizin zu ermöglichen.

Schlüsselwörter Intensitätsmodulierte Strahlentherapie · Krankheitsfreies Überleben · Stereotaktische Radiochirurgie · Klinische Studien · Interdisziplinäre Behandlung

Introduction

Pancreatic cancer is the fourth most common cause of death in the USA [1] with an increasing incidence by a factor of 1.23 in the last 6 years (2016 compared to 2010) [2, 3]. The overall 5-year survival rate among patients with pancreatic cancer is still poor with less than 10% [3] and has hardly improved in recent years. Complete surgical resection remains the only curative treatment option, but is initially only available for one third of the patients. Primarily inoperable refers to distant metastases or positive lymph node status beyond the technically possible operating area [4–7]. At the time of primary diagnosis, approximately one third of patients are in a distantly metastasized state and one third of the patients present without distant metastases but with local advanced pancreatic cancer (LAPC). The group of LAPC can be divided into a non-resectable group and borderline resectable pancreatic cancer (BRPC) that describes tumors, which are locally advanced but generally operable with, however, an increased probability for a R1 or R2 resection. Additional therapy is necessary in these cases as the R status has a high impact on progression-free survival (PFS) and overall survival (OS) [8]. Operability remains the most important goal of any additional therapy. In approximately one third of the patients primarily classified as BRPC or LAPC, resectability can be achieved with neoadjuvant therapy [9].

Chemotherapy as part of the treatment of resectable tumors and LAPC or in palliative care has been accepted for some time. Adjuvant chemotherapy improves the prognosis after surgical resection [10], facilitates resectability in some primarily inoperable cases [11] and increases OS in palliative situations [12].

The role of radiation therapy (RT) as a treatment option for patients with pancreatic cancer, however, has been controversially discussed in the literature over the last decades. Pancreatic tumors are known to be very heterogeneous [13] and in some cases, high rates of radioresistance, mainly due to tumor stem cells, have been described [14]. Nevertheless, combining RT and chemotherapy has been shown to improve the success of neoadjuvant/definitive treatment in terms of operability, R status [8], median and OS [15]. The use of RT is an efficient antitumorigenic treatment option with effective tumor downsizing to achieve a secondary resectability and therefore provides a positive long-term prognosis. The treatment of pancreatic cancer is still an unsolved health problem in industrialized countries and revised guidelines based on clinical trials and experimental research are crucial. The recently published revised American Society of Cancer Oncology (ASCO) guidelines for the treatment of pancreatic cancer were used as an opportunity to comment on this topic, even though they partially disagree with the German guidelines on pancreatic cancer.

Advanced radiotherapeutic techniques

Novel technological progress in radiation oncology was developed over the past few years and enabled an improved RT in comparison to conventional methods. In previous years, protecting radiosensitive organs in close proximity to the pancreas, such as the small bowels, stomach and kidneys, meant applying a maximum of 40–50 Gy to the tumor. Modern techniques, such as stereotactic body radiotherapy (SBRT) or intensity modulated radiotherapy (IMRT) are strategies to deliver high local doses with steep dose gradients towards surrounding tissue. In 2016 Prasad et al. presented an analysis comparing gastrointestinal toxicity in patients treated with IMRT or 3D-conformal planning [16]. They found lower side effects in the patients treated with IMRT despite significantly higher radiation doses.

Intensity modulated radiotherapy

Nowadays, IMRT is often combined with a simultaneous integrated boost (SIB). Local dose escalation is applied to certain tumor subregions as SIB during normal irradiation instead of a sequential procedure, leading to shortened treatment duration and the targeted delivery of RT to different tumor subvolumes in the context of dose painting. There is a high level of evidence that hypoxic areas of the tumor are more resistant to radiation [17]. Applying SIB to the hypoxic center of the tumor can safely deliver very high doses with an improved radiation response. Even if a benefit for patients due to an improved tumor control is unknown, there is no significant toxicity from its use [18]. Further evaluation needs to be done. In LAPC, tumor infiltrations of vessels or nerves limit the possibility of surgical resection. Using SIB as a technique of local targeting to these areas could improve the outcome and enable secondary surgical resection. Furthermore, modern radiation techniques, including particle therapy, are a major focus of research for treating high-risk areas that require locally escalated doses.

While these procedures are theoretically advantageous compared to conventional concepts, there is insufficient data to assure improved clinical outcome.

Stereotactic body radiotherapy

The SBRT technique is defined as a method of external beam radiotherapy (EBRT) that precisely delivers high doses of radiation to small tumor volumes excluding tumors located in the brain or spine. It is either applied as radiosurgery or as fractionated stereotactic RT within few fractions. Due to potentially high risks to organs at risk special concepts for dose constraints are necessary [19].

Depending on the location of the tumor, computed tomography (CT)-guided imaging, individual positioning aids and respiratory gating are essential for the accurate targeting of the tumor. The great advantages of SBRT, such as the option of dose escalation and less toxicity by relative sparing of organs at risk, make it interesting especially in cases of an oligometastatic state or in cases of relapse and previous RT. The general feasibility of this strategy has been shown by Crane and Willett [20]. In 2008, a single institution, prospective phase II study examined SBRT with gemcitabine (GEM) and resulted in comparable survival to conventional chemoradiation (CRT) and good local control: however, there was a significant rate of duodenal ulcer development due to RT [21]. Similar results have been shown in 2013: in a single institution retrospective trial 57 patients with BRPC and 16 patients with LAPC were evaluated after GEM-based induction chemotherapy for 3 months, followed by a fractionated SBRT in 5 consecutive daily fractions. Most BRPC patients had a significant radiographic response on restaging and a R0 resection was performed in 96.9% of the resected patients with BRPC [22].

In another retrospective trial, 5 patients with LAPC and 7 with BRPC received a neoadjuvant CRT. The majority were treated with GEM-based chemotherapy (90.9%) and either a single fraction dose of 24 Gy ($n = 5/12$) or a hypofractionated course of 36 Gy in 3 fractions ($n = 7/12$). The mean time to surgery was 3.3 months. Additional chemotherapy in the adjuvant setting was performed in some cases and 91.7% of the patients were margin-negative after tumor resection and the OS was 47.2 months [23].

Recently, a review summarizing the management of oligometastatic pancreatic cancer was published, focusing on para-aortic lymph nodes as well as isolated hepatic and pulmonary metastases. Using SBRT as an alternative treatment to surgery showed a good local control and extended survival [24]. In a single institution retrospective study, SBRT to oligometastatic lymph nodes in 18 patients with a gastrointestinal primary tumor was performed. No grade ≥3 toxicities were reported and SBRT provided an excellent local control with 1 and 2-year local controls of 94% and 47%, respectively [25].

Intraoperative radiotherapy

Intraoperative radiotherapy (IORT) means applying the boost before the extended field is irradiated. It therefore does not necessitate consideration of the wound healing process. For this procedure, an applicator is used under visual control after the surgical resection. The use of IORT creates the unique opportunity to protect uninvolved radiosensitive organs at risk, such as the small bowel by displacing the bowel from the irradiation field or covering it with lead shielding. In IORT increased effective radiation doses are delivered via electrons to gross residual tumor tissue or regions of suspicious surgical margins with a safety margin. In 2012 Jingu et al. presented 322 patients who had been treated with IORT and reached a local control of 71% after 2 years, even though only 17% received adjuvant EBRT and only 39% received adjuvant chemotherapy [26], a fact which might explain the early metastatic spread others described after similar treatment [27, 28].

Hypofractionated-accelerated radiotherapy

While in 2013 Chuong et al. [22] presented data concerning the general feasibility of single fractions of 5–10 Gy with a cumulative dose of 30 Gy after induction chemotherapy and good results concerning the achievement of resectability, hypofractionated-accelerated RT should remain part of clinical studies only.

Imaging and image-guided radiotherapy

Besides modern radiation techniques, improved imaging is an important component of high quality RT. Several strategies of precise imaging modalities for treatment planning, such as contrast-enhanced CT (CECT) complemented by positron emission tomography CT (PET-CT) or magnetic resonance imaging (MRI) help to identify the tumor volume with potential surrounding edema or potentially affected lymph nodes. Furthermore, 4-dimensional planning CT considers the effect of respiratory motion in each breathing phase to ensure full coverage of the planning target volume (PTV) at all times. Besides improved imaging, motion compensation techniques enable a reduction of the dose in organs at risk. In order to obtain an optimal dose distribution in the tumor with maximum sparing of surrounding tissue, vacuum stabilization systems, abdominal pressure devices, respiratory gating, tumor tracking or endoscopically implanted fiducial markers for an exact daily patient positioning are clinically well established. A daily image guidance radiotherapy (IGRT), e. g. with integrated CT, en-

ables an exactly reproducible fusion with the original treatment plan, increasing of accuracy of the delivery of high precision RT to the PTV, even leading to an improved treatment outcome in some clinical situations [29]. The introduction of MRI-guided linear accelerators (MRI linac) into clinical stages, with its highly detailed images of tumors and surrounding tissues, may further improve patient RT.

According to the guidelines for the treatment of pancreatic cancer of the American Society of Cancer Oncology (ASCO) in 2016, a multiphase CT scan or MRI of the abdomen and pelvis should be performed to evaluate the extent of the disease. Additionally, a standard chest x-ray to exclude pulmonary metastases and the serum level of the tumor marker CA 19-9 are recommended for staging. It is advisable to discuss the treatment of all patients with pancreatic cancer with leading specialists in tumor conferences. Multidisciplinary collaborations have great importance in the treatment progress and prognosis.

Overview of state of the art and current clinical studies

The guidelines for each stage of pancreatic cancer are described in detail.

Definitive chemoradiotherapy

According to the ASCO guidelines of 2016, after a phase of 3–6 months of induction chemotherapy patients with ongoing non-metastatic but non-resectable pancreatic cancer should undergo combined simultaneous CRT protocols for effective tumor downsizing with the main aim of achieving secondary resectability with better long-term prognosis or at least prolonged stable disease with increased local control for long-term non-resectable patients. A CRT can also be performed for those patients with local disease progression, unacceptable chemotherapy-related toxicities or reduced performance status due to chemotherapy. While the

Table 1 Studies on definitive concepts

Author	Study design	Number of patients	Median OS (months)	Median PFS (months)	Stable disease (%)	OS (%)	Mean dose (Gy) in number of fractions
Li et. al (2003) [31]	GEM CCRT	18	14.5	7.4	50	–	54.2 in 30
	5-FU CCRT	16	6.7	2.7	13	–	54.3 in 30
Schellenberg et al. (2007) [21]	GEM + SBRT	16	11.4	9.0	81	–	25 in 1
Loehrer et al. (2010) [32]	Arm A: GEM	35	9.2	6.7	35	–	–
	Arm B: GEM + RT	34	11.1	6.0	68	–	45.9 in 25
Rwigema et al. (2010) [40]	SBRT	71	10.3	–	64.8	–	24 in 1
Huguet et al. (2006) [33]	Arm A: Ind.-GEM + oxaliplatin /CRT with 5FU	72	15	–	–	65.3 (1 year)	–
	Arm B: Ind.-GEM + 5FU + Leukovorin	56	11.7	–	–	47.5 (1 year)	–
Chauffert et al. (2007) [39]	Arm A: CRT with 5FU/ Cisplatin /adj. GEM	59	8.9	–	–	32 (1 year)	60 in 30
	Arm B: GEM/ adj. GEM	60	13	–	–	53 (1 year)	
Huguet et al. (2013) [34]	Arm A: Ind.-GEM ± Erlotinib /CRT with Capecitabine	133	11	–	–	–	54 in 30
	Arm B: GEM ±- Erlotinib	136	9.2	–	–	–	

GEM gemcitabine, *CCRT* concurrent chemoradiotherapy, *CRT* chemoradiotherapy, *PFS* progression-free survival, *OS* overall survival, *RT* radiotherapy, *SBRT* stereotactic body radiotherapy, *FU* fluorouracil

German guidelines are much more reserved in the strength of the recommendations and recommend participation in clinical trials, sequential application of chemotherapy and CRT also marks the central treatment strategies of LAPC [30].

In 2003 Li et al. compared the efficacy and tolerability of GEM-based CRT with 5-fluorouracil (5-FU)-based CRT for LAPC. The GEM-based CRT appeared to be more effective than 5-FU-based CRT. Both treatment arms had a tolerable and comparable profile of adverse events; however, GEM-based CRT provided significant improvement in pain control, performance status, and quality-adjusted life months of survival in comparison with 5-FU concurrent chemoradiotherapy (CCRT) [31]. Similar results were shown in 2011, when Loehrer et al. showed the superiority of CRT with GEM in comparison to chemotherapy with GEM alone in terms of median survival (11.1 months versus 9.2 months; $p = 0.017$). The toxicity for the first type of therapy, however, was also increased [32].

The prognostic superiority of combined therapy had already been described in 2007 in a retrospective analysis, where Huguet et al. found an improvement in median survival of 3.3 months in the CRT arm compared to chemotherapy only [33]. While they could not strengthen this difference in survival in a phase III study (16.2 months versus 15.2 months), the rates of local failure were much lower in the CRT arm compared to the chemotherapy arm (32% versus 46%, $p = 0.03$) and the time free of therapy was notably increased (159 days versus 96 days; $p = 0.05$) [34, 35].

In the multicenter, open-label, randomized SCALOP trial, improved quality of life of patients with LAPC after induction chemotherapy followed by capecitabine or GEM-based CRT has been shown. While the differences in OS, median survival and median PFS did not significantly differ, the results suggest a superiority of capecitabine compared to GEM [36]. In contrast, Brunner found superiority of the more toxic GEM over capecitabine-based CRT [37].

These data are summarized in Table 1 but do not remain unchallenged. While some found tentative but promising data in favor of CRT [38], others actually found an advantage for chemotherapy alone. The latter results, however, can mostly be explained by outdated doses of RT or sequential CRT [39].

Neoadjuvant chemoradiotherapy

The aim of neoadjuvant therapy is to increase the chance for operability, to improve the rates of margin-negative resectability and to realize effective tumor downstaging. Some key studies comparing different neoadjuvant therapeutic approaches are discussed in the following and summarized in Table 2.

At the ASCO meeting in Illinois in 2016 Idrees et al. [41] presented the data on their therapy scheme for LAPC or BRPC: induction chemotherapy with the FOLFIRINOX regimen or nab-paclitaxel + gemcitabine followed by CRT in 71% of the cases. In 84% of the cases, operability was achieved and 86% of the resected patients had an R0 resection. They also showed that an adjuvant chemotherapy administered in 44% of the cases further improved OS. Patients who showed complete pathological response had a median survival of 53 months, whereas it was only 25 months for those without or with only partial response.

For BRPC, neoadjuvant therapy is of great importance. The biggest trial so far was published by colleagues from the University of Texas MD Anderson Cancer Center in 2008 [42]. In the case of CRT, 30 Gy cumulative dose with single fractions of 3 Gy or 50.4 Gy cumulative dose with a single fraction of 1.8 Gy were used in combination with 5-FU, capecitabine, paclitaxel or GEM. In 50% of the whole collective of patients, resection could take place and was R0 in 94% of the cases. In 2014 Oh et al. presented similar data with achieved resectability in 53% of the patients [43]. In the case of LAPC, in more than 90% of the cases CRT is the therapy of choice with a cumulative dose of 50.4 Gy in single fractions of 1.8 Gy in combination with either GEM or 5-FU. In 3–5% of the cases complete remission is possible [44]. It was even shown that tumor response and secondary resectability after combined CRT lead to OS rates similar to patients with initially resectable tumors [45]. Furthermore, even patients with tumor recurrence after initial curative resection can be effectively and safely treated with CRT protocols and subsequently undergo a further resection [46, 47]. Nevertheless, most data are gained from retrospective analyses and one-armed trials.

The safety of neoadjuvant CRT for primarily resectable tumors with respect to toxicity and perioperative morbidity as well as mortality, has been shown in a randomized trial in comparison with resection only [48]. In 2015 Golcher et al. published a randomized trial of 66 patients where neoadjuvant CRT could not significantly improve median OS or R0 resection rate compared to primary resection [48]. In the same year Casadei et al. [49] published similar results of a randomized group of 38 patients. Both trials, however, were too small to find differences in OS of a few months only.

Chemoradiation versus chemotherapy: an ongoing randomized phase III study

As of yet, there is no randomized study answering the question whether the polychemotherapy FOLFIRINOX regimen alone is sufficient to treat primarily unresectable pancreas carcinoma and is possibly even sufficient to surpass the

Table 2 Studies on neoadjuvant chemoradiation

Author (year)	Study design	Number of patients	Resection rate (%)	R0 resection rate (%)	Median OS (months)	Median PFS (months)	Overall survival (%)	Total dose (Gy) in number of fractions
Unresectable, borderline resectable (BRPC) or locally advanced pancreatic cancer (LAPC)								
Habermehl et al. (2011) [47]	CRT resected	51	–	39.2	22.1	10.8	–	52.2 in 29
	CRT Non-resected	147	–	–	11.9	5.9	–	52.2 in 29
Chuong et al. (2013) [22]	CRT	57 BRPC	–	96.9	16.4	9.8	–	25 in 5 (tumor) 35 in 5 (SIB)
		16 LAPC	–	–	15	9.7	–	–
Rajagopalan et al. (2012) [23]	CRT	7 BRPC 5 LAPC	–	91.7	47.2	27.4	–	24 in 1 or 36 in 3
Aristu et al. (2002) [50]	CRT with 5FU + cisplatin ± paclitaxel or with GEM + cisplatin	47 (primary unresectable)	19	44	All: 10 Resected: 23	–	All: 0 (3 years) Resected: 48 (3 years)	45 in 25 unresectable: + IORT or EBRT boost with 10–20 Gy
Evans et al. (2007) [51]	CRT with GEM	86	74	88	All: 22.7 Resected: 34	15.4	All: 27 (5 years) Resected: 36 (5 years)	30 in 10
Varadhachary et al. (2008) [52]	Ind.-GEM+cisplatin /CRT with GEM	90 (62 BRPC, 28 LAPC)	58	98	All: 17.4 Resected: 31	–	50 (2 years)	30 in 10
Idrees et al. (2015) [41]	–	86 (58 BRPC, 27 LAPC)	84	86	27.4	–	–	–
Resectable pancreatic cancer (RPC)								
Golcher et al. (2014) [48]	Resection with Gem+Cisplatin	33 (33 RPC)	100	48	14.4 Resected: 18.9	–	–	–
	CRT/ resection	33 (33 RPC)	88	52	17.4 Resected: 25.9	–	–	55.8 in 31 (45.0–57.6 in 25–32)
Casadei et al. (2015) [49]	Resection	20	75	25	19.5	–	–	–
	Ind.-GEM/ CRT with GEM/ resection	18	61	40	22.4	–	–	45 in 25 54 in 30 (tumor)

BRPC boderline resectable pancreatic cancer, *CRT* chemoradiotherapy, *EBRT* external beam radiotherapy, *FU* fluorouracil, *GEM* gemcitabine, *IORT* intraoperative radiotherapy, *LAPC* locally advanced pancreatic cancer, *PFS* progression-free survival, *OS* overall survival, *RPC* resectable pancreatic cancer, *RT* radiotherapy, *SBRT* stereotactic body radiotherapy, *SIB* simultaneous integrated boost

amount of R0 resections of BRPC or whether RT should be an essential part in the treatment.

The Chemoradiation Compared with Chemotherapy Alone After Induction Chemotherapy (CONKO 007) randomized trial examines the effectiveness of CRT compared to chemotherapy alone after 12 weeks of induction chemotherapy with 3 cycles of GEM or 6 cycles of FOLFIRINOX in patients with histologically proven locally advanced, non resectable and non-metastatic pancreatic cancer. After exclusion of patients with secondary metastatic spread the patients are then randomized to either continue chemotherapy with the same substance for 3 (GEM) or 6 cycles (FOLFIRINOX) or CRT is performed using GEM administered on days 1, 8, 15, 22 and 29 of RT

and on days 57, 64 and 71. After 3D treatment planning, RT is delivered up to doses of 50.4 Gy with single fractions of 1.8 Gy to regional lymph nodes and planning target volume. Operability of the tumor is evaluated at week 11 after randomization. The primary endpoint is defined as OS at the end of follow-up after 5 years. Secondary endpoints are tumor-free survival, rate of local recurrence or local progression, rate of distant metastasis, acute and late toxicity of the CRT, quality of life, rate of remission, rate of curative resections (R0) after chemotherapy and CRT.

Intraoperative RT (IORT)

The IORT is a promising strategy in cases of recurring or residual tumors. In several publications based on retrospective analyses, it was shown that surgery in combination with IORT can result in an improved local control and OS without an increase of postoperative morbidity or mortality compared to surgery alone. Different dose levels (15 Gy, 20 Gy or 25 Gy) were applied as IORT and did not show any difference in the endpoints. In 49 patients with locally limited disease, IORT significantly prolonged the time to local failure from a median of 12 to 17.5+ months and the OS (13 vs. 18.5+ months) with respect to surgery alone [28]. Roeder et al. observed a local control of 83% using IORT as a boosting strategy in combination with maximum surgery and moderate doses of EBRT. A prolonged survival was shown in resectable pancreatic cancer patients who remained free of local recurrence for more than 2 years after surgery and IORT (5-year OS 28%) compared to those who failed locally (5-year OS 0%) [53]. At this point in time, however, IORT remains experimental and is recommended only in selected cases according to ASCO 2016 [54].

Adjuvant chemoradiotherapy

While OS seems to be independent of the resection status [55, 56], R1 status after resection has been proven to be a negative prognostic marker [8]. This affects a high number of patients after surgery as there are high rates of positive margins in the resected pancreatic tissue due to the tumor growth of pancreatic cancer close to challenging locations, e.g. vessels and neural structures [10]. One unsolved problem, however, remains the different classifications concerning the label R1 resection. A more and more often accepted definition was proposed by Wittekind et al. in 2009 [57], where circumferential resection margin (CRM) adapted from rectal cancer was introduced into the classification pancreatic resections, with positive CRM (=R1) meaning tumor cells within 1 mm of the resection margin.

Due to results from the much discussed ESPAC-1 trial [55] with worse median survival after adjuvant CRT compared to adjuvant chemotherapy, data supported by the meta-analysis by Liao et al. [58] or equal results in the ESPAC-4 trial, adjuvant CRT is not commonly performed [54]. In the USA, however, CRT is an important part of adjuvant therapy. The recommendation based on data provided in the GITSG trial [59] and the EORTC study [60], is further strengthened by data provided by Hall et al. who examined effects of adjuvant therapy on OS [61].

In accordance with results shown by Khorana et al. [62], ASCO guidelines 2016 recommend an adjuvant CRT for patients who did not receive preoperative therapy and present microscopically positive margins (R1) after resection and/or who had node-positive disease after completion of 4–6 months of systemic adjuvant chemotherapy. The German guidelines, however, recommend 6 months of adjuvant chemotherapy, independent of the resection status. Adjuvant CRT is advised not to be performed outside clinical trials.

Palliative care

According to the ASCO guidelines the two frontline regimens for patients with metastatic pancreatic cancer are FOLFIRINOX and GEM plus nanoparticle albumin-bound (NAB) -paclitaxel. Palliative RT or chemotherapy, which were not further specified, may be considered to augment pain management [63]. According to the German guidelines, a palliative chemotherapy with GEM should be performed in patients with locally advanced or metastasized pancreatic cancer depending on the Eastern Cooperative Oncology Group (ECOG) performance status. A palliative RT is recommended in patients with symptomatic metastasis (in particular bone or brain metastases) for symptom control or prevention of complications.

Summary of the ASCO and German guidelines

Table 3 presents a comparative overview of the ASCO and German guidelines for the interdisciplinary management of resectable, locally advanced, and metastatic disease.

State of the art and outlook of recent experimental progress

In an age of interdisciplinary tumor conferences and the knowledge of identified prognostic subgroups of patients with pancreatic cancer, the need of individualized therapy regimens in the context of personalized therapy is clear. In addition to clinical trials, experimental stratification of innovative concepts focusing on individualized RT play an essential role. In the past, the preclinical evaluation was

Table 3 Comparison of the recommendation of the ASCO and German guidelines

	ASCO guidelines 2016	German guidelines 2013
Potentially curable pancreatic cancer	Primary surgical resection of the primary tumor and regional lymph nodes	Primary surgical resection of the primary tumor and regional lymph nodes
	Neoadjuvant CT or CRT within trials	Neoadjuvant CT or CRT only within randomized controlled trials
Locally advanced, unresectable pancreatic cancer	Initial systemic therapy, CRT or SBRT	Neoadjuvant CT or CRT
Metastatic pancreatic cancer	Palliative CT with FOLFIRINOX or gemcitabine plus nanoparticle albumin-bound (NAB) -paclitaxel	Palliative CT with gemcitabine
	RT for pain management	RT of symptomatic metastases for symptom control or prevention of complications
Adjuvant therapy	R0 resection: adjuvant CT with gemcitabine or FU plus folinic acid	R0 resection: adjuvant CT with gemcitabine or FU/folinic acid for 6 months
	R1 resection, no preoperative therapy: CRT	R1 resection: additive CT for 6 months
	N + after adjuvant chemotherapy for 4–6 months: CRT	R0/R1 resection: CRT only within randomized controlled trials

CT chemotherapy, *CRT* chemoradiotherapy

limited to in vitro experiments, because targeted application of RT was not practical with conventional irradiation units.

Munich is one of the few locations worldwide with the possibility of performing high-precision RT in animal-based tumor models with the Small Animal Radiation Research Platform (SARRP, Xstrahl, Camberley, UK). The SARRP offers an exclusive technology with its unique image guidance RT set-up and simulates the clinical situation in oncology departments around the world for the first time [64]. The research group intends to identify targeted treatments within the context of radiation therapy using preclinical pancreatic cancer models and aims to translate them into novel radiation therapy regimens for clinical application.

Important key preclinical experiments within in vivo translational approaches were performed by Thorek et al. [65] who used an intraperitoneal administration of radiopaque iodinated contrast agent to detect orthotopic pancreatic cancer models and abdominal organs by X-ray CT. Doses of 12 Gy, 15 Gy and 18 Gy were applied in a 360° arc technique via a small animal micro-irradiator. Precise X-ray radiation therapy of defined orthotopic tumors was confirmed using γH2AX staining. The results allow evaluation of tumor progression and therapeutic response in preclinical models for the first time.

Apart from developing better and more sparing techniques, understanding mechanisms and results on a cellular level and beyond becomes more and more important. In the CONCO 007 study, the translational program aims to understand the collaboration of tumor therapy and immune system, including immune phenotyping techniques.

Conclusion

Due to the necessity for multidisciplinary therapy of pancreatic cancer in all stages, the treatment should be evaluated by multidisciplinary consensus at tumor boards depending on tumor stage, performance status and secondary diagnoses to guarantee a therapy at the highest scientific standards for every patient. Performing a neoadjuvant RT should at least be considered for the treatment of patients with potentially curable or locally advanced, unresectable pancreatic cancer outside clinical trials. A palliative RT to achieve symptom control and prevention of complications should be evaluated for all patients with metastatic pancreatic cancer.

A truly personalized medicine can be perfectly realized by individualized high-precision RT regimens combined with additional treatment options in all different tumor stages of pancreatic cancer, giving rise to hope for long-term-survival for patients who would have been counted as palliative patients, despite only having advanced local tumor without systemic metastatic spread. While several clinical trials, often retrospective analyses, proved RT to be effective and well-tolerated, even in combination with concurrent chemotherapy, prospective randomized trials are sparse. This aspect leads to discrepancies on the international level. This can easily be seen when comparing the German guidelines 2013 and those published by ASCO in 2016. While for ASCO, CRT is recommended as a tool usable in several situations before and after surgery, the German guidelines recommend CRT to be performed mainly in clinical trials; however, the German guidelines are not as restrictive in the definitive situation. It is our job as radiation oncologists to refine those treatment strategies for pancreatic cancer for our local patients and to present the positive

results. The main benefit of advanced RT is a good local control and tumor downsizing thus often allowing indispensable secondary surgical resectability even for patients primarily unresectable due to LAPC or high probability of R1 resection. An even more efficient antitumorigenic and less toxic effect is expected from improved modern radiation techniques and individualized concepts, such as SBRT or SIB or optimized concepts of CRT. Further clinical and experimental evaluations are still desirable. It is highly recommended to include patients in clinical trials in a multidisciplinary team. The results of the ongoing randomized phase III study CONKO-007 will be available soon where a combined neoadjuvant chemotherapy and CRT are compared to chemotherapy alone.

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