Ann Surg Oncol (2015) 22:295–301
DOI 10.1245/s10434-014-3898-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

FOLFIRINOX for Locally Advanced Pancreatic Adenocarcinoma: Results of an AGEO Multicenter Prospective Observational Cohort

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ABSTRACT

Background. First-line treatment with FOLFIRINOX significantly increases overall survival (OS) in patients with metastatic pancreatic adenocarcinoma (PA) compared with gemcitabine. The aim of this observational cohort was to evaluate the tolerability and efficacy of this regimen in unresectable locally advanced PA (LAPA).

Patients and Methods. From February 2010 to February 2012, all consecutive patients from 11 French centers treated by FOLFIRINOX for a histologically proven LAPA were prospectively enrolled. Unresectability was defined independently by each center's multidisciplinary staff at diagnosis. Absence of metastatic disease was confirmed by chest-abdomen-pelvis computed tomography scan. FOLFIRINOX was delivered every 2 weeks as previously reported until progressive disease, major toxicity, or consolidation treatment by radiotherapy and/or surgery.

Results. Seventy-seven patients were enrolled. They received a median number of five cycles (1–30). Grade 3–4 toxicities were neutropenia (11 %), nausea (9 %), diarrhea (6 %), fatigue (6 %), and anemia (1 %). Grade 2–3 sensory neuropathy occurred in 25 % of patients. No toxic death was reported and only 6 % of patients had to stop treatment because of toxicity. Disease control rate was 84 with 28 % of objective response (Response Evaluation Criteria in Solid Tumors). Seventy-five percent of patients received a consolidation therapy: 70 % had radiotherapy and 36 % underwent a surgical resection, with a curative intent. Within the whole cohort, 1-year OS rate was 77 % (95 % CI 65–86) and 1-year progression-free survival rate was 59 % (95 % CI 46–70).

Conclusion. First-line FOLFIRINOX for LAPA seems to be effective and have a manageable toxicity profile. These promising results will have to be confirmed in a phase III randomized trial.

Pancreatic adenocarcinoma (PA) is a frequent and severe disease with an overall 5-year survival rate of approximately 6 %.[1–3] The only way to cure patients is radical surgical resection, but this is possible in less than

First Received: 27 March 2014;
Published Online: 19 July 2014

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20 % of cases, and only increases the 5-year survival rate to 10–27 %[4–6] according to the administration of adjuvant chemotherapy.

Locally advanced PA (LAPA) represents about 30 % of pancreatic cancer and its prognosis is half-way between that of metastatic and resectable pancreatic cancer. Its definition remains controversial because resectability criteria differ between centers. Its treatment consists of palliative chemotherapy, classically with gemcitabine similar with metastatic PA treatment.

The ACCORD-11/PRODIGE-4 trial,[7] a randomized, phase III trial, compared the FOLFIRINOX regimen with gemcitabine in metastatic PA. It showed a significant improvement of median overall survival (OS) and progression-free survival (PFS), as well as an increase in response rate. Increased toxicities were also reported with this three-drug chemotherapy regimen, but the general tolerability profile was acceptable. However, no cases of LAPA were treated in ACCORD-11/PRODIGE-4 and this aggressive treatment has not been evaluated in this category of patients. We therefore decided to evaluate the tolerability and efficacy of FOLFIRINOX in patients with LAPA, in an AGEO (Association des Gastro-Entérologues Oncologues) multicenter, prospective, observational series.

PATIENTS AND METHODS

Patients

Patients with LAPA treated with the FOLFIRINOX regimen as first-line therapy, between February 2010 and February 2012 in 11 French centers, were prospectively enrolled in our database. To be eligible, patients had to be 18 years of age or older, have an Eastern Cooperative Oncology Group performance status (ECOG-PS) score of 0, 1, or 2, and a histologically or cytologically proven PA which was non-metastatic but deemed unresectable during a multidisciplinary meeting with radiological and surgical expertise. Chest-abdomen-pelvis computed tomography (CT) scans were used to check for the absence of metastases. Unresectability criteria were determined by each institution's multidisciplinary staff and were, in all cases, arterial and/or major venous involvement (at least more than 180° tumor contact, encasement). Previous chemotherapy or radiotherapy for pancreatic cancer was an exclusion criterion. The demographic and clinical characteristics of patients were computerized. As FOLFIRINOX is considered a potential standard treatment for non-operable pancreatic cancer, with normal bilirubin levels and good performance status, in France, no informed consent was needed for this observational series, as stated by the Ethics Committee consulted prior to the start of the work.

Tumor

The following tumor-related information was collected: date of diagnosis, size of the tumor in millimeters, location of the tumor (head, body, or tail of the pancreas), absence or presence of locoregional lymph node involvement on CT scan, and unresectability criteria described as venous (superior mesenteric vein, portal vein, portal thrombosis) or arterial (superior mesenteric artery, celiac trunk) involvement. The presence of a biliary stent was noted. Initial evaluation included measurement of carbohydrate antigen 19–9 (CA 19–9).

Treatment

One cycle of FOLFIRINOX consisted of a 2-h intravenous infusion of oxaliplatin (85 mg/m^2) followed by a 2-h intravenous infusion of leucovorin (400 mg/m^2) concomitantly with a 90-min intravenous infusion of irinotecan (180 mg/m^2), followed by a bolus (400 mg/m^2) and a 46-h continuous infusion (2,400 mg/m^2) of 5-fluorouracil. The FOLFIRINOX regimen was delivered every 2 weeks until disease progression, patient refusal, unacceptable toxicity, or consolidation therapy by external radiotherapy and/or surgery. Primary prophylaxis of neutropenia using granulocyte colony-stimulating factor (G-CSF) was initiated at the physician's discretion.

Outcomes

Treatment Tolerability The day of the first infusion of FOLFIRINOX and the number of cycles performed were recorded. Treatment tolerability was assessed by recording all chemotherapy-related adverse events occurring during the study. Nausea and vomiting, diarrhea, fatigue, sensory neuropathy, hand–foot syndrome, mucositis, alopecia, neutropenia, thrombocytopenia, and anemia were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events V3.0.[8] Serious adverse events, including treatment-related deaths, grade 3 or 4 toxicities, toxic withdrawals, and dose reductions associated with adverse events, were noted.

Efficacy Disease assessment was performed every 2 months by means of chest-abdomen-pelvis CT scans and CA 19–9 monitoring. Radiological tumor response was defined according to the Response Evaluation Criteria in Solid Tumors (RECIST)[9] on CT scans. Tumor response was classified into four groups: complete response, partial response, stable disease, or progressive disease.

Consolidation therapy by surgical resection and/or external radiotherapy were recorded, together with the day, type of surgery (duodenopancreatectomy, splenopancreatectomy, or

TABLE 1 Characteristics of patients and tumors

	$N = 77$ (%)
Sex	
Male	46 (60)
Female	31 (40)
Age (years; median [range])	61 [37–79]
ECOG-PS	
0	31 (40)
1	45 (59)
2	1 (1)
Weight (kg; median [range])	68 [42–107]
Tumor location	
Head	50 (65)
Body	23 (30)
Tail	4 (5)
Tumor size (mm; median [range])	32 [25–69]
Node involvement	
Yes	42 (55)
No	35 (45)
Vascular invasion	
Arterial involvement	50 (65)
Venous involvement	51 (66)
Biliary stent	
Yes	36 (47)
No	41 (53)

ECOG-PS Eastern Cooperative Oncology Group performance status

total pancreatectomy), quality of the resection (R0 or R1), and the 30-day postoperative complications for patients who underwent surgical resection, and the dose of radiation administered for those who received radiotherapy. Local or metastatic relapse and death after consolidation therapy were recorded. In the case of progressive disease, if second-line chemotherapy was administered this was recorded.

Statistical Analysis

Patients' records were prospectively entered into the database. Quantitative data were described with the median (range), and qualitative data were described with the percentage. There was no statistical hypothesis. A χ^2 test was used to compare qualitative data such as resection rate among patients with or without arterial involvement.

Objective response was defined as patients with complete response or partial response. Disease control rate was defined as patients with complete response, partial response, or stable disease. PFS was defined as the time elapsed from the start of FOLFIRINOX chemotherapy until the date of progression or death (all causes), whichever occurred first. OS was defined as the time elapsed from the start of FOLFIRINOX chemotherapy until death (all causes). Patients without events were censored at the last follow-up date. Survival curves were estimated using the Kaplan–Meier method. Median follow-up was calculated with the reverse Kaplan–Meier method. All analyses were performed with a two-sided alpha type 1 error of 5 %.

TABLE 2 FOLFIRINOX toxicities [*n* (%)]

	Grade 1	Grade 2	Grade 3	Grade 4
Nausea and vomiting	21 (27)	12 (16)	7 (9)	0 (0)
Diarrhea	14 (18)	17 (22)	5 (6)	0 (0)
Fatigue	10 (13)	12 (16)	5 (6)	0 (0)
Sensory neuropathy	20 (26)	16 (21)	3 (4)	0 (0)
Hand–foot syndrome	1 (1)	0 (0)	0 (0)	0 (0)
Mucositis	3 (4)	1 (1)	0 (0)	0 (0)
Alopecia	3 (4)	6 (8)	0 (0)	0 (0)
Neutropenia	10 (13)	8 (10)	8 (10)	1 (1)
Thrombocytopenia	9 (12)	9 (12)	0 (0)	0 (0)
Anemia	22 (29)	4 (5)	1 (1)	0 (0)
Maximal toxicity	14 (18)	30 (39)	19 (25)	1 (1)

RESULTS

Characteristics of Patients and Tumors

Between February 2010 and February 2012, 77 patients were enrolled. Their baseline characteristics are summarized in Table 1. Most patients had a good performance status, ECOG-PS 0 or 1. Most tumors were located in the head of the pancreas and 36 patients (47 %) needed a biliary stent before starting chemotherapy. Fifty patients had arterial involvement (65 %), concomitantly with a venous involvement for half of them, and 26 patients (35 %) had no arterial involvement but a major venous involvement (>180°, encasement) which contraindicated surgical resection.

Tolerability

The median number of cycles administered was five (range 1–30). No toxic death occurred and only five patients (6 %) had to stop chemotherapy because of toxicity. Treatment was stopped for disease progression in 12 cases (16 %) and for consolidation therapy (radiotherapy or surgery) in 58 cases (75 %). Grade 3–4 toxicities occurred in 20 patients (26 %) and are described in Table 2. Grade 2–3 sensory neuropathy occurred in 19 patients (25 %). A dose reduction was necessary in 50 cases (65 %). The 5-fluorouracil bolus was stopped in 25 patients (32 %) because of cytopenia, oxaliplatin was stopped in 24 patients (31 %) after at least six cycles because of neurotoxicity, and the irinotecan dose was reduced in 22 patients

TABLE 3 Efficacy results

	N (%)	95 % CI
Response		
Complete response	0 (0)	
Partial response	22 (28)	18–39
Stable disease	43 (56)	44–67
Progressive disease	12 (16)	7–24
Median progression-free survival	13 months	11–19
Median overall survival	22 months	17–ND

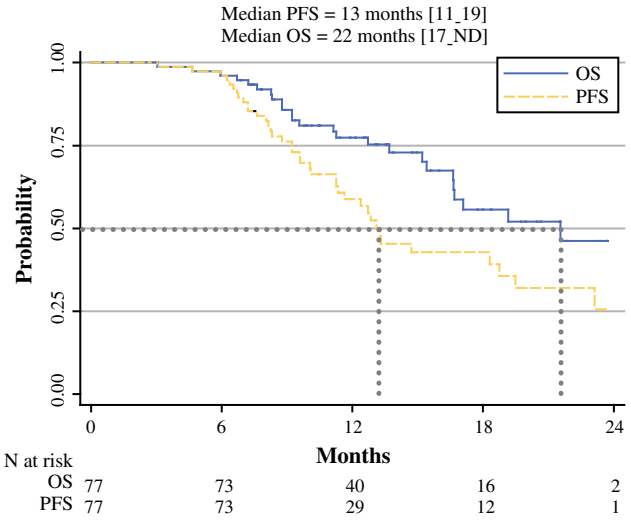

FIG. 1 Overall and progression-free survival. Median PFS = 13 months (11–19), median OS = 22 months [17–ND]. *OS* overall survival, *PFS* progression-free survival

(29 %). Prophylactic G-CSF treatment was used in 63 patients (82 %). Only 10 patients (13 %) lost more than 5 % of their total body weight and 11 patients (14 %) gained more than 5 %.

Efficacy

Survival and tumor response results are summarized in Table 3.

Response Partial response rate was observed in 22 patients (28 %) and stable disease in 43 patients (56 %), leading to a disease control rate of 84 % (95 % CI 76–93). Among the 60 patients with baseline CA 19.9 > 37 IU/mL, 38 (63 %) exhibited a significant decrease (>30 %) in plasma CA 19.9 level, and 21 (35 %) normalized their CA 19.9.

Moreover, 58 patients (75 %) could undergo post-chemotherapy consolidation therapy: 54 patients (70 %) received external radiotherapy with a median dose of 54 Gy (range 45–65 Gy) and 28 (36 %) had a pancreatic resection. Consolidation therapy was decided after the first tumor evaluation in 74 % of cases ($n = 43/58$).

Survival With a median follow-up of 15 months (range 3–31), median OS was 22 months, with an upper limit of the 95 % CI not reached. The OS rates at 6, 12, and 18 months were 96 % (95 % CI 88–99), 77 % (95 % CI 65–86), and 56 % (95 % CI 40–69), respectively. The PFS rates at 6, 12, and 18 months were 96 % (95 % CI 88–99), 59 % (95 % CI 46–70), and 43 % (95 % CI 29–56), respectively (Fig. 1).

Consolidation Therapy and Outcome Among the 12 patients with a progressive disease despite the FOLFIRINOX regimen, 11 (92 %) underwent second-line chemotherapy, all but one by gemcitabine. Among the 28 patients who underwent surgical resection, all were controlled by FOLFIRINOX and 24 (86 %) were treated by external radiotherapy before surgery. R0 resection on pathological examination was described in 25 patients (89 %). Only seven patients (25 %) had nodal involvement and four patients (14 %) achieved complete histological response on pancreatectomy specimen. Twenty-five patients (89 %) had a duodenopancreatectomy, two patients (7 %) had a splenopancreatectomy, and one patient (4 %) had a total pancreatectomy. Among patients who achieved surgical resection, 12 (43 %) had initial venous involvement only and 16 (57 %) had arterial involvement ($p = 0.22$). Among patients with venous involvement only, 44 % ($n = 12/27$) were resected; among those with arterial involvement, 32 % ($n = 16/50$) were resected. Twelve patients (43 %) had postoperative complications. Two patients (7 %) died, both from mesenteric ischemia (one at day 2 and the other at day 19). Other postoperative complications were bleeding ($n = 3$), infection ($n = 3$), ascites ($n = 2$), gastroparesis ($n = 2$), anastomotic fistulae ($n = 1$), respiratory dysfunction ($n = 1$) and lymphorrhea ($n = 1$). Altogether, 22 of 28 operated patients (79 %) were still alive at the end of the study. In these patients who were amenable to surgery, median PFS and OS were 22.5 months (95 % CI 12.9–ND) and 24.9 months (95 % CI 21.1–ND) from the date of the first chemotherapy cycle, respectively. Median PFS was 13.2 months (95 % CI 7.4–ND) from the date of surgery. Among the 30 patients who underwent consolidation therapy by external radiotherapy only, the median number of folfirinox infusions received was 6 (range 3–16). In these patients, median PFS and OS from the date of first chemotherapy cycle were 11.7 months (95 % CI 6.9–12.8] and 15.9 months (95 % CI 13.4–ND), respectively. Eighteen patients relapsed (60 %), with distant metastases in 14 cases (47 %).

TABLE 4 Summary of CT or RTCT studies in locally advanced pancreatic adenocarcinoma

	No. of patients	Treatment	OR (%)	Median PFS (months)	Median OS (months)
Loehrer et al.[12]	74	Arm A = CT	5	6.7	9.2
		Arm B = RTCT	6	6	11.1
Huguet et al.[13]	181	All patients	–	6.3	11.4
		Arm A = CT − RTCT		10.8	15
		Arm B = CT		7.4	11.7
Chauffert et al.[15]	119		–	1 year	
		Arm A = RTCT − CT		14 %	8.6
		Arm B = CT		32 %	13
Conroy et al.[18]	11/47	Folfirinox	27.3	–	15.7
Hosein et al.[19]	14/18	Folfirinox	–	1 year	1 year
				83 %	100 %
Faris et al.[20]	22	Folfirinox followed by RTCT	27.3	11.7	–
Gunturu et al.[21]	16/35	Folfirinox	50	–	–
Current study	77	Folfirinox	28	13	22

CT chemotherapy, *RT* radiotherapy, *OR* objective response, *PFS* progression-free survival, *OS* overall survival

DISCUSSION

During the period of our study, from 2010 to 2012, the standard treatment of borderline or locally advanced pancreatic cancer was gemcitabine-based chemotherapy with or without subsequent consolidation chemoradiotherapy.[10–14] In this setting, for the whole population starting gemcitabine monotherapy, PFS of 7 months and OS of 9–13 months were reported.[12,13,15] In the subgroup of patients who had disease control after 3 months of chemotherapy, consolidation radiochemotherapy resulted in PFS of 11 months and OS of 15 months in a large cohort of 181 patients.[13] These treatments allowed secondary surgical resection in up to 21 % of patients.[16,17]

However, the very recent report of the LAP 07 study presented at the American Society of Clinical Oncology (ASCO) 2013 annual meeting showed the absence of benefit of consolidation radiotherapy in LAPA compared with chemotherapy alone, making consolidation radiotherapy debatable today. More intensive chemotherapeutic regimens thus seem an interesting option in this particular population with limited disease and potential secondary resection possibilities.

Few data about FOLFIRINOX in LAPA are currently available. In a phase II trial[18] evaluating this schedule, both metastatic (76 %) and locally advanced (24 %) pancreatic cancer were included. In another work, Hosein et al.[19] recently published a retrospective cohort study of non-metastatic PA treated by FOLFIRINOX including 23 % of resectable tumors. Two other retrospective studies evaluated 16 and 22 patients treated by FOLFIRINOX for LAPA[20,21] and showed a good response rate—27 and 50 % respectively. The present study is based upon the largest cohort of patients with LAPA treated with FOLFIRINOX. With 28 % of patients with an objective response, a disease control rate of 84 %, and median PFS and OS of 13 and 22 months, respectively, this regimen seems to be effective. However, it has to be stated that a significant impact of post-FOLFIRINOX treatment (e.g. chemoradiotherapy and/or surgery) could have substantially influenced the outcomes of different patients from different centers along with impacted the OS. In fact, tumor control and downsizing allowed 75 % of patients to have consolidation therapy, including pancreatic resection with a curative intent. Seventy percent of patients received external radiotherapy and 36 % had a pancreatic resection. These results compare favorably with those obtained with gemcitabine-based chemotherapy[10,11] or radiochemotherapy[12,13] and are in line with the series of patients treated with FOLFIRINOX mentioned previously.[18–21] Table 4 summarizes efficacy results reported in patients with LAPA treated with chemotherapy or chemoradiotherapy.

In the metastatic setting, FOLFIRINOX is more toxic than gemcitabine;[7] however, its safety profile seems more favorable in our patients with LAPA. One-quarter of our patients had grade 3–4 toxicities, but with only 6 % of treatment withdrawal because of tolerability problems. No toxic death occurred. Furthermore, although studies should be compared with caution, the tolerability of FOLFIRINOX was better in our study than in those reported by Conroy et al. and Hosein et al.[18,19] In these studies, the cumulative rate of grade 3–4 toxicities was higher than 40 %. These differences could be explained by the better condition of LAPA patients, but also by the chemotherapy

dose reduction which occurred in 2/3 of our patients and the use of prophylactic G-CSF in 82 % of our patients.

Fifty-eight patients received consolidation therapy. Some patients received radiotherapy ($n = 30$), others had surgical resection ($n = 4$), and some received both ($n = 24$). Preoperative chemoradiotherapy was administered to the vast majority of patients who underwent surgery. Among patients who underwent a pancreatic resection, we recorded two early postoperative deaths, leading to a postoperative mortality rate of 7 %, which is in line with the US in-hospital mortality rate published by Teh et al.[22] in 2009. Both patients had extended pancreatic resections and received a combined treatment with chemotherapy and radiotherapy before surgery, and these are known to increase the rates of morbidity and mortality of pancreatic surgery.[16,17,23–25]

However, this prospective, multicenter study has limitations as the number of patients was limited and it was not a phase II trial but an observational cohort. Moreover, only good general condition patients with 0–1 performance status and normal bilirubin levels were enrolled. However, the large homogenous cohort of LAPA patients of the present study seems representative of the general population of patients in this setting. Indeed, the majority of patients were men, had pancreatic head cancer with lymph node involvement, required a biliary stent, and had a tumor of 3 cm or more, as reported in previous work on LAPA.[12,13,15,17,19] Moreover, the evaluation of non-resectability criteria was independently defined by each center at a multidisciplinary staff meeting, as in real-life conditions. For this reason, it might be argued that some patients included in this prospective study may have had borderline rather than unresectable pancreatic cancer, particularly among patients with venous involvement only, who represented one-third of our population study. Indeed this may be partly true as the definition of unresectability was based, in our study, on real-life multidisciplinary staff decisions and we did not realize a centralized analysis of CT scans. However, this also reflects the variability of definitions of borderline and locally advanced in the literature (Society of Surgical Oncology/AHPBH; National Comprehensive Cancer Network; MD Anderson).[26] Nevertheless, it is of note that the resection rate among patients with venous involvement and those with arterial involvement was similar, and that the surgical resection rate in the subgroup of patients with arterial involvement was high (32 %). Finally, most patients who achieved surgical resection had also received previous radiotherapy; it is therefore difficult to know if the good resection rate observed was due to the FOLFIRINOX regimen, to consolidation radiotherapy, or both. However, our efficacy results compare favorably with previous results of chemotherapy followed by radiotherapy,[13] as mentioned before, and the negative results of the LAP 07 study mentioned previously may favor our intensive chemotherapeutic regimen.

CONCLUSIONS

The FOLFIRINOX regimen seems feasible, with a manageable toxicity profile, and gives promising efficacy results in LAPA. A randomized trial assessing FOLFIRINOX versus gemcitabine in this setting is currently ongoing.

DISCLOSURES L. Marthey, A. Sa-Cunha, J.F. Blanc, M. Gauthier, A. Cueff, E. Francois, I. Trouilloud, D. Malka, J.B. Bachet, R. Coriat, E. Terrebonne, C. De La Fouchardière, S. Manfredi, D. Solub, C. Lécaille, A. Thirot Bidault, F. Carbonnel, and J. Taieb have declared no conflicts of interest.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62:10–29.
2. Sant M, Allemani C, Santaquilani M, Knijn A, Marchesi F, Capocaccia R; EUROCARE Working Group. EUROCARE-4. Survival of cancer patients diagnosed in 1995–1999: results and commentary. *Eur J Cancer*. 2009;45:931–991.
3. Réseau français des registres du cancer Francim. Evolution de l'incidence et de la mortalité par cancer en France de 1978 à 2000: Institut national de la santé et de la recherche médicale, Inserm, InVS; 2003.
4. Katz M, Wang H, Fleming J, et al. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. *Ann Surg Oncol*. 2009;16:836–87.
5. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine versus observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267–277.
6. Neoptolemos J, Stocken D, Friess H, et al., for the European Study Group for Pancreatic Cancer. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004;350:1200–10.
7. Conroy T, Desseigne F, Ychou M, et al., for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817–1825.
8. Cancer Therapy Evaluation Program. Common terminology criteria for adverse events, version 3.0. Division of Cancer Treatment and Diagnosis, National Institutes of Health; 2003.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst*. 2000;92:205–216.
10. Burris HA, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol*. 1997;15:2403–2413.
11. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer : a phase III trial of national cancer institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25:1960–1966.
12. Loehrer P, Feng Y, Cardenes H, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced

pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol*. 2011;29:4105–4112
13. Huguet F, Andre T, Hammel P, et al. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II et III studies. *J Clin Oncol*. 2007;25:3:326–331.
14. Huguet F, Girard N, Guerche CS, Hennequin C, Mornex F, Azria D. Chemoradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systematic review. *J Clin Oncol*. 2009;27:2269–77.
15. Chauffert B, Mornex F, Bonnetain F, et al. 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. *Ann Oncol*. 2008;19:1592–1599.
16. Ammori J, Colletti L, Zalupski M, et al. Surgical resection following radiation therapy with concurrent gemcitabine in patients with previously unresectable adenocarcinoma of the pancreas. *J Gastrointest Surg*. 2003;7:766–72.
17. Sa Cunha A, Rault A, Laurent C, et al. Surgical resection after radiochemotherapy in patients with unresectable adenocarcinoma of the pancreas. *J Am Coll Surg*. 2005;201:359–365.
18. Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer. A Groupe Tumeurs Digestives of the Federation Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol*. 2005;23:1228–1236.
19. Hosein PJ, Macintyre J, Kawamura C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer*. 2012;12:199.
20. Faris J, Blaszkowsky L, McDermott S, et al. Folfirinox in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist*. 2013;18:543–548.
21. Gunturu KS, Yao X, Cong X, Thumar JR, Hochster HS, Stein SM, et al. Folfirinox for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity. *Med Oncol*. 2013;30:361.
22. Teh SH, Diggs B, Deveney C, Sheppard B. Patient and hospital characteristics on the variance of perioperative outcomes for pancreatic resection in the United States: a plea for outcome-based and not volume-based referral guidelines. *Arch Surg*. 2009;144:713–721.
23. Crane CH, Abbruzzese JL, Evans DB, et al. Is the therapeutic index better with gemcitabine-based chemoradiation than with 5-fluorouracil-based chemoradiation in locally advanced pancreatic cancer? *Int J Radiat Oncol Biol Phys*. 2002;52:1293–1302.
24. Hartwig W, Hackert T, Hinz U, Hassenpflug M, Strobel O, Büchler MW, et al. Multivisceral resection for pancreatic malignancies: risk-analysis and long term outcomes. *Ann Surg*. 2009;250:81–87.
25. Gillen S, Schuster T, Meyer Zum Büschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med*. 2010;7:e1000267.
26. Evans DB, Erickson BA, Ritch P. Borderline resectable pancreatic cancer: definitions and the importance of multimodality therapy. *Ann Surg Oncol*. 2010;17(11):2803–5.