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The Role of Adjuvant Chemotherapy for Patients with Resected Pancreatic Cancer: Systematic Review of Randomized Controlled Trials and Meta-Analysis

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Key Words
Adjuvant chemotherapy · Chemoradiation · Meta-analysis · Pancreatic cancer

Abstract
Background: In patients undergoing surgery for resectable pancreatic cancer prognosis still remains poor. The role of adjuvant treatment strategies (including chemotherapy and chemoradiotherapy) following resection of pancreatic cancer remains controversial. ***Methods:*** A Medline-based literature search was undertaken to identify randomized controlled trials that evaluated adjuvant chemotherapy after complete macroscopic resection for cancer of the exocrine pancreas. Five trials of adjuvant chemotherapy were eligible and critically reviewed for this article. A meta-analysis (based on published data) was performed with survival (median survival time and 5-year survival rate) being the primary endpoint. ***Results:*** For the meta-analysis, 482 patients were allocated to the chemotherapy group and 469 patients to the control group. The meta-analysis estimate for prolongation of median survival time for patients in the chemotherapy group was 3 months (95% CI 0.3–5.7 months, $p = 0.03$). The difference in 5-year survival rate was estimated with 3.1% between the chemotherapy and the control group (95% CI –4.6 to 10.8%, $p > 0.05$). ***Conclusion:*** Currently available data from randomized trials indicate that adjuvant chemotherapy after resection of pancreatic cancer may substantially prolong disease-free survival and cause a moderate increase in overall survival. In the current meta-analysis, a significant survival benefit was only seen with regard to median survival, but not for the 5-year survival rate. The optimal chemotherapy regimen in the adjuvant setting as well as individualized treatment strategies (also including modern chemoradiotherapy regimens) still remain to be defined.

Introduction

Pancreatic cancer is currently the 4th to 5th most frequent cause of solid tumor deaths in Western industrialized countries. Despite advances in the understanding of the underlying biology, improvements of diagnostic tools and the development of new effective agents, the majority of patients diagnosed with pancreatic cancer still have a fatal outcome, and 5-year survival rates rarely exceed 5% [1].

The minority of pancreatic cancer patients present with resectable disease at first diagnosis. Approximately 10–15% of patients undergo partial or complete pancreaticoduodenectomy as the established standard of care [2, 3]. Morbidity and mortality associated with the Kausch-Whipple procedure have decreased during the last 2 decades, especially in high-volume centers. Despite the curative intent of surgery and optimized application

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of supportive therapy, median survival after resection of pancreatic cancer remains in the range of 11–20 months and is associated with a 5-year survival of 7–25% [3, 4]. Primary sites of disease recurrence are the retroperitoneum (34–87%), the peritoneum (19%-53%), the liver (38–73%) and extra-abdominal sites such as the lungs (8–29%) [3]. Recent efforts to improve outcome by more radical resection procedures or extensive lymphadenectomy have not improved the course of disease, which can be explained by early distant metastasis occurring in most patients, while isolated local recurrence is less frequent [5]. Important predictors of recurrence include tumor size (defined by T stage), nodal involvement, positive resection margins, and vascular, lymphatic and perineural invasion [6]. As the poor prognosis of patients with pancreatic cancer is primarily determined by systemic and not local failure, it becomes self-evident that adjuvant treatment strategies should predominantly focus on an improvement of systemic treatment.

The aim of the present article was to systematically review randomized controlled trials that evaluated the role of adjuvant chemotherapy after macroscopically complete resection of pancreatic cancer. Additionally, a meta-analysis (based on published data) for adjuvant chemotherapy was conducted, which also included the survival data from the recently published CONKO-001 study [7].

Methods

Selection Criteria for Trials Included in the Systematic Review and Meta-Analysis

This analysis only included randomized clinical trials that were conducted in patients with histologically proven cancer of the exocrine pancreas. In each trial, patients underwent surgery with curative intent (R0 or R1 resection, negative or positive nodal status); adjuvant treatment consisted of chemotherapy alone or chemoradiotherapy (CRT) followed by sequential full-dose chemotherapy (only in the ESPAC-1 study). Trials were identified by a literature search using the Medline database. In addition, relevant abstract publications from scientific meetings (for example the American Society of Clinical Oncology) were included, and previous reviews and meta-analyses were screened for any other relevant trials.

Statistical Methods for Meta-Analysis

A meta-analysis of randomized trials for adjuvant chemotherapy was performed on the basis of published data. The endpoint of this meta-analysis was survival, defined by median survival time and the 5-year survival rate. Five randomized trials met the criteria for the meta-analysis (table 1); 4 of these 5 trials compared chemotherapy versus observation only, whereas the ESPAC-1 trial compared chemotherapy versus no chemotherapy and CRT versus no CRT using a 2 × 2 factorial design. Overall, 482 patients were allocated to the chemotherapy group, whereas 469 patients were allocated to the control group (observation and no chemotherapy).

Meta-analyses of differences in absolute 5-year survival rates between the chemotherapy and control groups were performed as follows: the published 5-year survival rates for the chemotherapy, $\theta_{treat,k}$, and control, $\theta_{control,k}$, groups of each study were extracted from the published results and the standard error for each calculated by published numbers at risk at 5 years using the formula of Peto et al. [8]. The variance of the difference in 5-year survival rates, $\theta_k = \theta_{treat,k} - \theta_{control,k}$, equals the sum of the squared standard errors and its inverse is used as the study weight, w_k, for study k for the k = 1, …, K studies, where $K = 5$. A test of heterogeneity of study effects was performed by comparing the statistic $Q = \Sigma_k(\theta_k - \theta)^2$ for $\theta = \Sigma_k w_k\theta_k/\Sigma_k w_k$ to a χ^2 distribution with $K - 1$ degrees of freedom [9]. If the test was not significant, the analysis was performed assuming a normal fixed effects model with known study-specific variances. Otherwise, the results were analyzed using a normal random effects model with fixed study-specific variances and a random between-study variance component, τ^2, to compensate for the heterogeneity between the studies. Meta-analysis results are reported in terms of average difference, θ, with 95% confidence interval (CI). All statistical tests were performed at the 2-sided 0.05 level and all statistical computations were done using the R statistical package (version 2.4.1).

Meta-analyses of differences in median survival times between the chemotherapy and control groups were performed analogously, but using published median survival times and an approximation to the standard error of median times provided by assumption of an exponential distribution (standard error of median = median/square root of number of events) for studies that did not publish CI for the medians [10, 11]. Log transformation of median survival times for the Wald-type analysis gave very similar results, so no transformation was used.

Results

Randomized Trials for Adjuvant Chemotherapy

In view of the high rate of systemic relapse in patients after resection with curative intent, there is a clear scientific rationale to investigate systemic adjuvant chemotherapy in pancreatic cancer. Table 1 summarizes survival results from randomized trials investigating adjuvant chemotherapy for patients with resected pancreatic cancer.

Norwegian Trial

Bakkevold et al. [10] were among the first to investigate adjuvant chemotherapy in a small randomized multicenter trial: systemic chemotherapy with 5-fluorouracil (5-FU) 500 mg/m^2, doxorubicin 40 mg/m^2 and mitomycin C 6 mg/m^2 (applied every 3 weeks for 6 cycles; FAM regimen; n = 30) was compared to observation alone (n =

Table 1. Survival results from randomized trials comparing adjuvant chemotherapy to observation [7, 10, 11, 12] or to no chemotherapy [14]

Reference	Regimen	Duration of treatment, months	Subjects n	Median OS months	5-year OS %
Bakkevold et al. [10]	FAM regimen every 3 weeks for 6 cycles	4.5	30	23*	4
	Observation		31	11	8
Takada et al. [12]	MF regimen until disease recurrence	NA	81	NA	11.5
	Observation		77	NA	18.0
Kosuge et al. [11]	5-FU + cisplatin every 4–8 weeks for 2 cycles	2–4	45	12.5	26.4
	Observation		44	15.8	14.9
ESPAC-1 [14]	5-FU/FA on days 1–5 every 4 weeks for 6 cycles	6	147	20.1	21
	No chemotherapy		142	15.5**	8
CONKO-001 [7]	Gemcitabine weekly 3 times every 4 weeks for 6 cycles	6	179	22.1***	22.5
	Observation		175	20.2	11.5

OS = Overall survival; FAM = 5-fluorouracil + doxorubicin + mitomycin C; MF = mitomycin C + 5-fluorouracil; 5-FU = 5-fluorouracil; FA = folinic acid; NA = data not available. * p = 0.02 for median test and p=0.10 by Wilcoxon test; ** p = 0.009 for Cox proportional hazards ratio test; *** p = 0.06 for log rank test.

31) in patients with pancreatic cancer and carcinomas of Vater's ampulla. Application of adjuvant chemotherapy for a planned duration of 4.5 months induced a significant improvement of median survival (23 vs. 11 months, p = 0.02), but the 5-year survival was not significantly changed (4 vs. 8%, p = 0.10, generalized Wilcoxon test).

Japanese Trials

Kosuge et al. [11] recently reported a randomized trial where R0 resected patients either received 2 cycles of 5-FU (500 mg/m^2/day, days 1–5) plus cisplatin (80 mg/m^2, day 1) every 4–8 weeks (n = 45) or were attributed to an observational arm (n = 44). No significant improvement of median survival (12.5 vs. 15.8 months) was reported; also, no significant advantages for the treatment arm with regard to the 5-year survival rate (26.4 vs. 14.9%, p = 0.94) and the recurrence rate at 5 years (73.6 vs. 80.8%, p = 0.80) were observed.

Takada et al. [12] performed a large randomized study comparing postoperative chemotherapy to observation in 508 patients with resected pancreaticobiliary cancers. Within this trial, 173 patients with pancreatic cancer were randomly assigned to either adjuvant chemotherapy using the MF regimen (mitomycin C 6 mg/m^2 on the day of surgery plus 5-FU 310 mg/m^2 for 5 days during postoperative weeks 1 and 3, followed by daily oral 5-FU 100 mg/m^2 from postoperative week 5 until recurrence of disease) or observation. In 158 eligible patients, adjuvant chemotherapy with MF (n = 81) neither improved the 5-year disease-free survival (DFS) rate (8.6 vs. 7.8%, p = 0.84) nor the 5-year overall survival rate (11.5 vs. 18.0%, p = not significant) compared to patients in the control group (n = 77).

ESPAC-1

In 2001 and 2004, the European Study Group of Pancreatic Cancer (ESPAC) reported their results from a large randomized multicenter trial performed in the adjuvant setting (ESPAC-1 study) [13, 14]. After R0/R1 resection, patients were randomized to 1 of 4 treatment arms: adjuvant chemotherapy (5-FU 425 mg/m^2 and folinic acid 20 mg/m^2, days 1–5, monthly for 6 months) or CRT [analogous to the Gastrointestinal Tumor Study Group (GITSG) regimen], a sequence of CRT and chemotherapy or observation only. While 541 patients were randomized overall [13], only 289 patients were included into the 2 × 2 factorial design comparing chemotherapy versus no chemotherapy or CRT versus no CRT [14].

At a median follow-up of 47 months, the analysis of the 2 × 2 factorial design patients indicated a median survival of 20.1 months for the chemotherapy group and 15.5 months for the no chemotherapy group (hazard ratio = 0.71, 95% CI 0.55–0.92, p = 0.009). Also, the estimated 5-year survival rate was greater in the chemotherapy group (21 vs. 8%) [14]. The median time to disease recurrence was 15.3 months among patients in the chemotherapy arm and 9.4 months among patients who did not receive chemotherapy (p = 0.02). This trial has been criticized not only for statistical, but also for methodological flaws, including the fact that in the chemotherapy

Table 2. Subgroup analysis (according to resection margin, nodal involvement and T stage) of DFS and overall survival from the CONKO-001 trial [7]

Subgroup	Number		Median DFS, months		p value	Median OS, months		p value
	Gem.	Obs.	Gem.	Obs.		Gem.	Obs.	
R0	145	148	13.1	7.3	<0.001	21.7	20.8	0.18
R1	34	27	15.8	5.5	<0.001	22.1	14.1	0.07
N–	52	48	24.8	10.4	0.003	34.0	27.6	0.04
N+	127	127	12.1	6.4	<0.001	18.5	18.2	0.44
T1–2	25	24	48.2	10.0	0.02	50.2	27.6	0.28
T3–4	154	151	12.9	6.7	<0.001	20.5	19.1	0.11

OS = Overall survival; Gem. = gemcitabine; Obs. = observation only.

arm only 50% of patients received treatment according to the protocol and that 17% of patients did not receive chemotherapy at all. Thus, the data from the ESPAC-1 trial are highly suggestive, but not sufficient to derive a strong treatment recommendation.

CONKO-001

More recently, final results from the German CONKO-001 trial were published; 368 patients were recruited into this trial, which compared chemotherapy with gemcitabine (1,000 mg/m^2, days 1, 8 and 15 every 4 weeks for 6 months) administered within 6 weeks after R01/R1 resection to observation [7]. The primary endpoint of this trial was DFS and the primary hypothesis an increase on chemotherapy of at least 6 months. The final results of this study showed a significant increase in DFS in the treatment group (13.4 months) compared to the observation only group (6.9 months, $p < 0.001$). However, at the time of evaluation, there was no significant difference in median survival between the 2 groups (gemcitabine vs. observation: 22.1 vs. 20.2 months, $p = 0.06$). The 5-year overall survival rate was estimated with 22.5% (gemcitabine arm) versus 11.5% (observation arm). The authors stated that these findings on survival may be explained, at least in part, by the fact that patients from the control group received gemcitabine upon disease recurrence as a standard of care in the palliative setting. Data from a nonpredefined subgroup analysis of CONKO-001 are summarized in table 2. The beneficial effect of adjuvant chemotherapy on DFS was demonstrated in all subgroups, classified by resection margin, nodal involvement and T stage. The effect of gemcitabine treatment on DFS was most pronounced in the subgroup of node-negative patients (N–; difference in DFS, $\Delta_{DFS} = 14.4$ months) and in patients with small primary tumors (T1–2; $\Delta_{DFS} = 38.2$ months). However, in light of the low numbers in the subgroups and with regard to the post hoc approach of this analysis, these results cannot be the basis for far-reaching conclusions.

In summary, adjuvant chemotherapy performed for 4.5–6 months has induced a significant benefit in median survival in 2 trials: the Norwegian trial and the ESPAC-1 trial. The CONKO-001 trial clearly met its primary endpoint and showed a significant prolongation of DFS by adjuvant chemotherapy with gemcitabine over 6 months. However, this study has failed to demonstrate a significant prolongation of overall survival so far.

Meta-Analysis of Randomized Trials for Adjuvant Chemotherapy

Based on the selected trials identified by a systematic review of the literature, a meta-analysis was performed only for studies investigating adjuvant chemotherapy. Two meta-analyses have already been published on adjuvant CRT [15, 16]; the meta-analysis by Stocken et al. [15] also included randomized trials of adjuvant chemotherapy, however, their study did not contain the recently published CONKO-001 data (368 patients) [7].

Study-specific differences in 5-year survival rates between chemotherapy and control groups of trials included in the meta-analysis are shown in table 3a; only the ESPAC-1 study demonstrates a statistically significant improvement in 5-year survival in the chemotherapy group according to the 95% CI computed by our method. There is statistically significant heterogeneity among the results of the 5 analyzed studies ($p = 0.03$), with all other studies except the ESPAC-1 study showing no statistically significant difference between the chemotherapy and

Table 3. Meta-analysis for survival of randomized trials investigating adjuvant chemotherapy

a Study-specific differences in 5-year survival rates and 95% CI

Study	Difference (chemotherapy – control) in 5-year survival rate, %	95% CI, %
Bakkevold et al. [10]	–4.0	–10.9 to 2.9
Takada et al. [12]	–6.5	–17.4 to 4.4
Kosuge et al. [11]	11.5	–10.0 to 33.0
ESPAC-1 [14]	13.0	0.6 to 25.4
CONKO-001 [7]	11.0	–1.8 to 23.8
Meta-analysis[1]	3.1*	–4.6 to 10.8

b Study-specific differences in median survival times and 95% CI

Study	Difference (chemotherapy – control) in median survival times, months	95% CI months
Bakkevold et al. [10]	12.0	1.5 to 22.5
Takada et al. [12]	NA	NA
Kosuge et al. [11]	–3.3	–9.9 to 3.3
ESPAC-1 [14]	4.6	0.7 to 8.5
CONKO-001 [7]	1.9	–3.0 to 6.8
Meta-analysis[1]	3.0**	0.3 to 5.7

NA = Data not available. * $p > 0.05$; ** $p = 0.03$.
[1] Meta-analysis combined estimate.

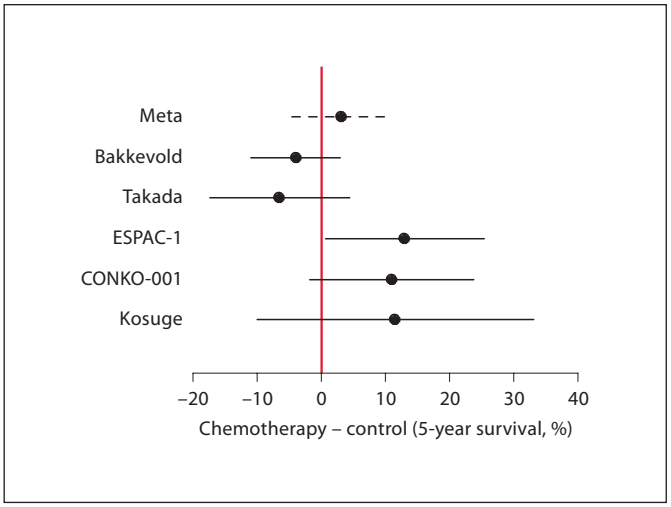

Fig. 1. Differences in 5-year survival rate between chemotherapy and control groups and CI among the 5 studies included in the meta-analysis. Studies are ordered by length of CI (uncertainty in estimates).

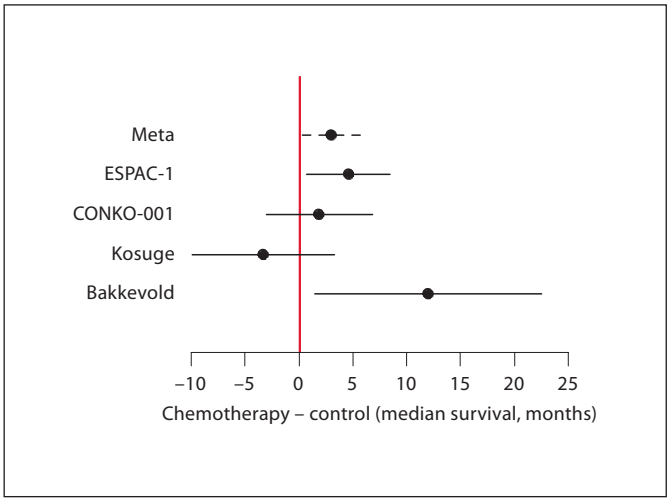

Fig. 2. Differences in median survival time between chemotherapy and control groups and CI among the 4 studies included in the meta-analysis. Studies are ordered by length of CI (uncertainty in estimates).

control groups. The combined meta-analysis estimate of a 5-year survival advantage of 3.1% in the chemotherapy group is also nonsignificant ($p > 0.05$). Figure 1 shows a funnel plot for the results of table 3a.

For comparison of median survival times between chemotherapy and control, 4 studies listed in table 3b provided information for a meta-analysis. There was no statistically significant heterogeneity among the 4 studies ($p = 0.07$). The Bakkevold and ESPAC studies showed a significant improvement in median survival in the chemotherapy arms and the CONKO-001 and Kosuge studies showed no significant difference in median survival between the 2 arms. A combined fixed effects meta-analysis indicated a statistically significant median survival extension on chemotherapy of 3 months (95% CI 0.3–5.7 months, $p = 0.03$). Results from table 3b are displayed by a funnel plot in figure 2.

We additionally assessed whether results for treatment differences in 5-year survival rates or median survival times depended on the total number of patients randomized to the study or the year of publication of the study (fig. 3). Studies published in the later years tended to have larger improvements on the chemotherapy arm in terms of 5-year survival rates but smaller improvements in median survival times. As the number of studies is small (5 and 4), it is not possible to draw definitive conclusions on these trends.

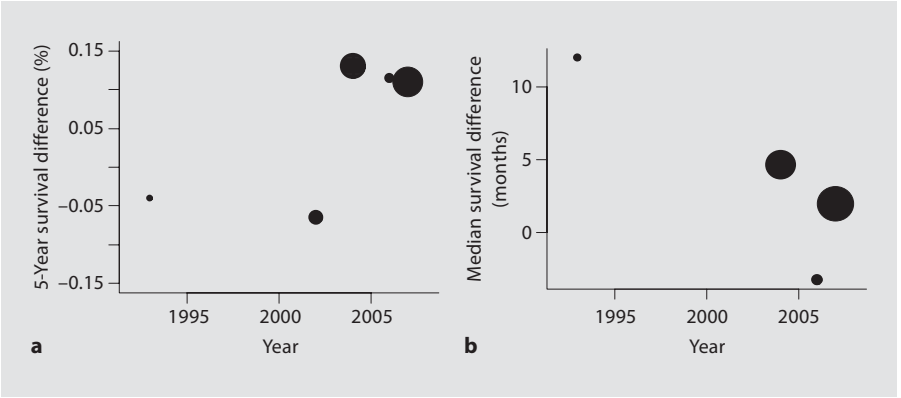

Fig. 3. Five-year survival difference (**a**) and median survival difference (**b**; chemotherapy – control) by year of publication with size of dots proportional to number of patients randomized to study. Included trials: Bakkevold et al. [10], 1993 (n = 61); Takada et al. [12], 2002 (n = 158); ESPAC-1 [14], 2004 (n = 289); Kosuge et al. [11], 2006 (n = 89); CONKO-001 [7], 2007 (n = 354).

Discussion

The currently available data from randomized trials indicate that adjuvant chemotherapy may prolong DFS and even median overall survival. This observation is also underlined by our meta-analysis of 5 randomized trials that showed a significant prolongation of median survival with the use of adjuvant chemotherapy. However, the 5-year survival rate in the meta-analysis did not show a statistically significant benefit of adjuvant chemotherapy, possibly also caused by the low number of patients (number at risk) for this endpoint in each trial. Notably, most trials showing a benefit from adjuvant chemotherapy investigated a treatment duration of about 5–6 months. By contrast, the trial reported by Kosuge et al. [11] used a shorter treatment duration (2–4 months) and failed to show an improvement in median survival compared to the observational arm. Considering that most recurrences occur within the first 2 years after surgery, there may be a good rationale to investigate prolonged adjuvant therapy in this highly malignant disease.

Both recently published European trials were able to show a statistically significant and clinically meaningful benefit for DFS (CONKO-001) and time to disease recurrence (ESPAC-1) with the use of adjuvant chemotherapy. In both studies, the median gain for these endpoints was about 6 months, which is equivalent to the duration of adjuvant chemotherapy. However, the observed advantage for DFS and time to disease recurrence translated into a significant overall survival benefit only in the ESPAC-1, but not the CONKO-001 study [7, 14]. Thus, the question arises which reasons may be defined for these divergent observations: one major confounding factor that may influence survival results of adjuvant trials is the treatment patients received upon relapse. Palliative chemotherapy is known to provide a significant survival benefit in patients with advanced pancreatic cancer [17]. None of the 2 studies, however, reported data on the treatment that was applied to the study patients upon disease recurrence. Furthermore, the ESPAC-1 trial recruited patients between 1994 and 2000; thus, it is conceivable that a major part of patients did not have access to palliative therapy with gemcitabine, the current standard of care (introduced in 1997) in the palliative setting. Therefore, it may be argued that an early adjuvant chemotherapy has a comparable effect on overall survival as an identical late palliative chemotherapy (for example with single-agent gemcitabine), specifically when an effective second-line therapy is not defined [7].

One main goal for adjuvant treatment strategies is to increase the number of patients that can be cured after surgery for different types of cancer (for example breast and colorectal cancer). Should this also be a (realistic) goal for patients with resected pancreatic cancer? This cancer is thought to show a systemic spread very early in the course of disease, and the majority of patients experience relapse by developing distant metastasis soon after curative-intent surgery. Induction of a long-term survival or even cure may be reflected by the 5-year survival rate of an adjuvant trial. However, the available data from randomized trials do not provide a clear and consistent superiority for this endpoint for patients with pancreatic cancer receiving adjuvant chemotherapy (table 1). Even in studies that show a significant prolongation of median survival, the 5-year survival rate may be comparable [10]. This observation is also underlined by the findings of our meta-analysis (table 3).

The role of CRT still remains controversial in pancreatic cancer. To date, 4 randomized trials have been performed in the adjuvant setting [14, 18–21]. The basis for

adjuvant CRT was set in the 1980s when the GITSG performed a small randomized trial showing that adjuvant CRT (5-FU-based split course external beam radiation therapy followed by a once-weekly bolus 5-FU maintenance chemotherapy for 2 years) was more effective than observation, inducing an overall survival of 20 versus 11 months [18, 19]. However, it still remains unclear to which extent CRT alone or the additional maintenance chemotherapy with 5-FU were responsible for the observed effect. While the ESPAC-1 study did not show a survival benefit for adjuvant CRT, the results from the RTOG 9704 trial indicate that gemcitabine is superior to continuous infusion of 5-FU in a combined modality approach where chemotherapy was applied before and after adjuvant 5-FU-based CRT in patients with cancers of the pancreatic head only [21]. The RTOG 9704 clearly was not designed to answer the question of the importance of CRT in adjuvant therapy. Furthermore, 2 previously published meta-analyses also did not show any consistent benefit for adjuvant CRT [15, 16]. Thus, only well-designed randomized studies using modern CRT regimens (including intensified modulation radiotherapy, 5-FU as continuous infusion or gemcitabine, and even targeted agents) will be able to better define the role of radiation treatment in the adjuvant setting [22–25].

Selection of different treatment strategies according to prognostic factors plays an important role in many different types of cancer. So far, clinical trials for pancreatic cancer performed in the adjuvant setting have not yet provided a sufficient database to support risk-adapted treatment recommendations. Recently published data suggest the serum tumor marker CA 19-9 could aid in establishing different risk-adapted treatment strategies after surgical resection of pancreatic cancer [26–28]. Additionally, it still remains unclear if different subgroups of patients (for example R0/R1 resected patients, patients with or without nodal involvement) should be regarded as different entities for adjuvant treatment options.

Especially for patients after R1 resection, the role of either adjuvant CRT or chemotherapy remains controversial. As local control may be an important clinical goal for R1 resected patients, one might consider adjuvant CRT as a treatment of choice [23]. However, based on data from randomized trials, no evidence-based recommendation can be given for treatment decisions in this patient population. In subgroup analyses performed in patients after R1 resection in the ESPAC-1 study (n = 101), there were no significant survival differences comparing adjuvant CRT versus no CRT or chemotherapy versus no chemotherapy [14, 29]. R1-resected patients included in the CONKO-001 trial (n = 61) experienced a prolongation in DFS ($p < 0.001$) and overall survival ($p = 0.07$) when treated with gemcitabine compared to observation only (table 2) [7]. However, the nearly identical DFS and overall survival for R0 and R1 resected patients receiving adjuvant gemcitabine within the CONKO-001 study represent a quite unexpected observation (table 2). One possible explanation could be the fact that there was no standardization of pathological examination and reporting in this multicenter study. Furthermore, the resection status (R0 vs. R1) is also known as a factor difficult to assess, especially for the posterior (retroperitoneal) margin [30]. Thus, the presently available data from the ESPAC-1 and CONKO-001 trials only reflect post hoc subgroup analyses performed in small patient groups. These data can only be regarded as hypothesis generating and definitive recommendations can therefore not be expected. Nevertheless, further investigation of these arising questions in prospective clinical trials is strongly recommended.

In conclusion, several randomized trials – as well as our meta-analysis – support the benefit from adjuvant chemotherapy with either 5-FU/folinic acid or gemcitabine as the treatment of choice after resection of pancreatic cancer. While adjuvant chemotherapy clearly improves DFS, its effect on long-term survival still has to be verified. The currently available data do not allow a definitive conclusion on the importance of modern CRT in the adjuvant treatment of pancreatic cancer.

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