Radiotherapy in Pancreatic Cancer

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Purpose and Approach: To summarize the current knowledge on the role of radiotherapy in the treatment of pancreatic ductal adenocarcinoma (PDAC). The results of meta-analyses, phase III-studies, and phase II-studies using chemoradiation (CRT) and chemotherapy for resectable and non-resectable PDAC are reviewed.
Results and Conclusion: The role of CRT is undefined in the adjuvant setting but there may be a role as additive treatment after R1 resection. Locally advanced borderline resectable tumors may shrink down and be subject to potentially curative resections. In locally advanced clearly unresectable cancers the effect of CRT as well as chemotherapy is poorly defined and the sequence of chemotherapy and CRT should be re-evaluated. Patients with PDAC should always be treated within studies to identify optimal treatment results.

Key Words: Pancreatic cancer · Chemoradiation · Locally advanced · Adjuvant · Neoadjuvant

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Die Rolle der Strahlentherapie bei der Behandlung des Pankreaskarzinoms

Ziel und Vorgehen: Zusammenfassung des derzeitigen Wissens über die Rolle der Radiotherapie für die Behandlung des duktalen Adenokarzinoms des Pankreas (PDAC). Die Ergebnisse von Metaanalysen, Phase-III- und Phase-II-Studien mit Radiochemotherapie und Chemotherapie werden für Patienten mit resektablem und irresektablem PDAC dargestellt.
Ergebnisse und Schlussfolgerung: Im adjuvanten Ansatz ist die Rolle der Radiochemotherapie nicht definiert, jedoch ist eine Rolle als additive Therapie in der R1-Situation möglich. Lokal fortgeschrittene, borderline-resektable Tumoren können verkleinert werden und dann potentiell kurativen Resektionen zugänglich gemacht werden. Für lokal fortgeschrittene, eindeutig irresektable Tumoren ist der Effekt der Radiochemotherapie wie der Chemotherapie schlecht definiert and die Abfolge von Radiochemotherapie und Chemotherapie sollte neu untersucht werden. Patienten mit PDAC sollten immer im Rahmen von Studien behandelt werden, um optimale Behandlungsergebnisse zu identifizieren.

Schlüsselwörter: Pankreaskarzinom · Radiochemotherapie · Lokal fortgeschritten · Adjuvant · Neoadjuvant

Introduction

Despite of considerable progress in oncology [48, 49] the bad prognosis of patients with ductal pancreatic adenocarcinoma (PDAC) could not be improved significantly. PDAC still ranks fourth of cancer associated lethality both in Europe and in USA [27]. More than 80% of the patients with PDAC cannot be resected at diagnosis. Half of these have no distant metastasis (locally advanced pancreatic carcinoma, LAPC), the other half have distant metastasis. This article reviews the currently available data on the use of radiotherapy for PDAC and highlights the open questions.

Adjuvant Chemoradiation

Performance status and cachexia have a significant negative influence on the outcome of (neo)adjuvant studies with a difference of resection rates of almost 20% [3] but these factors are largely neglected in trial reports. Adjuvant (after R0-resection) or additive chemoradiation after R1- or doubtful complete resection (Table 1) aims to prolong survival by improved local tumor control. A large non-randomised single centre phase II-study including 173 patients from the Johns Hopkins Hospital [64] resulted in prolonged survival compared to observation after R0-resections, pN1-status and a maximal size of the primary tumors of ≥ 3 cm and adjuvant chemoradiation. Resectional status (R0, R1 or R2), N-status (N0 or N1) and size of the primary tumor therefore appear to be reasonable parameters for stratification in future trials.

The results of the phase III RTOG study 97-04 have recently been published [45]. This study tested if the effect of an adjuvant 5-Fluorouracil (5-FU) based chemoradiation (50.4

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Gy; 250 mg 5-FU/m²/day continuous infusion) could be enhanced by adding gemcitabine (G-arm). After resection, gemcitabine was given at 1 g/m² for 3 weeks, followed by CRT and then by another 3 months of treatment with gemcitabine at the same dose (d1, 8, 15, q28d). The analysis comprised 442 patients. The overall survival of patients with tumors of the pancreatic head was significantly longer in the G-arm compared to the control arm with 5-FU chemotherapy (20.6 vs. 16.9 months at the median, 32% vs. 21% after 3 years; p = 0.033). At multivariate analysis three parameters reached statistical significance: the treatment arm (p = 0.025), the nodal status (p = 0.003) and the maximal tumor diameter (p = 0.03). The non-haematological toxicity (> Grad 3) did not differ between both arms. Grade 4 haematotoxicity was 14% in the G-arm and 2% in the 5-FU arm, without difference in the rate of febrile neutropenia.

In the United States, chemoradiation with concurrent 5-FU followed by gemcitabine continues to represent the standard for adjuvant therapy of tumor of the pancreatic head. The short 14.2 months overall survival time of the chemoradiation arm of the phase III ESPAC-1 (adjuvant chemoradiation followed by chemotherapy) trial should be compared with these results of the RTOG trial 97-04 [1]. In ESPAC-1, adjuvant chemotherapy resulted in a better median overall survival time of 21.6 months (19.7 months in the entire group) which is very similar to the data of RTOG 97-04 that had a more unfavourable distribution of the risk factors resection status, pN-category and largest tumor diameter. The ESPAC-1 trial was inappropriate to test the value of chemoradiation because of the use of a split-course technique [5], of an underdosed radiotherapy (40 Gy) [45], of a lack of radiotherapy quality control, of a poor protocol compliance and of the use of the outdated bolus 5-FU/leukovorin regimen [46]. Furthermore, the higher mortality of patients in the CRT group with a peak after 2 years as compared to the control group suggests increased renal toxicity caused by improper renal sparing [19]. Last but not least the way of reporting the survival results was confusing: chemoradiation (± chemotherapy) was compared with an aggregate of chemotherapy and observation. Similarly, the aggregate of chemotherapy (± chemoradiation) was compared with the aggregate of chemoradiation and observation, i.e. the so-called 'chemotherapy' results are a mix of chemotherapy and chemoradiation plus chemotherapy treatment.

To date, there are two meta-analyses addressing adjuvant chemoradiation in pancreatic carcinoma which result in discrepant conclusions. A recent meta-analysis by Khanna et al. [32] investigated the effect of an adjuvant chemoradiation compared with surgery only. Five prospective studies with a total of 607 patients (229 resected vs. 378 resected plus chemoradiation) were included. The 2-year overall survival rates reached 15–37% after resection only and 37–43% after resec-

Table 1. Phase III-studies for adjuvant therapy. Median overall survival rates from five randomized studies in patients with resected pancreatic carcinoma. None of these studies employed postoperative imaging to exclude tumor persistence or distant metastasis. 5-FU: 5-Fluorouracil; Cx: chemotherapy; CRT: chemoradiation; Gem: gemcitabine; n. a.: not available. [a]: The EORTC study included 218 patients with periampullary and pancreatic carcinoma. The figures in the table are based upon the 114 patients with pancreatic carcinoma. [b]: The ESPAC-1 study included 541 patients, but only 289 were included into the 2 × 2 factorial randomization. Arms: observation, chemotherapy, chemoradiation, chemoradiation followed by chemotherapy. The survival rates are given for the best treatment arm (chemotherapy) and observation. [c]: The RTOG 9704-study included a total of 442 patients, 380 of them had pancreatic head tumors.

Tabelle 1. Phase-III-Studien zur adjuvanten Therapie. Mediane Überlebensraten aus fünf randomisierten Studien bei Patienten mit reseziertem Pankreaskarzinom. Keine dieser Studien setzte postoperative Bildgebung ein, um die Abwesenheit einer Tumorpersistenz oder einer Fernmetastasierung auszuschließen. 5-FU: 5-Fluorouracil; Cx: Chemotherapie; CRT: Radiochemotherapie; Gem: Gemcitabin; n. a.: nicht angebbar. [a]: Die EORTC -Studie umfasste 218 Patienten mit periampullären und Pankreaskarzinomen. Die hier gezeigten Ergebnisse basieren auf den 114 Patienten mit Pankreaskarzinomen. [b]: In die ESPAC-1-Studie wurden 541 Patienten eingeschlossen, aber nur 289 wurden in die 2 × 2 faktorielle Randomisierung eingeschlossen. Arme: Beobachtung, Chemotherapie, Radiochemotherapie, Radiochemotherapie gefolgt von Chemotherapie. Die Überlebensraten für den besten Behandlungsarm (Chemotherapie) und Beobachtung sind gezeigt. [c]: The RTOG-9704-Studie umfasste insgesamt 442 Patienten, 380 hatten ein Pankreaskopfkarzinom.

Study/Year [Reference]	Patients (n)	Inclusion criteria R-Status	(Months)	Control arm (months)	p-value	Preoperative imaging	Postoperative imaging	Inked resection margin
GITSG-1985 [31]	49	R0	CRT 21.0 5-FU based	10.9	0.005	no	no	no
EORTC-1999 [34]	114[a]	R0	CRT 17.1 5-FU based	12.6	0.099	no	no	no
ESPAC-1-2004 [40, 41]	289[b]	R0 or R1	Cx 21.6 5-FU based	16.9	n. a.	no	no	no
CONKO-1-2007 [42]	368	R0 or R1	Cx 22.1 Gem	20.2	0.06	yes	no	n.a.
RTOG 9704 [45]	442/380[c]	R0 or R1	CRT+Cx 20.6 CRT+Gem	16.9 CRT + 5-FU	0.033	yes	n.a.	n.a.

tion and adjuvant chemoradiation. The percent gain in survival by adjuvant chemoradiation was 3%–27% in the absence of a statistically significant prolongation of survival in any of the respective studies on their own. In total, an absolute gain in survival of 12% was calculated after 2 years (95% CI, 3%–21%, p = 0.011). However, the relative prolongation of survival decreased with more recent studies over time and did not reach statistical significance in the latest trials. A meta-analysis from Stocken et al. [54] analysed adjuvant chemoradiation and adjuvant chemotherapy. The group concluded that adjuvant-additive chemoradiation is more effective than chemotherapy after R1-resections only. After R0-resections only adjuvant chemotherapy prolonged survival but not adjuvant chemoradiation. The significance of this meta-analysis is somewhat limited because most of the included patients are from only one phase III trial. Furthermore, no standardised definition of R1-resections was used in the included studies.

In summary, the value of adjuvant therapy currently is a matter of many discussions and controversies and was tested in five reports of randomised phase III-studies on chemotherapy and CRT [31, 34, 40–42, 45]. Four of the fully published studies which comprise radiotherapy [31, 34, 40, 41] have substantial shortcomings as to the design and the realisation of radiotherapy as discussed in detail elsewhere [20]. Therefore, the efficacy of adjuvant CRT according to current quality standards is unidentified. This unsatisfactory situation on the significance of adjuvant CRT can be summarized in the following way:

- The European and the US-American trials are based upon different treatment paradigms. Whilst in northern America CRT is regarded to be standard based upon the GITSG-data [31], in Europe adjuvant chemotherapy is preferentially performed.
- To define the role of adjuvant CRT, a large randomised study exploiting the full options of the respective therapeutic modules needs to be planned carefully and interdisciplinarily. Such a study should be accompanied by broad therapeutic monitoring.

Summary

After R0-resection, patients should receive adjuvant chemotherapy in the face of the overall relatively weak data on adjuvant CRT. In principle however, 5-FU-based CRT followed by gemcitabine chemotherapy appears to be a reasonable treatment option, especially in patients with tumors of the pancreatic head, pN1-status and a maximal tumor diameter of > 3 cm. Additive CRT can be recommended after R1-resection. The recently published German S3-guideline is more restrictive in this respect [2]. Due to a general paucity of data on this subgroup these patients should be treated within studies preferentially.

Neoadjuvant Therapy

The superiority of neoadjuvant treatment over adjuvant treatment has been proven recently in resectable rectal carcinoma with a high risk for local relapse (phase III study of the German Rectal Cancer Group): neoadjuvant treatment allowed a higher rate of sphincter preserving operations with lower toxicity and a lower rate of local recurrences [51]. In pancreatic carcinoma the situation may be similar (Table 2). Raut and co-workers concluded an increase in the rate of R0-resections, a reduction of the rate of local relapses as well of the rate of distant metastasis in comparison to immediate surgery in their review [44]. In another retrospective evaluation, neoadjuvant CRT was better tolerated allowing to treat a larger number of patients compared to adjuvant therapy [57]. Accordingly, 20% of the patients who were operated at diagnosis were found to be irresectable intraoperatively. Another 25–50% of the patients did not get adjuvant treatment because of postoperative toxicity or because of refusal of adjuvant therapy. In total, only 40–60% of the patients with primary resectable carcinoma indeed have received full adjuvant treatment. This compared with 60–65% of the patients with the neoadjuvant approach: 20–25% of the patients had rapid progression of the disease and therefore were not amenable to resection. These patients had unfavourable tumor biology and would not benefit from resection sparing these patients from unnecessary morbidity following a resection. Further 20% of the patients were not resected because of intraoperatively detected, extrapancreatic disease. However, these patients had by then already received an effective locoregional therapy for locally advanced pancreatic cancer [57].

To identify patients with potentially resectable tumors for neoadjuvant treatment a strict definition of resectability and accurate imaging staging are important criteria which are currently not used and available. Furthermore, a safe approach for pathohistological confirmation of the disease is required. This can be achieved endosonographically or CT-guided. Two distinctive patient groups need to be differentiated:

1. Patients with resectable tumors
2. Patients with initially irresectable tumors

Based on currently available data a rate of 10–20% of patients with initially unresectable tumors can be estimated to be converted to R0-resectability after CRT from phase II and retrospective data [8, 53, 61]. Conversion to resectability has not been reported so far after neoadjuvant chemotherapy.

The efficacy of neoadjuvant treatment can only be deduced from phase II-studies or retrospective reports because up to date no prospectively randomized phase III-study has been completed. In a prospective comparative phase II study at the Mount Sinai Hospital in New York City [53] computed tomography followed by endosonography, angiography or laparoscopy or laparotomy was used to determine resectability pretherapeutically. Patients with locally invasive tumors deemed to be non-resectable (T3, N0–1, M0; n = 68) were treated with split-course-chemoradiation (5-FU, streptozotocin and cisplatin) and if possible subsequently resected after CRT. Resectable tumors (T1–2, N0–1, M0; n = 91) underwent

immediate pancreaticoduodenectomy. Sixty-three of 91 patients received adjuvant radio- or chemotherapy. Thirty of 68 patients with initially irresectable tumors were operated and downsizing was observed in 20 patients. The median overall survival time of all patients receiving preoperative treatment was 23.6 months compared to 14.0 months of patients with initial tumor resections ($p = 0.006$).

A group of 86 patients was treated in a phase II study with neoadjuvant chemoradiation (10×3.0 Gy) with concurrent gemcitabine (400 mg/m²/week) at the M.D. Anderson Cancer Center [62]. The operation was performed eleven to twelve weeks later. This resulted in resections in 74% of the tumors. Better efficacy was observed after gemcitabine compared to previous phase II studies from the same group combining radiation with 5-FU [18, 43]. Pathologic tumor response grading (TRG) showed a destruction of more than 50% of the tumor cells in 58% of the resected tumors. This high rate of pathohistological tumor response is important because response rate at CT imaging are typically below 10% probably due to the false positive imaging of fibrotic masses. Median overall survival time of the patients was 36 months. At the Duke University Medical Center in Durham, North Carolina, 111 patients with non-metastasized pancreatic carcinoma were treated with chemoradiation (45 Gy, 5.4 Gy Boost, 5-FU/mitomycin C/cisplatin, retrospective analysis) [59]. Seventy-two percent had a R0-resection and 70% were staged ypN0. The total survival rate of the resected patients was 32% after 2 years. In our own phase II-experience 58 patients with immediate resection had a median overall survival (mOS) of 21 months whereas 21 patients with initially unresectable tumors underwent CRT followed by resection and had a mOS of 54 months [23].

The first multicenter randomised study for neoadjuvant therapy in pancreatic carcinoma is currently recruiting [9]. This study will compare the results after immediate operation with those of patients with resection after neoadjuvant treatment in patients deemed to be initially resectable. The resection is followed by adjuvant chemotherapy in both arms. Because of the unique position of this study in the neoadjuvant

Table 2. Selected studies of neoadjuvant chemoradiation. 5-FU: 5-fluorouracil; adj: adjuvant therapy; cDDP: cisplatin; FCCC: Fox Chase Cancer Center, Philadelphia, PA; Gem: gemcitabine; Gy: Dose in Gray; i.p.r.: initially potentially resectable; i.l.a.: initially locally advanced, MDACC: M.D. Anderson Cancer Center Houston, TX; MMC: mitomycin C; n.a.: not available; neo: neoadjuvant; OS: overall survival; res: resected patients, RT: radiotherapy; Tax: paclitaxel; vs.: versus. [a]: initially unresectable patients ± resection after chemoradiation. [b]: This study indicates overall survival as explained: (1) patients with chemoradiation, (2) numbers in brackets: patients with chemoradiation and resection, (3) right to 'vs.': patients after primary resection; [b]: numbers in brackets in this row give results of the 20/68 resected patients with CRT. [c]: This study compared patients with immediate tumor resection (n = 58) with non-resectable patients who subsequently underwent neoadjuvant chemoradiation.

Tabelle 2. Ausgewählte Studien zur neoadjuvanten Radiochemotherapie. 5-FU: 5-Fluorouracil; adj: adjuvante Therapie; cDDP: Cisplatin; FCCC: Fox Chase Cancer Center, Philadelphia, PA; Gem: Gemcitabin; Gy: Strahlentherapiedosis in Gray; i.p.r.: initial potentiell resektabel; i.l.a.: initial lokal fortgeschritten, MDACC: M.D. Anderson Cancer Center Houston, TX; MMC: Mitomycin C; n.a.: nicht vorliegend; neo: neoadjuvant; OS: Gesamtüberleben; res: resezierte Patienten, RT: Radiotherapie; Tax: Paclitaxel; vs.: versus. [a]: initial irresektable Patienten ± Resektion nach Radiochemotherapie. [b]: Diese Studie gibt das Gesamtüberleben folgendermaßen an: (1) Patienten mit Radiochemotherapie, (2) Zahlen in Klammern: Patienten mit Radiochemotherapie und Resektion, (3) rechts von 'vs.': Patienten nach primärer Resektion; [b]: Zahlen in Klammern in dieser Reihe geben die Ergebnisse der 20/68 resezierten Patienten mit Radiochemotherapie an. [c]: Diese Studie verglich Patienten mit sofortiger Tumorresektion (n = 58) mit irresektablen Patienten, die zunächst eine neoadjuvante Radiochemotherapie hatten.

Study/ Institution	Number of patients	Total dose of XRT (Gy)	Chemo-therapy (mg/m²)	Median OS (months)	1 (2, 4, 5)-year-OS-rate (%)	Rate local recurrence (%)	Rate of resectability (%)	Rate of clear resections
Hoffman et al. 1998 [24, 25] Multi-centric	53	50.4	5-FU/MMC	9.7 all pts 15.7 res	2y: 27 res	24/53 (26%) 3/24 (13%) res	24/53 (45%)	n.a.
Snady et al. 2000 [53] Mount Sinai	159 68[a] (20 res[b]) 91 adj	54 + 14 Gy	5-FU/cDDP/ Streptozotocin 14.0	23.6[a] (32 res)	1y: 86[a] (89) vs. 64 2y: 58[a] (60) vs. 32 3y: 27[a] (40) vs. 17	n.a.	20/68 (29%) –	95% neo 84% adj
Breslin et al. 2001 [6] MDACC	132	45 or 50.4 Gy or 10 × 3 Gy ± IORT	5-FU, or Tax or Gem	21	1y: 75 2y: 40 5y: 23	8/132 (6%)	–	88%
Sasson et al. 2003 [50] FCCC	116 61 neo 55 adj	50.4	5-FU/MMC or Gem	all 18 neo 23 adj 16	n.a.	n.a.	–	39% n.a. n.a.
White et al. 2005 [60] Duke	193 i.p.r.: 102 i.l.a.: 91	45 + 5.4 Gy	5-FU or Gem	23 39 i.p.r. 20 i.l.f.	3y: 37 res 5y: 27 res	n.a.	70/193 (36%) 54/102 (53%) 16/91 (18%)	73% n.a. n.a.
Golcher et al. [23] Erlangen	79 21 neo[a] 58 res[c]	50.4 Gy + 5.4 Gy	5-FU or Gem	54 neo 21 res	2y: 56 neo 43 res	n.a.	21/103 (20%)	90% neo 78% res

sector this study is highly relevant and interested potential study centres are welcome to participate.

Summary

No conclusions can be drawn to date for neoadjuvant therapy. There are first data that suggest that neoadjuvant therapy may prolong survival because of a higher rate of curative resections (R0), because of a higher rate of negative lymph nodes and e.g. resulting in enhanced local control. In patients with locally advanced, initially irresectable tumors chemoradiation allows secondary resectability in about 10–20% of the patients.

Table 3. Median survival times after therapy for locally advanced pancreatic cancer. 5-FU: 5-fluorouracil; Cis: cisplatin; Gem: gemcitabine; Fol: folinic acid; Iri: irinotecan; MMC: mitomycin C; n.a.: not available; n.s.: not significant; Ox: oxaliplatine; PVI: protracted venous infusion, SMF: streptozotocin, mitomycin, 5-fluorouracil.

Tabelle 3. Mediane Überlebenszeiten beim lokal fortgeschrittenen Pankreaskarzinom. 5-FU: 5-fluorouracil; Cis: Cisplatin; Gem: Gemcitabin; Fol: Folsäure; Iri: Irinotecan; MMC: Mitomycin C; n.a.: nicht angebbar; n.s.: nicht signifikant; Ox: Oxaliplatin; PVI: intravenöse Dauerinfusion; SMF: Streptozotocin, Mitomycin, 5-Fluorouracil.

Authors (number of patients)	Radiotherapy (Gray)	Chemotherapy	Median survival time (months)	p-value
GITSG (1985) [21] (25/83/86)	60 40 60	– 5-FU 5-FU	5.2 9.6 9.2	p < 0.01
GITSG (1988) [22] (24/24)	54 –	SMF SMF	6.5 5.1	p < 0.02
Klaassen [33] (44/47)	40 –	5-FU 5-FU	8.3 8.2	n.a.
Chauffert [13] (59/60)	60 –	5-FU/Cis + Gem Gem	8.0 14.5	p = 0.03
Loehrer [36] (36/38)	50.4 –	Gem + Gem Gem	11.0 9.2	p = 0.034
Crane [16] (53/61)	30 (10b)	Gem 5-FU	11 9	p = n.s.
Li [35] (18/16)	50.4	Gem 5-FU	14.5 6.7	p = 0.027
Ishii [28] (20)	50.4	5-FU (PVI)	10.3	n.a.
McGinn [39] (37)	24–42	Gem	11.6	n.a.
Shinchi [52] (16/15)	50.4 –	5-FU (PVI)	13.2 6.4	n.a.
Brunner [11] (40/42)	55.8 55.8	Gem/Cis + Gem Gem/Cis	13 8	p < 0.0001
Huguet [26] (72/56)	55 –	5-FU + As below FolFuGem, GemOx	15 11.7	p = 0.0009
Kachnic [30] (23)	50.4	5-FU + Gem	13	n.a.
Johnson [29] (157)	–	Lithium Gamonelate	5.4	n.a.
Maisey [38] (44/46)	–	5-FU PVI 5-FU/MMC	32% (1 year) 43% (1 year)	n.a.
Louvet [37] (47/50)	– (some: 55)	Gem Gem/Ox	10.3 10.3	p = n.s.
Rocha Lima [47] (24/27)	– (some)	Gem Gem/Iri	11.7 9.8	p = n.s.
Van Cutsem [56] (80/82)	–	Gem Gem/tipifarnib	8.7 11	p = 0.2

Locally Advanced Tumors

About one third of the patients with PDAC present with locally advanced pancreatic cancer (LAPC) at diagnosis. The definition of LAPC is unresectable disease and absence of distant metastasis. Recently, the NCCN Practice Guidelines in Oncology have been published and these distinguish between resectable, borderline resectable and unresectable disease [55]. Borderline resectable tumors should be regarded as LAPC because of a high likelihood of an incomplete (R1 or R2) resection. Patients with LAPC are potentially curable and therefore should be treated with the intention of cure. Nevertheless, there is an ongoing controversy about optimal therapy for this group of patients (Table 3).

Early randomised phase III studies of the eighties showed, that combined CRT with total radiation doses of 40 Gy and 5-FU followed by additive chemotherapy was superior to radiotherapy alone or best supportive care. Median overall survival times of 8–9 months were reported. In the GITSG trial [22 patients were randomised for either radiotherapy or CRT and high dose CRT. Combined CRT was significantly superior to radiotherapy only but a total dose of 60 Gy did not result in better results whilst being more toxic. The problem with the radiotherapeutic techniques at that time was that large volumes of the small intestine were irradiated which lead to dose-limiting toxicity [22, 41]. Even if the studies on LAPC are not fully consistent [14], there is general consensus that radiotherapy should be performed as CRT in LAPC.

In the past, the direct comparison of CRT with chemotherapy showed some advantage for CRT in randomised phase II-studies in terms of local control and overall survival [22, 33]. On the other hand, a recent phase III-trial [13] resulted in inferior results after CRT. However, the total dose of 60 Gy which can safely be prescribed with high quality standards was problematic in this trial

with poor quality radiotherapy and an unusual chemotherapeutic regimen for CRT in pancreatic cancer (5-FU and cisplatin). Only 42% received at least 75% of both the planned dose of irradiation and of concomitant chemotherapy and CRT also prevented the full dose administration of additive gemcitabine chemotherapy.

Recent phase II-studies and cohort studies employing CRT reported median overall survival times of 10–11 months and 1-year-survival rates of up to 40% [16, 28, 30, 39, 52]. The value and particularly the toxicity of additive chemotherapy after CRT have to be further assessed in studies [11, 26, 30]. In these retrospective studies combinations of CRT and chemotherapy reported median overall survival times of 13–15 months. This conclusion is supported by the results of the very recently presented phase III ECOG trial 4201 [36]. This trial compared gemcitabine chemotherapy (mOS = 9.2 months) with gemcitabine based chemoradiation (total dose 50.4 Gy) followed by additive gemcitabine chemotherapy (mOS = 11.0 months; p = 0.034; HR 0.574, 95% CI 0.342–0.963). This trial reported no significant differences for the frequencies of grade 3/4 toxicities. At the moment the optimal sequence of CRT and chemotherapy in LAPC has not been determined yet. This question is subject to a current study performed by a French trial group.

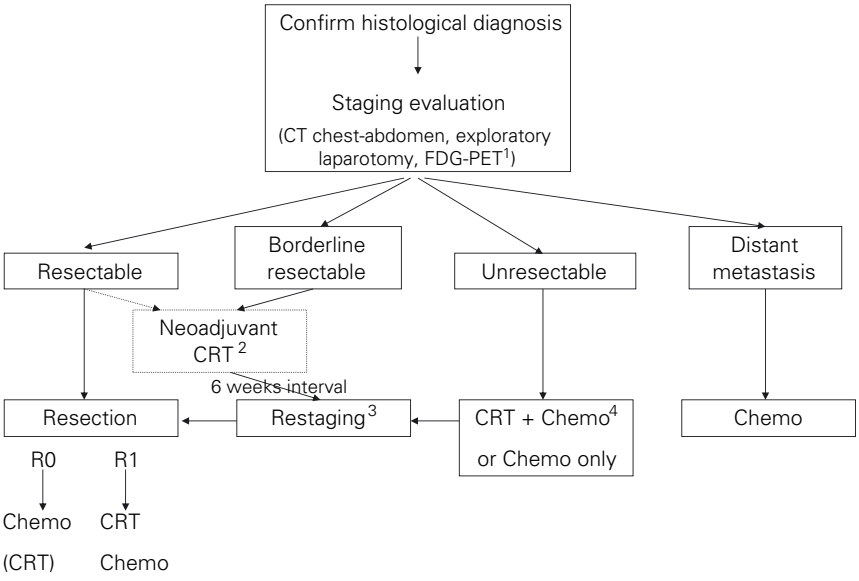

Figure 1. Treatment algorithm for the patient with newly diagnosed adenocarcinoma of the pancreas. Dotted arrows and frames: only in protocols. CT: computed tomography, CRT: chemoradiation, chemo: chemotherapy, R0: clear resection, R1: positive resection margins, R2: macroscopic residual tumor. The best management of any pancreatic cancer patient is in a clinical trial. [1]: Exploratory laparotomy and FDG-PET imaging are optional, FDG-PET imaging may help to detect regional and non-regional lymphatic disease. [2]: For any tumors where there is a higher likelihood of an imcomplete (R1 or R2) resection, it is suggested that chemoradiation be given prior to surgery within a clinical trial. [3]: FDG-PET staging and restaging is suggested to obtain additional response information as CT restaging is inaccurate because of desmoplasia. [4]: The optimal sequencing is not known currently (CRT/Chemo or Chemo/CRT).

Abbildung 1. Behandlungsalgorithmus für Patienten mit neu diagnostiziertem duktalem Adenokarzinom des Pankreas. Gepunktete Pfeile und Rahmen: nur in klinischen Studien. CT: Computertomographie, CRT: Radiochemotherapie, Chemo: Chemotherapie, R0: Resektion im Gesunden, R1: positive Resektionsränder, R2: makroskopischer Residualtumor. Die beste Behandlung für alle Patienten mit Pankreaskarzinom ist eine klinische Studie. [1]: Exploratorische Laparotomie und FDG-PET sind optional, FDG-PET kann bei der Detektion von regionären und nicht-regionären Lymphknotenmetastasen helfen. [2]: Neoadjuvante Radiochemotherapie im Rahmen von klinischen Studien wird für alle Tumoren nahegelegt, bei denen ein erhöhtes Risiko für eine imkomplette (R1 oder R2) Resektion besteht. [3]: FDG-PET-Staging und -Restaging wird empfohlen, um zusätzliche Information zum Ansprechen des Tumors zu erhalten, da die CT-Bildgebung wegen der ausgeprägten Desmoplasie limitiert in ihrer Aussage ist. [4]: Die optimale Abfolge ist derzeit noch nicht bekannt (CRT/Chemo oder Chemo/CRT).

Many chemotherapy trials included both, patients with metastasised and with LAPC. However, only studies with a subgroup analysis for LAPC allow for a cross-trial comparison with radiotherapy. Five randomised phase III-studies are suitable for such a comparison [4, 15, 29, 37, 38, 47, 56 and the achieved median overall survival times in the LAPC subgroup ranged between 5.4 and 11.7. In general, gemcitabine combinations have failed to achieve longer survival rates in advanced disease during the past decade (reviewed in [12]).

Fractionation of external radiotherapy is recommended to be 1.8–2.0 Gy per fraction, once daily and five fractions per week. Total dose should be 50–55 Gy at the ICRU reference point and total dose can be increased up to 60 Gy if multiple field techniques or IMRT together with restrictive target volume definitions are employed. The target volume comprises the primary tumor (PTV1) and the regional lymphatic areas (peripancreatic, coeliac, hepatoduodenal, mesenterial, paraaortal with the inferior mesenteric artery as the caudal margin) [10]. More than in other tumors, the tolerance of gemcitabine based simultaneous CRT depends on the total treatment volume in pancreatic carcinoma [17, 63]. Unusual high toxicities were reported especially if the radiation techniques insufficiently paid attention to these rules. Consequent and sufficient supportive therapy is the mainstay for the tolerance and the effectiveness of simultaneous CRT. This comprises stenting of the common bile duct, anti-emetic treatment, proton-pump inhibitor therapy, analgesia and parenteral feeding if necessary. Resectability should be re-evaluated 6–8 weeks after completion of CRT to exploit the possibility of a curative resection [7, 8, 53, 58, 60, 61]. Curative resection (R0) can be performed in 15–25% of the patients. It is also possible that tumor response appears with a delay of several months.

Summary

A direct comparison of CRT and chemotherapy is currently difficult to achieve. There are two positive phase III trials [22, 36] and one negative phase III trial [13] with a direct comparison of chemotherapy vs. chemoradiation. This emphasises the need for a better defined and qualitiy controlled radiotherapy used in studies and in the community setting. Overall survival rates have a tendency to be slightly longer after CRT compared to chemotherapy. Additive chemotherapy before or after CRT will have to be tested in randomised studies in order to determine the optimal sequencing. The most important argument for CRT is a 15– 25% rate of secondary resectability. This has not been reported with chemotherapy alone.

Clinical Consequences (Figure 1)

- After R0-resections, the currently available evidence argues rather for adjuvant chemotherapy than for chemoradiation followed by chemotherapy, even if chemoradiation is regarded to be standard therapy in Northern America.
- After R1-resections adjuvant chemoradiation followed by chemotherapy should be considered.
- Currently active randomised trials will have to set evidence for neoadjuvant chemoradiation.
- In locally advanced tumors a secondary resectability rate of about 20% should be kept in mind. These patients will obtain a chance for cure.

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