Cancer Chemother Pharmacol (2009) 64:1253–1259
DOI 10.1007/s00280-009-0995-8

ORIGINAL ARTICLE

Outcome of upfront combination chemotherapy followed by chemoradiation for locally advanced pancreatic adenocarcinoma

Michele Reni · S. Cereda · G. Balzano · P. Passoni · A. Rognone · A. Zerbi · R. Nicoletti · E. Mazza · P. G. Arcidiacono · V. Di Carlo · E. Villa

Received: 12 January 2009 / Accepted: 18 March 2009 / Published online: 21 April 2009

Abstract
Purpose The role and timing of chemotherapy and radiation for treating stage III pancreatic adenocarcinoma remains controversial.
Methods Treatment-naive patients with stage III non-resectable pancreatic adenocarcinoma were treated with PEFG/PEXG (cisplatin, epirubicin, 5-fluorouracil (F)/capecitabine (X), gemcitabine) or PDXG (docetaxel substituting epirubicin) regimen for 6 months followed by radiotherapy (50–60 Gy) with concurrent F or X or G.
Results Ninety-one patients were registered between April 1997 and December 2007. Forty-three patients (47%) had a partial remission and 38 (42%) had a stable disease. Thirteen patients (14%) were radically resected yielding one pathologic complete remission. Median survival (OS) was 16.2 months. Median progression-free survival was 9.9 months. Pattern of failure consisted of isolated local failure ($N = 26$, 35%); both local and systemic failure ($N = 14$, 19%); isolated systemic failure ($N = 35$, 47%).
Conclusion Combination chemotherapy with four-drug regimens followed by chemoradiation was a feasible strategy showing relevant results in stage III pancreatic adenocarcinoma.

Keywords Locally advanced pancreatic cancer · Chemotherapy · Stage III pancreatic cancer · Radiotherapy · Pancreatic cancer

M. Reni (✉) · S. Cereda · A. Rognone · E. Mazza · E. Villa
Department of Oncology, S. Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy
e-mail: reni.michele@hsr.it

G. Balzano · A. Zerbi · V. Di Carlo
Department of Surgery, S. Raffaele Scientific Institute, Milan, Italy

P. Passoni
Department of Radiotherapy, S. Raffaele Scientific Institute, Milan, Italy

R. Nicoletti
Department of Radiology, S. Raffaele Scientific Institute, Milan, Italy

P. G. Arcidiacono
Department of Gastroenterology, S. Raffaele Scientific Institute, Milan, Italy

Introduction

Pancreatic cancer is the fourth leading cause of cancer mortality in the Western world and, despite advances in our understanding of the molecular and genetic basis of pancreatic cancer and numerous phase III trials performed in the past decade, little improvement in outcome has been achieved. Complete surgical resection is considered the only therapy associated with a chance of cure. Even in this favorable prognostic group, 5-year survival is around 20% [1, 2].

Furthermore, 80–85% of patients have inoperable disease at the time of diagnosis. Among these patients, approximately one-third present with locally advanced disease and no evidence of distant metastases (stage III) [3]. As in the case of stage IV disease, patients with localized but unresectable disease are thought to be incurable with existing treatments and are commonly enrolled in phase III trials together with patients with metastatic disease. However, this choice may be disputable given the different natural histories and prognoses of metastatic compared with locally advanced stages.

The optimal therapeutic management of stage III pancreatic carcinoma is debated mainly because of the limited

number of stage-specific phase III trials, and of the controversy concerning the role and timing of chemotherapy and radiation. Chemoradiation has been shown to be superior to radiotherapy alone [4, 5]. Conversely, the results of four phase III trials comparing chemoradiation to chemotherapy are conflicting, as one trial showed no differences between arms [6], two trials suggested the superiority of combined treatment with 5-fluorouracil and gemcitabine, respectively, over chemotherapy with an SMF regimen (streptozotocin, mitomycin-C and 5-fluorouracil) [7] or with single agent gemcitabine [8] while the fourth showed better results with single agent gemcitabine when compared with chemoradiation [9]. All these trials were prematurely completed due to poor accrual and included a limited number of patients (43, 74, 91 and 119, respectively). Accordingly, definitive conclusions are difficult to draw. Similarly, a recent meta-analysis showed a survival benefit for chemoradiation over radiotherapy alone while demonstrating no survival advantage for chemoradiation followed by chemotherapy over chemotherapy alone [10]. The limited number of patients determined wide confidence intervals and did not allow the exclusion of important clinical differences, or the performance of other comparisons [10]. In this context, the retrospective exploratory analysis of prospectively collected data may generate attractive hypotheses for future trials. A retrospective analysis of patients with locally advanced pancreatic cancer enrolled between 2000 and 2005 in prospective phase II and III of the French Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) studies suggested that chemoradiation in patients whose disease had not progressed for at least 3 months during upfront chemotherapy may improve survival as compared to continuation of the same chemotherapy [11].

Induction chemotherapy followed by consolidation chemoradiation for patients without disease progression during chemotherapy was the therapeutic strategy utilized for patients with stage III disease in the context of five consecutive trials assessing four-drug combinations in advanced disease conducted at our Institution between April 1997 and January 2007 [12–16], and in the routine clinical practice afterward and until December 2007. Findings of retrospective analysis of prospectively collected data are reported.

Materials and methods

All chemonaive patients with cytologically or histologically proven stage III [3] adenocarcinoma of the pancreas treated with four-drug combinations at our Institution between April 1997 and December 2007 were considered eligible for this analysis.

In order to determine resectability, all patients underwent a three-phase, high-resolution total body CT scan and endoscopic ultrasound and were assessed by experienced pancreas-dedicated radiologist, surgeon and gastroenterologist. Tumors were considered unresectable in the presence of thrombosis or encasement >180° or longitudinal involvement >2 cm of one of the major peripancreatic vessels, with the exception of splenic vessels. Patients with extension to regional nodes without vascular involvement were considered resectable. Pre-treatment laparoscopy was not included in staging work-up. Patients with Vater's ampulloma or adenocarcinoma of the biliary tract were not eligible. Patients ≤75 years, Karnofsky performance status (PS) >60, measurable disease, adequate bone marrow (absolute neutrophil count ≥1,500 cells/mm^3, platelet count ≥100,000 cells/mm^3 and hemoglobin ≥10 g/dl), kidney (serum creatinine ≤1.5 mg/dL) and liver function [serum total bilirubin ≤1.5 mg/dL and serum transaminases ≤3 upper limit of laboratory normal (ULN)] were treated with four similar four-drug schemes.

The different schemes, reported in Table 1, were derived from the former PEFG combination [12, 13] with the aim of improving tolerability, manageability and patient compliance [14–16], and consisted of (1) a PEFG regimen (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in a phase II [12] and in a phase III trial [13]; (2) a modified PEFG regimen in a dose-finding [14] and in an observational study [15]; (3) a PEXG (cisplatin, epirubicin, capecitabine, gemcitabine) or PDXG regimen (cisplatin, docetaxel, capecitabine, gemcitabine) in a randomized phase II trial [16]; (4) a PEXG or PDXG regimen in the routine clinical practice. In all cases, cycles were repeated every 4 weeks.

Assessment of disease, including CA19.9 measure and three-phase, high-resolution total body CT scan of the abdomen and chest, was made at baseline, every 8 weeks

Table 1 Chemotherapy regimens

	PEFG	PEFGm	PEXG	PDXG
Cisplatin	40 mg/m^2 day 1	30 mg/m^2 day 1, 15	30 mg/m^2 day 1, 15	30 mg/m^2 day 1, 15
Epirubicin	40 mg/m^2 day 1	30 mg/m^2 day 1, 15	30 mg/m^2 day 1, 15	25 mg/m^2 day 1, 15
Gemcitabine	600 mg/m^2 day 1, 8	800 mg/m^2 day 1, 15	800 mg/m^2 day 1, 15	800 mg/m^2 day 1, 15
5-Fluorouracil	200 mg/m^2/day days 1–28	200 mg/m^2/day days 1–28	n.a.	n.a.
Capecitabine	n.a.	n.a.	625 mg/m^2 bid days 1–28	625 mg/m^2 bid days 1–28

m modified, *n.a.* not applicable

during chemotherapy and subsequently every 3 months or when progression (PD) was clinically suspected. Complete blood, platelet and differential counts were carried out every 2 weeks, while a biochemistry profile was performed on a monthly basis.

Patients without PD after a maximum of six cycles of induction chemotherapy received radiation with concurrent fluorouracil (250 mg/m^2/day), capecitabine (1250 mg/m^2/day) or gemcitabine (150–200 mg/m^2/week). Irradiation was performed with beams from 6 to 18 MV delivering daily fractions of 200 cGy to a total dose of 50–60 Gy in 25–30 fractions using CT-based, three-dimensional conformal radiation planning techniques. The planning target volume included the tumor mass and peripancreatic lymph nodes with a 1- to 2-cm margin. The kidneys, liver and spinal cord were contoured during the planning process and dose-volume histograms were used to ensure that normal tissue tolerances were not exceeded. No more than 50% of the liver received >30 Gy; no more that 50% of the combined renal volumes received >20 Gy, and the spinal cord received no more than 45 Gy.

Patients who became amenable to resection after the end of chemotherapy or after the end of radiotherapy were submitted to surgery with radical intent.

Toxicity was graded according to the NCI-CTC [17]. Anti-tumor treatment effects were registered using the RECIST response criteria [18]. PFS was calculated as the interval between the initiation of treatment and the occurrence of progressive disease (PD) or death, and survival was measured from initiation of treatment to date of death or to the last follow-up assessment.

Statistical analysis

As this was a retrospective analysis of prospectively collected data, no statistical design was performed. At univariate analyses, survival curves were estimated with the Kaplan–Meier method and compared by means of the log-rank test. All probability values were from two-sided tests. Analyses were performed with the Statistica 4.0 statistical package for Microsoft Windows.

Results

Overall treatment outcome

Between April 1997 and December 2007, 91 patients were treated. Patient characteristics are summarized in Table 2. Basal CA 19.9 was detected in 90 of 91 patients (99%) and was above the ULN in 75 patients (83%). Details on chemotherapy/chemoradiation efficacy and toxicity are reported below. Chemotherapy was administered to all patients; 11 patients (12%) underwent surgical resection after chemotherapy.

Table 2 Patient characteristics at baseline

Characteristic	Total	PEFG	PEFGm	PEXG	PDXG
Patients	91	27	28	20	16
Median age	62	62	65	61	64
Gender					
Male	52 (57)	14 (52)	17 (61)	13 (65)	8 (50)
Female	39 (43)	13 (48)	11 (39)	7 (35)	8 (50)
ECOG PS					
0	41 (45)	7 (26)	8 (29)	15 (75)	11 (69)
1	47 (52)	18 (67)	19 (68)	5 (25)	5 (31)
2	3 (3)	2 (7)	1 (3)	0 (0)	0 (0)

P cisplatin, *E* epirubicin, *F* 5-Fluorouracil, *G* gemcitabine, *X* capecitabine, *D* docetaxel, *m* modified, *PS* performance status

Sixty-two patients (68%) received planned chemoradiation, which was administered after surgery in eight patients. Reasons for not administering chemoradiation were: PD ($N = 21$), refusal ($N = 5$), pathologic complete remission ($N = 1$), surgical mortality ($N = 1$) and intercurrent disease ($N = 1$). Two more patients were radically resected after chemoradiation, accounting overall for 13 patients (14%) downstaged by the treatment.

At the time of report, seven patients were progression-free and four died while progression-free.

Among 80 patients with PD, pattern of failure was known in 75 patients (94%) and consisted of isolated local failure in 26 cases (35%), both local and systemic failure in 14 patients (19%) and isolated systemic failure in 35 patients (47%).

Median progression-free (PF) survival was 9.9 months and 6-month PFS was 74.7%. Median survival (OS) of the whole group was 16.2 months; actuarial 2y and 5y OS was 22 and 4%, respectively (Fig. 1). Nine patients are alive after a median follow-up of 26.6 months (range 17.0–32.0 months).

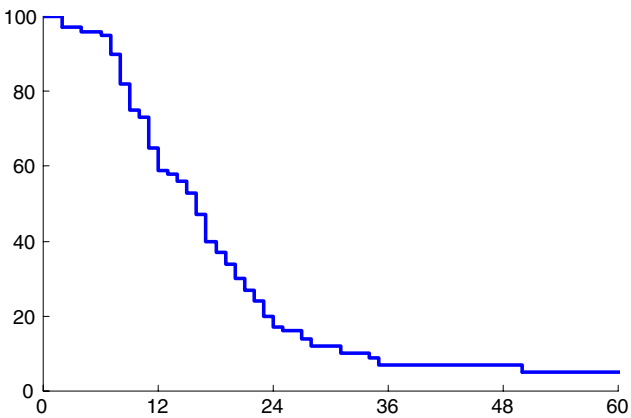

Fig. 1 Overall survival

Outcome of chemotherapy

Table 3 summarizes the main side effects observed.

Best response to chemotherapy was partial remission in 43 patients (47%) and stable disease in 38 (42%) (Table 4). At least one CA19-9 follow-up value was available for 72 of 75 patients (96%) with baseline value >1.0 ULN. According to the definition reported by Reni et al. [19], a major biochemical response (CA19.9 decrease >89%) was observed in 29 patients (40%) and a minor biochemical response (CA19.9 decrease between 50 and 89%) in 25 patients (35%). At time of first assessment, 10 patients (11%) had radiological PD ($N = 8$) or clinical deterioration ($N = 2$). Eleven further patients with initial SD ($N = 9$) or PR ($N = 2$) had PD before induction chemotherapy conclusion. Among 21 patients who did not receive chemoradiation due to PD before chemotherapy conclusion, the site of failure was known in 18, and included a systemic component in 13 cases (72%) and a local component in 11 cases (61%). Isolated local failure was observed in five cases, representing 5.5% of enrolled patients. Survival and PFS data based on chemotherapy regimen are summarized in Table 4.

Table 3 Grade 3–4 treatment-related toxicity per cycle

	PEFG	PEFGm	PEXG	PDXG
Number of cycles	128	129	111	77
Neutropenia	75 (59%)	18 (14%)	15 (14%)	2 (3%)
Platelets	42 (33%)	1 (1%)	1 (1%)	6 (8%)
Hemoglobin	6 (5%)	5 (4%)	7 (6%)	3 (4%)
Stomatitis	5 (4%)	2 (2%)	0 (0%)	0 (0%)
Nausea/vomiting	3 (2%)	3 (2%)	0 (0%)	1 (1%)
Diarrhea	1 (1%)	2 (2%)	1 (1%)	3 (4%)
Fatigue	0 (0%)	1 (1%)	4 (4%)	4 (5%)
Hand–foot syndrome	1 (1%)	1 (1%)	2 (2%)	0 (0%)

Table 4 Activity and efficacy analyses summary

Outcome measure	Total	PEFG	PEFGm	PEXG	PDXG
Best response during the treatment					
Partial response	43 (47)	14 (52)	12 (43)	9 (45)	8 (50)
Stable disease	38 (42)	11 (41)	13 (46)	9 (45)	5 (31)
Progressive disease	10 (11)	2 (7)	3 (11)	2 (10)	3 (19)
Progression-free survival (PFS)					
Median PFS	9.9	10.4	10.5	7.7	8.8
6-month PFS (%)	74.7	74.1	82.1	65.0	62.5
Overall survival (OS)					
Median OS	15.1+	14.1	16.2	12.7+	16.8

Among 43 partial responders to chemotherapy, median PFS was 11.1 months and 1y PFS was 42.2%; median OS was 17.0 months and 2y OS was 28.3%.

Among 38 patients with stable disease, median PFS was 9.3 months and 1y PFS was 40.9%; median OS was 12.2 months and 2y OS was 19%.

The difference in PFS and OS between patients with partial response and those with stable disease was statistically significant ($p = 0.04$ and 0.009, respectively).

Among 10 patients with PD, median PFS was 2.2 months and 1y PFS 0%; median OS was 6.5 months and 2y OS 0%.

Outcome of chemoradiation

Sixty-two patients received planned chemoradiation. External beam radiotherapy was administered with a median dose of 54 Gy (range 48–60 Gy). Concomitant chemotherapy consisted of either 5-fluorouracil ($N = 26$), capecitabine ($N = 19$) or gemcitabine ($N = 17$). Main G3-4 toxicity consisted of neutropenia (7%), thrombocytopenia (2%), anemia (5%) and mucositis (5%) among patients treated with concomitant fluoropyrimidine and of neutropenia (15%), thrombocytopenia (8%) and anemia (8%) among patients treated with concomitant gemcitabine.

Among 52 patients who received planned chemoradiation without surgery, the site of PD was unknown in 2 cases, 4 were progression-free, 2 died without PD, 15 had isolated local failure, 6 had both local and systemic failure and 23 systemic PD only. Thus, local PD was observed in 21 of 50 patients (42%) for whom the pattern of failure was known. All five patients who refused chemoradiation had PD that consisted of local failure in four cases (80%; including one patient with both local and distant failure) and of systemic PD in two cases (40%).

Patients undergoing resection

Overall, 13 patients underwent surgical resection. No margin involvement (R0) was observed in 9 patients, microscopic involvement (R1) in 3 patients, macroscopic residue (R2) in 1 patient. Nodal involvement was observed in five patients. yT0, yT2 and yT3 were reported in 1, 2 and 10 cases, respectively. One patient died due to surgical complications, one died while progression-free and one is alive and progression-free. Isolated local recurrence was observed in four cases; one patient had both local and distant recurrence and five had isolated distant failure. The 13 patients who were submitted to surgery had longer PFS than 30 partial responders who remained not amenable to resection (median PFS 13.0 vs. 10.5; 1y PFS 61.5 vs. 36.9%; $p = 0.027$) and lived longer (median OS 28.5 + vs. 17.5; 2y OS 68.4 vs. 11.1%; $p = 0.001$). Actuarial 5-year OS was 13.7%.

Discussion

The aim of the current analysis was to explore the tolerability, the activity and the pattern of failure of a strategy including induction chemotherapy with a four-drug regimen followed by chemoradiation in patients with stage III pancreatic adenocarcinoma. On the whole, treatment was well tolerated with acceptable toxicity. While the comparison of results across trials is problematic, the survival figures (median survival 16.2 months; 2-year OS 22%) observed in the present series appear promising. In fact, in previously reported series, the anticipated median and 2-year survival with chemoradiation or systemic chemotherapy with single agent or gemcitabine-based doublets was in the range of 8–14 months and of 11–21%, respectively [8–10, 20–26].

The possibility that the current results were related only to selection bias is low. In fact, this was among the largest series reported and baseline patient characteristics were in the range of the literature; the definition of locally advanced disease was rigorous and only stage III patients were included, while in previous trials, due to the eligibility of patients with extension to regional nodes without vascular involvement, the inclusion of patients with stage II, and the consequent risk of an overestimation of the outcome, cannot always be ruled out. The estimation of resectability was performed by an experienced team of pancreas-dedicated surgeons, radiologists and gastroenterologists at a single very high-volume institution [27]. This issue is also of paramount importance as resectability is dependent on the experience, confidence and motivation of the surgical team making the assessment. For example, surgeons at Johns Hopkins were able to resect disease in two-thirds of patients assessed as unsuitable for surgery elsewhere [28]. Accordingly, the lack of a central surgical resectability assessment in multicentre series may raise some concerns about the homogeneity of locally advanced disease definition, which is not the case for a single institution series.

Chemoradiation has long been regarded as the mainstay therapy for patients with locally advanced disease. However, systemic failure affected two-thirds of patients in the present series. This datum is consistent with prior observations which reported distant recurrence in 72–74% of cases [20–22]. Therefore, the presence of micrometastatic disease determines the prognosis and remains the main unresolved and pressing issue in stage III pancreatic adenocarcinoma. Systemic chemotherapy appears to be the most logical remedy because it may serve to eradicate micrometastatic disease and to select a subgroup of patients without early metastatic course who are most likely to benefit from locoregional therapy. Furthermore, induction chemotherapy may increase the probability of responding to subsequent chemoradiation by reducing the bulk of disease. It is noteworthy that four-drug regimens did not seem to increase toxicity or reduce the ability to administer the planned chemoradiation regimen, which was completed in 68% of patients compared with some 50–74% in other series [20–22, 25, 26]. The deferral of local treatment did not seem to jeopardize local disease control because only 23% of patients had PD during induction chemotherapy and as many as 72% had metastatic failure, while isolated local failure during this time interval was rare, involving only 5 of 91 initial patients (5.5%). Isolated local failure during induction chemotherapy was rare also in previous reported series (4%) [21]. Conversely, PD during induction chemotherapy occurred in 57% of patients treated with gemcitabine [22], in 19–32% of patients treated with gemcitabine plus cisplatin [21, 25] and in 12% of patients treated with gemcitabine plus oxaliplatin [26]. Chemotherapy regimens with an elevated rate of objective response may allow downstaging of the tumor and the possibility of rescue a number of patients to surgery with radical intent. Actuarial 5-year OS of 13 patients submitted to radical surgery in the present series was 13.7%, which was close to survival figures for patients with stage I–II disease. A further interesting finding of this study was that combination chemotherapy yielded disease control in 89% of patients (47% partial response and 42% stable disease). These promising results suggest that the four-drug chemotherapy may warrant further investigation in the neoadjuvant setting in resectable patients.

Chemoradiation may maintain a role for improving long-term survival after systemic chemotherapy, as previously suggested [10]. This issue is currently being addressed by an ongoing randomized phase III trial conducted by the GERCOR and Arbeitsgemeinschaft Internisttische Onkologie (AIO) groups [10]. Data from the present study showed good tolerability of chemoradiation, whereas it was difficult to assess the contribution of chemoradiation to local control. Despite the use of modern chemoradiation, including new imaging techniques, modern irradiation planning, elevated dosage and adequate concomitant radiosensitizing chemotherapy, local progression affected 42% of patients receiving chemoradiation without surgery and represented the single site of progression in 30% of cases. These findings were consistent with other series of patients treated by chemoradiation, chemotherapy or induction chemotherapy followed by chemoradiation, in which local failure and isolated local failure were observed in 32–57% and in 22–23% of cases, respectively [8, 20–22]. While local control remains another unresolved issue, these figures were double (80 and 60%, respectively) in five patients refusing treatment as compared to patients accepting treatment, providing a clue in favor of chemoradiation consolidation. Chemoradiation after systemic chemotherapy may also have a role for rescuing further patients to surgery (2% in the current series).

In conclusion, upfront combination chemotherapy seems the correct approach to locally advanced pancreatic adenocarcinoma, whereas the role of chemoradiation is still to be fully delineated. The results of the current analysis confirm the opportunity to perform prospective assessment of therapeutic strategies in stage III pancreatic cancer separately from stage IV disease, and strengthen the rationale for further development of sequential strategies including more active systemic and local treatment in the attempt to obtain an impact on the natural history of pancreatic adenocarcinoma. The possibility to identify prognostic factors allowing to distinguish patients more likely to experience local or systemic failure should be addressed as well.

References

1. Neoptolemos JP, Stocken DD, Friess H et al (2004) A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med 350:1200–1210
2. Oettle H, Post S, Neuhaus P et al (2007) Adjuvant chemotherapy with Gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer. A randomized controlled trial. JAMA 297:267–277
3. Sobin LH, Wittekind CH (eds) (2002) Exocrine pancreas. In: AJCC cancer staging manual, 6th edn. Springer, New York, p 157
4. Moertel C, Childs D, Reitmeier R, Colby MY Jr, Holbrook MA (1969) Combined 5FU and supervoltage RT for locally unresectable GI cancer. Lancet 2:865–867
5. Moertel CG, Frytak S, Hahn RG et al (1981) Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. Cancer 48:1705–1710
6. Klaassen DJ, MacIntyre JM, Catton GE et al (1985) Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—An Eastern Cooperative Oncology Group study. J Clin Oncol 3:373–378
7. Gastrointestinal Tumor Study Group (1988) Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst 80:751–755
8. Loehrer PJ Sr, Powell ME, Cardenes HR, Wagner L, Brell M, Ramanathan RK, Crane CH, Alberts SR, Benson III AB (2008) A randomised phase III study of gemcitabine in combination with radiation therapy versus gemcitabine alone in patients with localized, unresectable pancreatic cancer:E4201. Proc Am Soc Clin Oncol 26, OP 4506
9. Chauffert B, Mornex F, Bonnetain F et al (2008) Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000_01 FFCD/SFRO study. Ann Oncol 19(9):1592–1599
10. Sultana A, Tudur Smith C, Cunningham D, Starling N, Tait D, Neoptolemos JP, Ghaneh P (2007) Systematic review, including meta-analyses, on the management of locally advanced pancreatic cancer using radiation/combined modality therapy. Br J Cancer 96(8):1183–1190
11. Huguet F, Andre′ T, Hammel P et al (2007) Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR Phase II and III Studies. J Clin Oncol 20:326–331
12. Reni M, Passoni P, Panucci MG, Nicoletti R, Galli L, Balzano G, Zerbi A, Di Carlo V, Villa E (2001) Definitive results of a phase ii trial of PEF-G (cisplatin, epirubicin, 5-fluorouracil continuous infusion, gemcitabine) in stage IV pancreatic adenocarcinoma. J Clin Oncol 19:2679–2686
13. Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E, Di Carlo V (2005) Gemcitabine versus cisplatin, epirubicin, 5-fluorouracil, gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. Lancet Oncol 6:369–376
14. Reni M, Cereda S, Bonetto E et al (2007) Dose-intense PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in advanced pancreatic adenocarcinoma: a dose-finding study. Cancer Invest 25:594–598
15. Reni M, Cereda S, Bonetto E, Viganò MG, Passoni P, Zerbi A, Balzano G, Nicoletti R, Staudacher C, Di Carlo V (2007) Dose-intense PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in advanced pancreatic adenocarcinoma. Cancer Chemother Pharmacol 59:361–367
16. Reni M, Cereda S, Passoni P, Rognone A, Mazza E, Nicoletti R, Arcidiacono P, Zerbi A, Balzano G, Di Carlo V (2007) A randomized phase II trial of PEXG (cisplatin, epirubicin, capecitabine, gemcitabine) or PDXG (docetaxel) regimen in advanced pancreatic adenocarcinoma. Proc Am Soc Clin Oncol 25 (abstract 4628)
17. Therasse P, Arbuck SG, Eisenhaur EA, Wanders J, Kaplan RS, Rubinstein L et al (2004) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 92(3):205–216
18. Ajani JA, Welch SR, Raber MN, Fields WS, Krakoff IH (1990) Comprehensive criteria for assessing therapy-induced toxicity. Cancer Invest 8:147–159
19. Reni M, Cereda S, Balzano G, Passoni P, Rognone A, Ceraulo D, Fugazza C, Mazza E, Zerbi A, Di Carlo V, Villa E (2009) Carbohydrate antigen (CA)19-9 change during chemotherapy for advanced pancreatic adenocarcinoma. Cancer (in press)
20. Haddock MG, Swaminathan R, Foster NR, Hauge MD, Martenson JA, Camoriano JK, Stella PJ, Tenglin RC, Schaefer PL, Moore DF Jr, Alberts SR (2007) Gemcitabine, cisplatin, and radiotherapy for patients with locally advanced pancreatic adenocarcinoma: results of the North Central Cancer Treatment Group Phase II Study N9942. J Clin Oncol 25(18):2567–2572
21. Ko AH, Quivey JM, Venook AP, Bergsland EK, Dito E, Schillinger B, Tempero MA (2007) A phase II study of fixed-dose rate gemcitabine plus low-dose cisplatin followed by consolidative chemoradiation for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 68(3):809–816
22. Brade A, Brierley J, Oza A, Gallinger S, Cummings B, Maclean M, Pond GR, Hedley D, Wong S, Townsley C, Brezden-Masley C, Moore M (2007) Concurrent gemcitabine and radiotherapy with and without neoadjuvant gemcitabine for locally advanced unresectable or resected pancreatic cancer: a phase I–II study. Int J Radiat Oncol Biol Phys 67(4):1027–1036
23. Magnino A, Gatti M, Massucco P, Sperti E, Faggiuolo R, Regge D, Capussotti L, Gabriele P, Aglietta M (2005) Phase II trial of primary radiation therapy and concurrent chemotherapy for patients with locally advanced pancreatic cancer. Oncology 68(4–6):493–499
24. Crane CH, Ellis LM, Abbruzzese JL, Amos C, Xiong HQ, Ho L, Evans DB, Tamm EP, Ng C, Pisters PWT, Charnsangavej C, Delclos ME, O'Reilly M, Lee JE, Wolff RA (2006) Phase I trial evaluating the safety of bevacizumab with concurrent radiotherapy

and capecitabine in locally advanced pancreatic cancer. J Clin Oncol 24:1145–1151
25. Marti JL, Hochster HS, Hiotis SP, Donahue B, Ryan T, Newman E (2008) Phase I/II trial of induction chemotherapy followed by concurrent chemoradiotherapy and surgery for locoregionally advanced pancreatic cancer. Ann Oncol 15(12):3521–3531
26. Moureau-Zabotto L, Phelip J-M, Afchain P, Mineur L, André T, Vendrely V, Lledo G, Dupuis O, Huguet F, Touboul E, Balosso J, Louvet C (2008) Concomitant administration of weekly oxaliplatin, fluorouracil continuous infusion, and radiotherapy after 2 months of gemcitabine and oxaliplatin induction in patients with locally advanced pancreatic cancer: a Groupe Coordinateur Multidisciplinaire en Oncologie phase II study. J Clin Oncol 26:1080–1085
27. Balzano G, Zerbi A, Capretti G, Rocchetti S, Capitanio V, Di Carlo V (2008) Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. Br J Surg 95:357–362
28. Sohn TA, Lillemoe KD, Cameron JL et al (1999) Reexploration for periampullary carcinoma: resectability, perioperative results, pathology, and long-term outcome. Ann Surg 229:393–400