Downstaging of Pancreatic Carcinoma after Neoadjuvant Chemoradiation

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Background and Purpose: Neoadjuvant chemoradiation could improve survival in patients with pancreatic cancer because of a higher rate of R0 resections, lower rate of nodal metastasis (ypN) and of local recurrence. This approach was tested in a cohort to estimate its effect on survival.
Patients and Methods: Three-dimensional, conformal radiation to the primary tumor (55.8 Gy) and the lymphatics (50.4 Gy) was combined with chemotherapy. Resection was performed 6 weeks after completion of chemoradiation.
Results: 38 of 120 patients with locally advanced cancer underwent tumor resection thereafter. Three patients (8%) had pathologic complete response. Median tumor-specific survival was 29 months and overall survival 25 months. Patients with clear margins (35/38; 89%) had a 3-year disease-specific survival rate of 51% versus 0% with positive margins (p = 0.008). Nodal disease rate decreased from 50% at pretherapeutic imaging to 32% at resection. Patients with ypN0 status (n = 26/38) had a 3-year tumor-specific survival rate of 50% compared to 31% in patients with ypN1 status. At multivariate analysis, resection status and nodal spread significantly predicted tumor-specific survival. Chemoradiation was generally well tolerated.
Conclusion: The current results support randomized testing of neoadjuvant chemoradiation to prove survival prolongation. Compared to the literature this approach seems to reduce the number of positive nodes.

Key Words: Pancreatic cancer · Chemoradiotherapy · Neoadjuvant · Nodal status · Prognosis

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Downstaging von Pankreaskarzinomen nach neoadjuvanter Radiochemotherapie

Hintergrund und Ziel: Neoadjuvante Radiochemotherapie kann die Überlebenszeit von Patienten mit Pankreaskarzinomen potentiell verlängern, da eine höhere Rate von R0-Resektionen sowie eine niedrigere Rate von Lymphknotenmetastasen (ypN) und Lokalrezidiven erzielt werden. Dazu wurde dieser Ansatz in einer Kohorte von Patienten mit Pankreaskarzinomen untersucht.
Patienten und Methodik: Der Primärtumor (Dosis 55,8 Gy) und das Lymphabflussgebiet (Dosis 50,4 Gy) wurden dreidimensional konformal bestrahlt mit simultaner Chemotherapie. 6 Wochen danach wurde reseziert.
Ergebnisse: Die Tumoren von 38 von 120 Patienten mit lokal fortgeschrittenen Tumoren wurden reseziert. Drei Patienten (8%) zeigten eine pathologisch komplette Remission. Die mediane tumorspezifische Überlebenszeit betrug 29 Monate und die mediane Gesamtüberlebenszeit 25 Monate. Patienten mit R0-Resektion (35/38; 89%) wiesen eine krankheitsspezifische 3-Jahres-Überlebensrate von 51% versus 0% nach R1-Resektion auf (p = 0,008). Der Lymphknotenbefall nahm von 50% in der prätherapeutischen Bildgebung auf 32% bei der Resektion ab. Bei Patienten mit ypN0-Status (n = 26/38) fand sich eine krankheitsspezifische 3-Jahres-Überlebensrate von 50% im Vergleich zu 31% bei Patienten mit ypN1-Status. In der multivariaten Analyse waren der Resektionsstatus und der Lymphknotenbefall signifikante Prädiktoren des tumorspezifischen Überlebens. Die Radiochemotherapie wurde generell gut vertragen.
Schlussfolgerung: Die Ergebnisse unterstützen die randomisierte Prüfung der neoadjuvanten Radiochemotherapie, um eine Überlebensverlängerung zu bestätigen. Im Literaturvergleich scheint dieser Ansatz die Anzahl befallener Lymphknoten zu reduzieren.

Schlüsselwörter: Pankreaskarzinom · Radiochemotherapie · Neoadjuvant · Lymphknotenstatus · Prognose

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Introduction

Oncology has progressed impressively during the past 2 decades but patients with pancreatic ductal adenocarcinoma (PDAC) have been left out from this progress and still face a dismal prognosis [22]. PDAC ranks fourth in cancer-related mortality both in Europe and the USA [18]. Only about 20–30% of PDAC can be resected at diagnosis and clear resection (R0 resection) is mandatory for a potential curative chance. As a consequence, neoadjuvant treatment has been investigated to increase the rate of R0 resections, the number of negative nodes as well as the freedom from locoregional recurrence [2, 17, 43, 51]. This could parallel neoadjuvant trials in other tumor entities which have shown benefical effects [14, 21, 40]. This is supposed to result in an increase in overall survival (OS). In patients with locally advanced PDAC (LAPC) rates of curative resections of 10–30% have been reported [22]. These patients are of special interest for the neoadjuvant approach because they can be converted from a palliative to a potentially curative situation.

The prognosis for patients with PDAC who undergo curative surgical resection but do not receive neoadjuvant therapy has been shown to be strongly correlated with the status of pathologic tumor lymph node metastasis (pN) according to UICC [1, 24, 26]. Typically, the rate of lymphatic metastasis is 60–80% at primary resection [30, 37, 44] whereas the largest neoadjuvant series reported a rate between only 30% and 48% [2, 51] as a consequence of downstaging. However, it is not clear if prognostic significance is lost in PDAC after pretreatment.

In the current retrospective analysis, we investigated whether the extent of resection (R0 vs. R1) or the presence of involved lymph nodes at resection after chemoradiaton (CRT; ypN1) affected the survival of patients with carcinoma of pancreas. Long-term follow-up now allows us to estimate the effects of neoadjuvant treatment in our institution while we were able to activate the first known multicenter, randomized trial for neoadjuvant CRT comparing primary resection to preoperative CRT followed by resection [6].

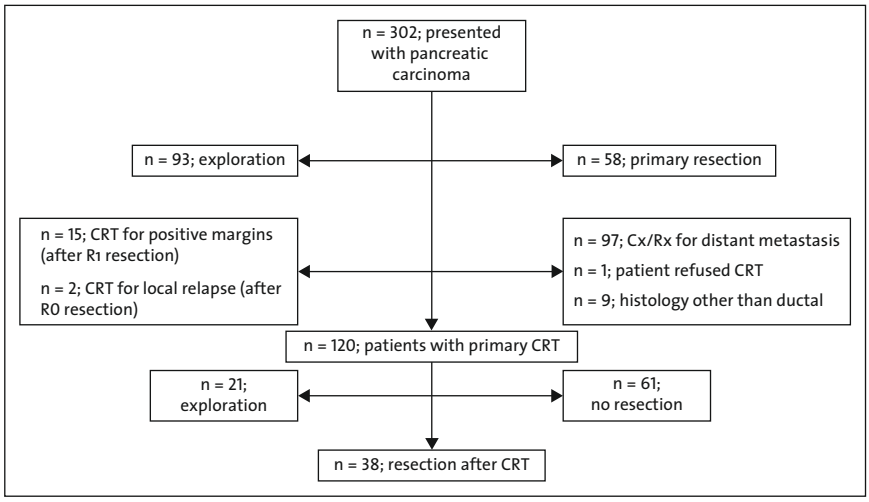


Figure 1. Algorithm of the patients with pancreatic carcinoma referred to the hospital between 09/1996 and 02/2006 and their selection process for neoadjuvant chemoradiation (CRT). Of 302 patients, 25% were resected (58 patients with primary resection plus 15 patients with R1 resection plus two patients with local relapse after R0 resection), 32% (97 patients) had distant metastasis, the remaining 40% had locally advanced pancreatic cancer (121 patients), one of these refused CRT, nine were later found to have nonductal carcinoma histologies. The decision for resection was taken according to the NCCN Practice Guidelines where CRT is recommended for borderline resectable and unresectable tumors [48]. Explorative laparotomy was performed in 93 patients after primary diagnosis and in 21 patients after CRT whose tumors were thought to be resectable at imaging. In these, resection could not be achieved because of local unresectability or distant metastasis. The group of patients with primary CRT (n = 120) includes all patients which were treated for locally advanced pancreatic carcinoma at our department.

Abbildung 1. Algorithmus der Patienten mit Pankreaskarzinom, die zwischen 09/1996 und 02/2006 der Klinik zugewiesen wurden, und ihr Selektionsprozess für eine neoadjuvante Radiochemotherapie (CRT). Von 302 Patienten wurden 25% reseziert (58 Patienten mit primärer Resektion plus 15 Patienten mit R1-Resektion plus zwei Patienten mit lokalem Rezidiv nach R0-Resektion), 32% (97 Patienten) hatten Fernmetastasen, die verbleibenden 40% ein lokal fortgeschrittenes Pankreaskarzinom (121 Patienten); einer dieser Patienten lehnte die Radiochemotherapie ab, bei neun stellte sich später heraus, dass sie histologisch kein duktales Pankreaskarzinom hatten. Die Entscheidung zur Resektion wurde gemäß den NCCN Practice Guidelines getroffen, in denen eine Radiochemotherapie für grenzwertig resektable und unresektable Tumoren empfohlen wird [48]. Bei 93 Patienten wurde nach der Primärdiagnose eine explorative Laparotomie durchgeführt, und bei 21 Patienten wurden die Tumoren nach Radiochemotherapie auf Grundlage der Bildgebung als resektabel eingestuft. Bei diesen konnte die Resektion nicht erreicht werden, da sie intraoperativ lokale Irrresektabilität oder Fernmetastasen aufwiesen. Die Gruppe der Patienten mit primärer Radiochemotherapie (n = 120) beinhaltet alle Patienten, die an unserer Klinik wegen eines lokal fortgeschrittenen Pankreaskarzinoms behandelt wurden.

Patients and Methods

Patient Selection

Between September 1996 and February 2006, 38/121 patients with LAPC were selected for neoadjuvant CRT at our local tumor board (Figure 1). Patients were eligible if the following criteria were met: histological proof of ductal adenocarcinoma prior to CRT or a hypodense mass in the pancreas in combination with clinical presentation and elevation of CA19-9 values > 200 U/ml. Tumors requiring resection of the superior mesenteric vein or portal vein were not considered for primary resection because of the poor prognosis of such patients [53]. In general, the decision

whether to resect or not to resect followed the Practice Guidelines in Oncology™ of the National Comprehensive Cancer Network [48]: for any tumors where there is a higher likelihood of an incomplete resection it is suggested that CRT be given prior to surgery. Patients were required to have a Karnofsky Performance Score ≥ 60%. The pretherapeutic laboratory requirements included white blood cell count ≥ 4,000/µl, platelet count ≥ 100,000/µl, bilirubin < 2.0 mg/dl, and a creatinine clearance ≥ 60 ml/min. Cardiac ultrasonography was performed to ensure that a volume load of 2.5 l/d was tolerable. Patients had to be chemotherapy- and radiotherapy-naive.

Patients who presented with jaundice before CRT underwent endoscopic retrograde cholangiopancreatography with bile duct stenting. A port-a-cath was implanted for chemotherapy and, if needed, for sufficient nutrition. The study protocol was approved by the local ethics committee, and all patients provided informed consent before therapy.

Chemoradiation

Conventionally fractionated, three-dimensional conformal irradiation was administered with a total dose of 55.8 Gy (PTV1 [planning target volume], tumor region) and 50.4 Gy (PTV2, regional lymph nodes), respectively (Figure 2). Treatment planning was performed three-dimensionally, the dose was prescribed to a reference point at the isocenter, and the organs at risk were protected as described earlier [7]. A strict definition of PTV [7] was applied to obtain small PTV volumes with minimal risk for both geographic miss and toxicities. The volume of the PTV in milliliters typically was around 600 ml, ranging from 400 ml to 850 ml. Concurrent chemotherapy consisted of 5-fluorouracil (5-FU, 1 g/m^2/d c.i.v. d1–5, d29–33) and mitomycin C (10 mg/m^2 bolus i.v. d1, 29) in eleven patients [4] and after January 1998 of gemcitabine (300 mg/m^2 in 30 min i.v. d1, 8, 22, 29) and cisplatin (30 mg/m^2 in 30 min i.v., d1, 8, 22, 29) in 27 patients [8].

Surgery and Further Therapy

6 weeks after completion of CRT computed tomography-(CT-)based restaging was performed to reevaluate resectability depending on vascular involvement and absence of distant disease. Pancreaticoduodenectomy or distal pancreatectomy and lymphatic dissection were performed only in patients with no evidence of extrapancreatic disease at laparotomy. A standardized technique was used to assess the resected specimen pathohistologically [2]. It was mandatory to perform histological analysis of the postoperatively paraffin-embedded tissue to exclude positive margins (R1 resection). No adjuvant chemotherapy was administered. Palliative chemotherapy was initiated after relapse and consisted in gemcitabine 1,000 mg/m^2 d1, 8, 15 q29.

Follow-Up and Statistical Analysis

Follow-up examinations were performed every 3 months for the first 2 years after surgery and thereafter every 6 months for at least 3 years. Examinations consisted of a physical examination, monitoring of the course of CA19-9, and ultrasound of the abdomen. Staging was complemented by CT of the abdomen and a chest X-ray every 6 months. Statistical data analysis was performed using the computer software Statistical Package for the Social Sciences®, version 11.0. The Kaplan-Meier plot was calculated for analysis of survival. Pairwise log-rank test served for comparison of the differences in survival in subgroups of patients and Cox regression analysis was performed for multivariate analysis. We used the RTOG toxicity criteria [11], the LENT-SOMA criteria [41] (side effects of radiotherapy), and the CTCAE v3.0 toxicity criteria of the National Cancer Institute (hematologic side effects) to classify acute and chronic treatment-related side effects.

The treatment was in accordance with the ethical standards of the local committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

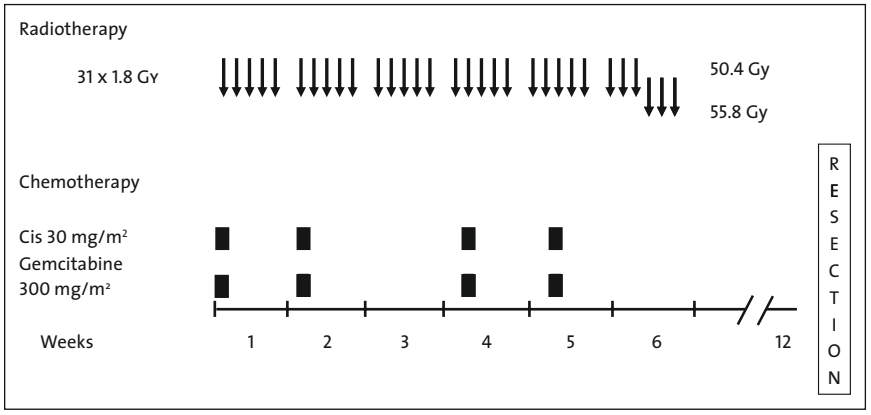


Figure 2. Graphic illustration of the treatment schedule for the combination of radiotherapy, gemcitabine and cisplatin (Cis). Radiotherapy fractions correspond to arrows in the upper half of the figure. The last three arrows represent a boost restricted to the tumor (= planning target volume 1), whereas the rest of the fractions additionally include the regional lymphatics (= planning target volume 2). 6 weeks after completion of chemoradiation restaging was performed followed by resection.

Abbildung 2. Graphische Darstellung des Behandlungsschemas der Kombination von Radiotherapie, Gemcitabin und Cisplatin (Cis). Die Radiotherapiefraktionen entsprechen den Pfeilen in der oberen Hälfte der Abbildung. Die letzten drei Pfeile stellen einen Boost auf den Tumor dar (= Planungszielvolumen 1), während die anderen Fraktionen zusätzlich das regionäre Lymphabflussgebiet umfassen (= Planungszielvolumen 2). 6 Wochen nach Ende der Radiochemotherapie wurde ein Restaging durchgeführt, danach reseziert.

Results

Patient Characteristics

Between September 1996 and February 2006, 120 patients with unresectable tumors were treated with CRT followed by pancreaticoduodenectomy (n = 34) or distal pancreatectomy (n = 4). The patients without subsequent resection were reported elsewhere [8]. The rate of resection did not depend on the chemotherapeutic regimen (5-FU and mitomycin 30.5% vs. gemcitabine and cisplatin 32%). Characteristics of the resected patients are listed in Table 1. All patients had an ECOG performance status of 0 or 1 prior to CRT. 29 patients had histologically proven PDAC prior to CRT. Additionally, histological proof of malignant disease could be obtained at resection or at autopsy in the remaining patients. At resection, five patients had advanced periampullary (OS 5, 6, 9, 9, and 33 months) and one patient had gastric carcinoma (OS 6 months). The changes of diagnosis reflect that compared to resection specimen biopsy material not always contains sufficient malignant cells to be able to make the correct diagnosis.

Treatment

Radiotherapy was completed in all patients and 24/38 patients (63%) received all planned chemotherapy. 31/38 patients (82%)

Table 1. Patient characteristics. R0: clear resection; R1: positive margin; RX: resection margin uncertain.

Tabelle 1. Patientencharakteristika. R0: Resektion im Gesunden; R1: positive Ränder; RX: unbekannte Schnittränder.

Parameter	Patients (n)	Percentage
All patients	38	100
Age (years)		
• Median	61	
• Range	41–76	
Gender		
• Male	24	63
• Female	14	37
Primary at resection		
• Pancreatic adenocarcinoma	32	84
• Periampullary carcinoma	5	13
• Gastric carcinoma	1	3
Tumor location		
• Pancreatic head	32	84
• Pancreatic body	4	11
• Pancreatic tail	2	5
Radiosensitizer		
• Gemcitabine, cisplatin	27	71
• 5-fluorouracil, mitomycin C	11	29
Type of surgery		
• Whipple's procedure	34	89
• Distal pancreatectomy	4	11
Completeness of resection		
• R0	34	89
• R0, but close resection	2	5
• R1	1	3
• RX	1	3

Tables 2a and 2b. Comparison of pretherapeutic staging with staging at resection.
a) Stage migration from pretherapeutic tumor staging (cT) to pathohistological (p) assessment after neoadjuvant chemoradiation (y) and resection ypT. Bold numbers mark tumors whose T-category remained unchanged. Cells above bold numbers show downstaged tumors, cells below show upstaged tumors.
b) Stage migration from pretherapeutic nodal staging (cN) to pathohistological (p) assessment after neoadjuvant chemoradiation (y) and resection ypN. Bold numbers mark tumors whose N-category remained unchanged. Cells above the bold numbers show downstaged tumors, cells below show upstaged tumors.

Tabellen 2a und 2b. Vergleich des prätherapeutischen Stagings mit dem Staging bei Resektion.
a) Stadienmigration vom prätherapeutischen Tumorstaging (cT) zur pathohistologischen (p) Untersuchung nach neoadjuvanter Radiochemotherapie (y) und Resektion ypT. Fett gedruckte Zahlen markieren Tumoren, deren T-Kategorie unverändert blieb. Zellen über fett gedruckten Zahlen zeigen herabgestufte Tumoren, Zellen unterhalb zeigen hochgestufte Tumoren.
b) Stadienmigration vom prätherapeutischen Lymphknotenstaging (cN) zum pathohistologischen (p) Staging nach neoadjuvanter Radiochemotherapie (y) und Resektion ypN. Fett gedruckte Zahlen markieren Tumoren, deren N-Kategorie unverändert blieb. Zellen über fett gedruckten Zahlen zeigen herabgestufte Tumoren, Zellen unterhalb zeigen hochgestufte Tumoren.

a) UICC 1997	cT1 n = 3	cT2 n = 13	cT3 n = 12	cT4 n = 10
ypT0				
n = 3		1	1	1
ypT1				
n = 7	**2**	2	2	1
ypT2				
n = 7		**3**	2	2
ypT3				
n = 19	1	6	**6**	6
ypT4				
n = 2	–	1	1	–
Responders	0	3	5	10

b) UICC 1997	cN0 n = 19 (50%)	cN1 n = 19 (50%)
ypN0		
n = 26 (68%)	**13**	13
ypN1		
n = 12 (32%)	6	**6**
Responders	–	13

received > 80% of the planned chemotherapy doses. Hematotoxicity was the most frequent reason for chemotherapy dose reduction or omission. Toxicity of treatment is reported below.

34 patients were resected at our institution and four patients outside of it. Clear resections (R0) were achieved in 36/38 patients (95%). One patient had a positive margin (R1 resection). In one patient the resection status was unclear (RX resection) because of multiple tumor fractions. Two of the 36 patients with R0 resection had close margins.

Five patients (13%) died within 90 days after surgery. Causes of death were infections in three patients (peritonitis, pneumonia, and MRSA [methicillin-resistant *Staphylococcus aureus*] MRSA infection). The cause for peritonitis was an insufficiency of the biliodigestive anastomosis. Two patients had a bleeding from an abdominal artery. One of them had a bleeding from the common hepatic artery, the other patient was estimated to be unresectable in our institution but underwent resection in an external hospital where postoperative fatal bleeding occurred. In our institution three patients died within 90 days after surgery from September 1996 through 1998 compared to only one patient since.

Comparison of Pretherapeutic Staging with Pathohistological Staging

Accuracy of clinical staging is lower than pathohistological staging and both over- and understaging have been described [13, 28, 38, 47, 49]. However, downstaging is expected after CRT. Therefore generally, the ypTNM stage at resection should be lower than the cTNM stage prior to CRT (Tables 2a and 2b). For both, T- and N-stage, downstaging was more frequent than upstaging. The comparison of T-categories showed 18/38 tumors (47%) being downstaged and 3/38 patients had complete remission of the tumor. In 11/38 tumors (29%) there was no change in T-category, whereas 9/38 tumors (24%) were upstaged after treatment. The tumor classified as ypT4 was a periampullary carcinoma with > 2 cm invasion into the pancreas (= pT4) that was staged as a cT3 pancreatic carcinoma prior to treatment. For nodal disease downstaging, no change and upstaging were observed in 13/38 patients (34%), 19/38 (50%), and 6/38 (16%), respectively. Of those without change, 13/38 patients (34%) were staged cN0 before and ypN0 after therapy.

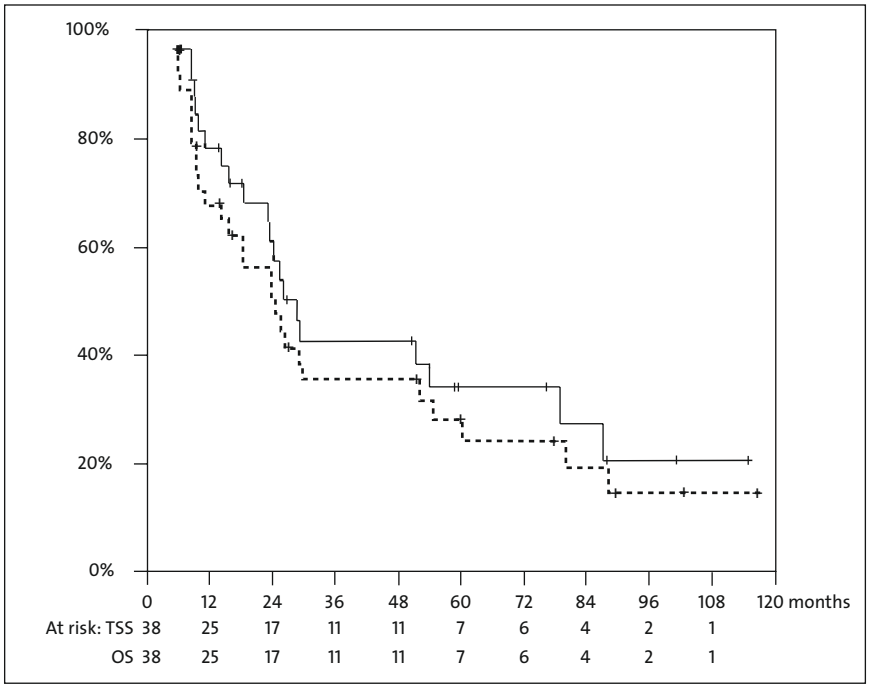


Figure 3. Kaplan-Meier plot of tumor-specific survival (TSS, solid line) and overall survival (OS, broken line) of patients with neoadjuvant chemoradiation followed by resection (n = 38). Median TSS 29 months; 1-year TSS: 79%; 3-year TSS: 44%; 5-TSS: 36%. Median OS 25 months; 1-year OS: 68%; 3-year OS: 36%; 5-year OS: 30%.

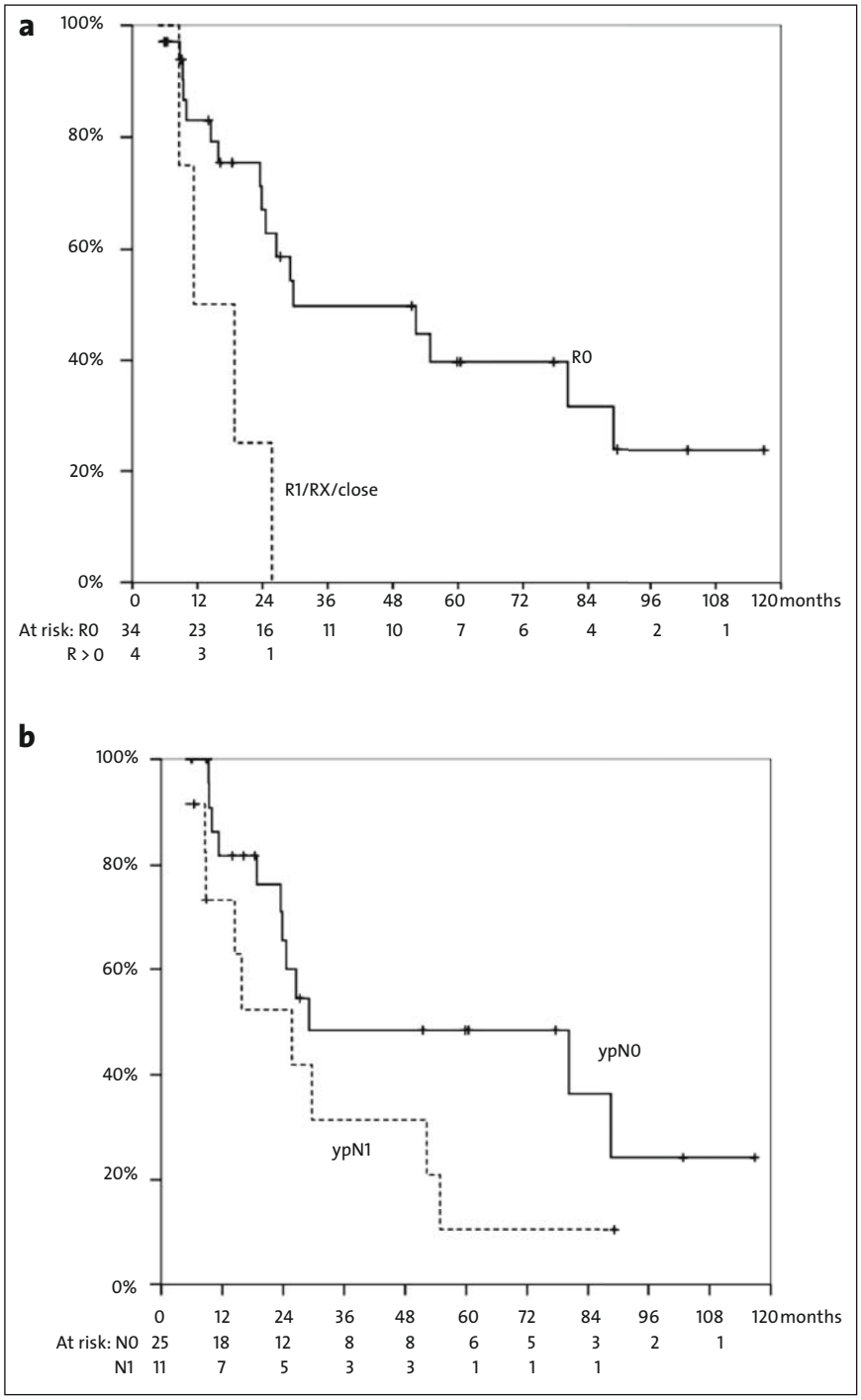
Abbildung 3. Kaplan-Meier-Kurve des tumorspezifischen Überlebens (TSS, durchgezogene Linie) und Gesamtüberleben (OS, gestrichelte Linie) von Patienten mit neoadjuvanter Radiochemotherapie gefolgt von Resektion (n = 38). Medianes TSS 29 Monate; 1-Jahres-TSS: 79%; 3-Jahres-TSS: 44%; 5-Jahres-TSS: 36%. Medianes OS 25 Monate; 1-Jahres-OS: 68%; 3-Jahres-OS: 36%; 5-Jahres-OS: 30%.

Pathologic Results and Survival Following Resection

Median follow-up for patients alive at analysis (n = 10) was 63 months (range 12–125 months). Tumor-specific survival (TSS) is shown in Figure 3 and median TSS time was 29 months. Median OS time for all patients was 25 months (1-year OS rate: 68%; 3-year OS rate: 36%; 5-year OS rate: 30%). Nodal spread was a significant prognostic factor for OS and TSS ($p = 0.043$ and $p = 0.045$, respectively). TSS of patients with clear resection was significantly ($p = 0.008$) longer compared to the group of patients with either R1 resection (n = 1), close resection (n = 2) or uncertain R-stage (RX, n = 1). Median TSS time of both groups was 52 months versus 11 months, respectively (Figure 4a). Median TSS time for PDAC was 29 months and median OS time was 26 months. OS of patients with other tumor types was 5, 6, 9, 9, and 33 months for periampullary carcinoma (n = 5), and 6 months for gastric carcinoma (n = 1). Survival was not influenced by treatment protocols (gemcitabine/cisplatin vs. 5-FU/mitomycin C).

In the 38 patients a median of 24 lymph nodes was analyzed (range four

to 60). The rate of patients with ypN1 disease was 31.6% (n = 12/38). Patients with positive nodes had a median of one node with tumor spread (range one to four nodes) and a median of 33 nodes analyzed (range eight to 53). Two patients with histologically confirmed nodal disease in the paraaortic compartment (pM1a) at pretherapeutic laparotomy had no nodal disease at resection after neoadjuvant CRT (OS 29 and 52 months, both died from disease). Six patients had one single node, four patients had two nodes, and two patients had four positive nodes within PTV2. Two patients had positive nodes at the margin or outside the treatment volume (one patient in the proximal hepatoduodenal ligament, one patient paraaortic). The latter patient additionally had two peritumoral positive nodes inside the PTV. Patients with ypN0 disease (n = 26) had a trend to longer survival when compared to those with ypN1 disease (p = 0.08, Figure 4b). However, nodal disease (cN) prior to CRT had no impact at all on survival time. Multivariate analysis confirmed the prognostic value of both, nodal spread (p = 0.032) and resection status for TSS (p = 0.027).



Figures 4a and 4b. Kaplan-Meier plot of tumor-specific survival (TSS) according to resection status (p = 0.008; a) and nodal status (p = 0.084; b).
a) The solid line represents patients with clear tumor resections (R0; n = 34) and the dotted line patients with positive (n = 1), unknown (n = 1) or close (n = 2) resections (R1/RX/close). *R0:* median TSS 52.2 months; 1-year TSS: 83%; 2-year TSS: 68%; 3-year TSS: 51%; 5-year TSS: 42%. *Non-R0:* median TSS 11.3 months; 1-year TSS: 50%; 2-year TSS: 25%; 3-year TSS: 0%.
b) The solid line represents patients without nodal disease (ypN0; n = 26) and the dotted line patients with nodal disease (ypN1; n = 12). *ypN0:* median TSS 80.2 months; 1-year TSS: 83%; 2-year TSS: 67%; 3-year TSS: 50%; 5-year TSS: 50%. *ypN1:* median 25.7 months; 1-year TSS: 73%; 2-year TSS: 52%; 3-year TSS; 31%; 5-years TSS: 11%.

Abbildungen 4a und 4b. Kaplan-Meier-Kurve des tumorspezifischen Überlebens (TSS) nach Resektionsstatus (p = 0,008; a) und Nodalstatus (p = 0,084; b).
a) Die durchgezogene Linie repräsentiert Patienten mit Resektionen im Gesunden (R0; n = 34) und die gestrichelte Linie Patienten mit positiven (n = 1), unbekannten (n = 1) oder nahen (n = 2) Schnitträndern (R1/RX/close). *R0:* medianes TSS 52,2 Monate; 1-Jahres-TSS: 83%; 2-Jahres-TSS: 68%; 3-Jahres-TSS: 51%; 5-Jahres-TSS: 42%. *Nicht-R0:* medianes TSS 11,3 Monate; 1-Jahres-TSS: 50%; 2-Jahres-TSS: 25%; 3-Jahres-TSS: 0%.
b) Die durchgezogene Linie repräsentiert Patienten ohne nodalen Befall (ypN0; n = 26) und die gestrichelte Linie Patienten mit nodalem Befall (ypN1; n = 12). *ypN0:* medianes TSS 80,2 Monate; 1-Jahres-TSS: 83%; 2-Jahres-TSS: 67%; 3-Jahres-TSS: 50%; 5-Jahres-TSS: 50%. *ypN1:* Median 25,7 Monate; 1-Jahres-TSS: 73%; 2-Jahres-TSS: 52%; 3-Jahre-TSS; 31%; 5-Jahres-TSS: 11%.

Patterns of Failure

Failure was determined in CT scans and distant metastasis was the site of failure in 19/38 patients (50%) as their first manifestation of recurrence. Distant metastasis occurred as peritoneal carcinomatosis (eleven patients) or as liver metastasis (eight patients). One patient (2.6%) developed an isolated local recurrence. Two other patients who had evidence of local recurrence had synchronous distant metastasis.

Tolerability of the Treatment

Toxicities are summarized in Table 3. No toxicity-related radiation treatment breaks were necessary. Chemotherapy was delayed in three patients due to leukocytopenia. Additionally, leukocytopenia was the major reason for reduced chemotherapy doses to < 80% of the planned doses in 6/7 patients and thrombocytopenia in the remaining patient. Hematologic toxicities consisted mainly in thrombopenia followed by leukopenia. Only 5% of the patients developed grade 4 leukopenia and 11% thrombopenia. None of the patients had thrombocytopenic bleedings or febrile neutropenia. Gastrointestinal toxicities were mild and nausea could be well treated with 5-HT_3 antagonists. Cholangitis due to stent occlusion occurred in four (10%) of the 38 patients and could be managed successfully by immediate stent replacement in all patients. No delayed gastrointestinal bleeding was observed.

Discussion

The patients of this trial survived longer compared to other studies reporting on neoadjuvant CRT (median OS 21–32 months) [2, 42, 43]. OS was only longer in the trial from the Mount Sinai Hospital (32 months) [43]. In the M.D. Anderson series, the high rate of vascular resections (43%) may have contributed to shorter survival compared to our trial [2]. In three studies median OS times were compared between adjuvant and neoadjuvant treatment schedules: median OS time was 14 versus 32 months [43] and 16 versus 23 months, respectively [42]. The group from Duke University observed a TSS of 26 months after preoperative treatment compared to 20 months after primary surgery [50]. Altogether these results support the hypothesis that neoadjuvant CRT results in longer survival compared to adjuvant treatment. Survival in adjuvant, randomized trials [19, 23, 33, 36] was also inferior (median OS 17–21 months) compared to the largest neoadjuvant series. To test this hypothesis in a prospective way, we have activated the first randomized (primary resection vs. neoadjuvant CRT followed by resection) multicenter phase II study [6]. To further increase survival, it is important to prevent distant failure after resection [34]. Therefore, adjuvant chemotherapy should be administered whenever possible.

Generally, resection margin is a recognized prognostic factor [25]. Nevertheless, data on the prognostic significance of the resection status were conflicting in recently reported trials (prognostic for survival [29, 32, 42, 46]; no influence on survival [3, 34, 36, 50]). In our study, resection status was the strongest prognostic factor found (median TSS 52 months vs. 11 months). Intriguingly, the ESPAC-1 trial, the largest phase III adjuvant trial published to date, reported lack of efficiency for adjuvant 5-FU chemotherapy in R1-resected patients whereas the same group of patients did benefit from CRT [33, 46]. A possible explanation for the inconsistency of the prognostic significance of the R-status is that there is probably a high rate of R0 resections being falsely negative [29]. This is due to the fact that the typical site for positive margins is retroperitoneal where surgical radicality is limited. To optimize reliability of resection status, close cooperation between the surgeon and the pathologist is crucial.

Table 3. Acute toxicity of chemoradiation (n = 38) according to the Common Toxicity Criteria of the National Cancer Institute. FM: 5-fluorouracil and mitomycin C (n = 11); GC: gemcitabine and cisplatin (n = 27), n: number of events. Percentages are related to the number of patients treated with per chemotherapeutic regimen.

Tabelle 3. Akuttoxizität der Radiochemotherapie (n = 38) gemäß den Common Toxicity Criteria des National Cancer Institute. FM: 5-Fluorouracil und Mitomycin C (n = 11); GC: Gemcitabin und Cisplatin (n = 27); n: Anzahl der Ereignisse. Die Prozentwerte beziehen sich auf die Anzahl der Patienten pro Chemotherapieprotokoll.

Grade	0 n (%)	1 n (%)	2 n (%)	3 n (%)	4 n (%)
Leukopenia	2 (5)	9 (24)	9 (24)	16 (42)	2 (5)
• GC	1 (4)	6 (22)	7 (26)	11 (41)	2 (7)
• FM	1 (9)	3 (27)	2 (18)	5 (46)	0
Platelets	9 (24)	10 (26)	11 (29)	4 (11)	4 (11)
• GC	6 (22)	8 (30)	7 (26)	3 (11)	3 (11)
• FM	3 (27)	2 (18)	4 (36)	1 (9)	1 (9)
Hemoglobin	14 (37)	12 (32)	12 (32)	0	0
• GC	7 (26)	9 (33)	11 (41)		
• FM	7 (64)	3 (27)	1 (9)		
Nausea/vomiting	9 (24)	13 (34)	14 (37)	2 (5)	0
• GC	7 (26)	9 (33)	9 (33)	2 (7)	
• FM	2 (18)	4 (36)	5 (45)	0	
Diarrhea	35 (92)	2 (5)	0	1 (3)	0
• GC	25 (93)	1 (4)		1 (4)	
• FM	10 (97)	1 (3)		0	
Cholangitis	34 (90)	4 (10)			
• GC	23 (85)	4 (15)			
• FM	11 (100)	0			

The rate of nodal disease at resection was surprisingly low in this trial (32%) and nodal disease is known to be one of the most significant prognostic factors after resection in pancreatic cancer [25]. Fisher's exact test comparing the rate of nodal disease between initially resected (n = 58) and pretreated patients (n = 21) from our institution showed that patients with pretreatment had a significantly higher rate of nodes without tumor ($p < 0.001$). Neoadjuvant CRT has consistently been shown to reduce the rate of nodal disease from 53–85% at primary resection [7, 20, 31, 46] to 30–48% at resections after neoadjuvant CRT [2, 51]. Patients with negative nodes after pretreatment had a trend to longer survival compared to patients with nodal disease in this study. The difference probably did not reach statistical significance because of the relatively low number of patients. The need to treat regional lymphatics is supported by the prognostic significance of the nodal stage after neoadjuvant CRT in other neoadjuvant studies [42, 43, 51]. The prognostic effect of sterilization of nodal disease has also been shown in other tumor entities after preoperative CRT [16, 39, 45].

Probably 10–20% of the patients with LAPC can be converted from nonresectable to resectable with clear margins after neoadjuvant CRT [5, 43, 52]. However, this has never been reported for neoadjuvant chemotherapy. The magnitude of the locoregional effect of preoperative CRT is also reflected in the excellent local tumor control of this study as well as other neoadjuvant trials [2, 17].

Tolerability of neoadjuvant CRT was excellent in this trial as in other recent trials using gemcitabine concurrently with radiation for pancreatic cancer [27, 54]. Acute toxicity was mostly hematologic and well manageable, and higher-grade gastrointestinal toxicity was very uncommon. This is in sharp contrast to a recently presented trial for patients with LAPC [9]. The group reported acute grade 3/4 hematologic and gastrointestinal toxicity in > 50% of the patients. However, the use of the uncommon combination of 5-FU/cDDP and quality issues in radiation therapy may explain the observed high toxicity. Toxicity of concurrent CRT is known to depend more than in other tumors on the size of the PTV [12] especially when gemcitabine is used concurrently. We have addressed this problem by a strict definition of the radiation technique and target volume [7]. Since postoperative lethality significantly decreased after the first 2 years after the start of the neoadjuvant approach in our institution, we postulate a training effect of surgeons who adapt to the new conditions. This observation and the fact that two of the four patients resected outside our center died postoperatively points to neoadjuvant CRT if the surgeon who performs the resection is not used to pretreatment. However, this effect did not persist as shown by an intrainstitutional comparison [15]. The effect of neoadjuvant CRT on mortality and morbidity for pancreaticoduodenectomy was recently analyzed retrospectively at the Duke University Medical Center comparing 79 patients resected after CRT and 67 patients without pretreatment [10]. Lethality rates were 3.8% and 4.5% in the respective groups and no increase in morbidity after CRT was observed. This is comparable with a lethality of 2% at the M.D. Anderson Cancer Center in a series of 132 patients resected after neoadjuvant treatment [2]. Additionally, there was no increased rate of postoperative morbidity or mortality.

One of the problems of neoadjuvant therapy for LAPC is the necessity to perform histological proof of disease prior to CRT. While this is mandatory in a recently activated prospectively randomized phase II trial [6], this was not the case in this study. It is common practice of many pancreatic surgeons to prove the histology of cancer not earlier than at an attempt for resection and we initially used the same guideline for patients who were eligible for neoadjuvant CRT if imaging and a high level of CA19-9 (> 300 U/ml) alleged this diagnosis. The patients without prior histological proof of disease all had malignant disease at resection. Intriguingly, pre-CRT histology cannot always correctly determine the tumor entity which is demonstrated by the patient who was finally diagnosed to have gastric carcinoma while the pretherapeutic biopsy was described as PDAC. Locally advanced periampullary carcinoma has an equally poor prognosis than PDAC [35]. The four patients who were ultimately found to have this malignancy had even shorter survival than patients with PDAC with 6, 9, 9, and 33 months.

Conclusion

Our data demonstrate that neoadjuvant CRT followed by resection achieves good survival data in patients with LAPC and can safely be administered. Neoadjuvant treatment decreases the frequency of nodal disease and of positive margins compared to series with initial resection. While to date, the evidence of the concept of neoadjuvant CRT cannot yet be fully evaluated, we have activated a randomized prospective trial testing the multimodal approach against primary resection in a different patient group with resectable tumors [6].

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