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TOPIC HIGHLIGHT

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Neoadjuvant strategies for pancreatic cancer

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Abstract

Pancreatic cancer (PC) is the fourth cause of cancer death in Western countries, the only chance for long term survival is an R0 surgical resection that is feasible in about 10%-20% of all cases. Five years cumulative survival is less than 5% and rises to 25% for radically resected patients. About 40% has locally advanced in PC either borderline resectable (BRPC) or unresectable locally advanced (LAPC). Since LAPC and BRPC have been recognized as a particular form of PC neoadjuvant therapy (NT) has increasingly became a valid treatment option. The aim of NT is to reach local control of disease but, also, it is recognized to convert about 40% of LAPC patients to R0 resectability, thus providing a significant improvement of prognosis for responding patients. Once R0 resection is achieved, survival is comparable to that of early stage PCs treated by upfront surgery. Thus it is crucial to look for a proper patient selection. Neoadjuvant strategies are multiples and include neoadjuvant chemotherapy (nCT), and the association of nCT with radiotherapy (nCRT) given as either a combination of a radio sensitizing drug as gemcitabine or capecitabine or and concomitant irradiation or as upfront nCT followed by nRT associated to a radio sensitizing drug. This latter seem to be most promising as it may select patients who do not go on disease progression during initial treatment and seem to have a better prognosis. The clinical relevance of nCRT may be enhanced by the application of higher active protocols as FOLFIRINOX.

Key words: Pancreatic cancer; Neoadjuvant; Chemotherap; Radiotherapy; Chemoradiation

Core tip: The present paper is a review on the upcoming issue of neoadjuvant strategies for pancreatic cancer patients. Protocols, timing and results of the largest series from different strategies are here presented and discussed. To authors knowledge this is the first published paper that considers even latest papers on neoadjuvant treatment for even potentially resectable pancreatic cancer.

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INTRODUCTION

Pancreatic cancer (PC) is the fourth-leading cause of death due to cancer in Western countries and accounts for nine cases per 100000 inhabitants per year in Europe[1]. The only chance for long-term survival is an R0 surgical resection that is feasible in about 10%-20% of

all cases. Cumulative survival after 5 years is less than 5% and rises to 25% for radically resected patients; in this latter group, local recurrences occur in about 50% of cases and distant metachronous metastases appear in more than 70% of patients[2,3].

Only about 20% of patients are diagnosed with surgically resectable pancreatic cancer; 40% of patients have the metastatic disease and the remaining 40% have locally advanced pancreatic cancer in either the Borderline Resectable Pancreatic Cancer (BRPC) or the Locally Advanced Pancreatic Cancer (LAPC) form[4].

DEFINITION OF LAPC AND BRPC

Due to the complexity of the anatomy in the pancreatic region, even small cancers may be found at an advanced stage where the vascular invasion is so far as to be deemed unresectable (UR). Thanks to technological progresses in the field of preoperative imaging in the last decade, a new pathological entity has arisen. BRPC is seen in a subgroup of patients in the LAPC group whose conditions are considered to be resectable with a need for vascular resection and reconstruction, but who remain at a higher risk for local recurrence. A definitive definition of BRPC is still lacking and currently there are two different classification systems: the MD Anderson Cancer Center[5] (MDACC) system and the American Hepatopancreatobiliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Society for Surgery of the Alimentary Tract (SSAT) system[6], which has been endorsed by the National Comprehensive Cancer Network (NCCN) guidelines. These two classification systems substantially overlap each other with one particular difference: the abutment of the celiac trunk is classified to be "borderline resectable" in the MDACC classification while it is considered to be unresectable in the AHPBA/SSO/SSAT/NCCN classification; this discrepancy is probably due the increased confidence in pancreatic surgery associated with vascular resections of some surgical groups as compared with other surgeries[7]. The criteria for the definition of UR, LAPC and BRPC are summarized in Table 1. Moreover, the MDACC added cancer feature data from tumors and the patient's biology as considerations to create three groups of patients: (1) patients with radiologically well defined cancers; (2) patients with inconclusive but suspicious metastatic disease radiologic findings; and (3) patients with a borderline status for major abdominal surgery. This last classification may have some importance in assigning patients to a somewhat personalized treatment but, on the other hand, it further enhances the discrepancies between classification systems.

STAGING OF PANCREATIC CANCER

Triphasic, thin-cut, contrast-enhanced CT scans show an 87% success rate in diagnosing vascular invasion from pancreatic cancer[8-11]. The main limitations of this technique include its poor effectiveness of diagnosing small amounts of hepatic and/or peritoneal spread[12,13]. As a consequence, approximately 20% of patients that were thought to be resectable on CT scans show the metastatic disease when a laparotomy is conducted[14,15].

Table 1 Definition of borderline resectable and locally advanced according to the MD Anderson Cancer Center and the American Hepatopancreatobiliary Association/Society of Surgical Oncology/Society for Surgery of the Alimentary Tract/National Comprehensive Cancer Network classification systems of stage III pancreatic cancer

Definition system	Vessel	BRPC	LAPC
MDACC	SMV	Short segment occlusion	No reconstruction feasible
	PV	Short segment occlusion	No reconstruction feasible
	SMA	Abutment	Encasement
	CHA	Abutment, short encasement	Long encasement
	CT	Abutment[1]	Encasement[1]
	Metastases	Absent	Absent
AHPBA/SSO/SSAT/NCCN	SMV	Abutment, Encasement, Occlusion	No reconstruction feasible
	PV	Abutment, Encasement, Occlusion	No reconstruction feasible
	SMA	Abutment	Encasement
	CHA	Abutment, Short encasement	Long encasement
	CT	Nor encasement or abutment[1]	Abutment[1]
	Metastases	Nor visceral nor extra-regional nodal	Nor visceral nor extra-regional nodal

[1]Differences. SMV: Superior mesenteric vein; PV: Portal vein; SMA: Superior mesenteric artery; CHA: Common hepatic artery; CT: Celiac trunk; BRPC: Borderline resectable; LAPC: Locally advanced; MDACC: MD Anderson Cancer Center; AHPBA: American Hepatopancreatobiliary Association; SSO: Society of Surgical Oncology; SSAT: Society for Surgery of the Alimentary Tract; NCCN: National Comprehensive Cancer Network.

Magnetic Resonance Imaging (MRI) is of limited interest in such a setting; this technique is effective only in cases of patients with ascites and a previously known intolerance to iodinated contrast media. Moreover MRI may be helpful in better characterizing small (< 1 cm) hepatic lesions shown by CT scans and small intrapancreatic lesions that have not yet altered the pancreatic profile[16,17].

Endoscopic ultrasounds are increasing important with an accuracy as high as 85%, with a 75% specificity and a 100% sensitivity of diagnosing pancreatic cancer resectability[18-20].

Staging laparoscopy, coupled with laparoscopic ultrasounds of the liver and pancreatic region, has shown to produce a better definition of either nodal invasion or the local invasiveness of the disease. This technique has been shown to be superior to CT scans in terms of accuracy in detecting the presence of hepatic metastases[13,21-24].

The most widely accepted criteria for selecting patients that should undergo staging laparoscopy for pancreatic cancer currently are pancreatic head tumors > 3 cm in maximum diameter, cancers located in the body and tail of the gland, and cancers with unclear margins

Table 2 Studies on chemotherapy for advanced pancreatic cancer

Ref.	CT regimen	Study	LAPC (*n*)	ORR (%)	OS median	Res rate (%)	Metastatic	ORR (%)	OS median
Conroy *et al*[33]	FOLFIRINOX *vs* Gem	Multicentric phase Ⅱ trial	0	NA	NA	NA	342	31.6 *vs* 9.4	11.1 *vs* 6.4
Louvet *et al*[45]	GEMOX *vs* GEM alone	phase Ⅲ	98	14.9 *vs* 27.3	10.3 *vs* 10.3	NA	215	18.3 *vs* 26.4	6.7 *vs* 8.5
Rocha Lima *et al*[46]	Irinotecan + GEM *vs* GEM alone	Multicenter, open label, phase Ⅲ	51	25.9 *vs* 4.2	9.8 *vs* 11.7	NA	293	14.9 *vs* 4.8	5.4 *vs* 5.9
Poplin *et al*[47]	GEM *vs* GEM FDR *vs* GEMOX	phase Ⅱ, multicentric	86	36	9.2	NA	737	NR	4.9 *vs* 6.2 *vs* 5.7
Kindler *et al*[49]	GEM + Bevacizumab *vs* GEM + placebo	Double blind, placebo controlled, phase Ⅲ	31	NA	NA	NA	189	NR	5.8 *vs* 5.9
Gunturu *et al*[53]	FOLFIRINOX	Single centre, retrospective	16	50	NA	NA	19	47	NA
Peddi *et al*[55]	FOLFIRINOX	Registry	18	34	NA	NA	22	18	NA

CT: Chemotherapy; LAPC: Locally advanced pancreatic cancer; ORR: Overall response rate; OS: Overall survival; Res: Resection; NA: Not available; NR: Not reported; FOLFIRINOX: 5-fluorouracil + leucovorin + oxaliplatin + irinotecan; GEM: Gemcitabine; GEM FDR: Gemcitabine fixed dose ratio.

on imaging and Carbohydrate Antigen 19.9 > 100 U/mL in patients with normal serum bilirubin levels[25].

BASIS FOR NEOADJUVANT THERAPY

Patients with LAPC and either BRPC or UR pancreatic cancer have about a 50% chance for curative resection, as compared with stage I and Ⅱ pancreatic cancers[5,26-28]. This is mainly due to the high frequency of invasion of the retroperitoneal margin and/or the nervous plexus of the SMA, whose resection adds further morbidity to the intrinsic morbidity related to pancreatic resections with vascular reconstructions[29-32]. The most significant factor predicting long-term survival in pancreatic cancer patients is an R0 resection, a widely accepted procedure. An R1 resection is associated, independent of the original stage of disease, with a prognosis similar to patients with the inoperable disease[33-42].

Early retrospective analyses showed that the chance to obtain an R0 resection for both UR-LAPC and BRPC patients was about one half compared with that for T1 and T2 patients[43-45].

At the same time, some randomized multicentric studies with adjuvant therapies for resectable pancreatic cancer showed a survival advantage for treated patients for both overall survival and disease-free survival[33,46,47], while studies performed with adjuvant radiotherapy and Intraoperative Radiotherapy showed a good efficacy in a local control of disease.

Recent meta-analyses done on early published studies on neoadjuvant treatments of BRPC and LAPC[48] showed an increased rate of R0 resections with unchanged mortality and morbidity as compared with those treated by upfront surgery. Moreover, these meta-analyses show some evidence of additional advantages over neoadjuvant strategies: (1) patients treated by upfront surgery often show a delay in the beginning of adjuvant treatment due to surgical complications, even minor ones. This fact leads to an evident survival handicap. Neoadjuvant therapy may avoid this handicap[25]. In three different studies, patients who underwent neoadjuvant therapies completed the cycles in 90%-100% of cases, compared with 62% of patients who completed adjuvant chemotherapy in the CONLO-001 study[25]; (2) neoadjuvant therapies may help in avoiding unnecessary major abdominal surgery for patients who go on disease progression during treatment; (3) giving chemotherapic agents to a patient with pancreatic tissue not yet altered by the trauma of surgery seems to have a better effect due to better vascularization and subsequent drug delivery to neoplastic tissues[34]; (4) for BRPC and LAPC patients, neoadjuvant therapy lead to a downstaging of the disease, increasing the rate of R0 resections[5,38-44]; (5) some studies report a decreased incidence of anastomotic fistulas after neoadjuvant therapies, probably due to the pancreatic and peripancreatic fibrosis inducted by treatment[45,49-51]; and (6) two recent comparative analyses on the costs of various treatments for pancreatic cancer showed an economic advantage in neoadjuvant treatment regimens[45,52].

NEOADJUVANT CHEMOTHERAPY FOR LAPC AND BRPC

Gemcitabine-based chemotherapy

Older randomized trials exploring the effects of neoadjuvant chemotherapy alone on pancreatic cancer included both BRPC/LAPC patients and metastatic pancreatic cancer patients (Table 2). Gemcitabine-based studies evaluated both metastatic and LAPC patients and showed a 20%-30% response rate without any difference between metastatic and locally advanced. In two studies, Gemcitabine was given with Oxaliplatin *vs* Gemcitabine alone[45,46]. In one study, Gemcitabine was given with Irinotecan *vs* Gemcitabine alone[47]. In another study, Gemcitabine was given with Bevacizumab *vs* Gemcitabine alone[49]. All of these studies showed that results were significantly superior in favor of the combination therapy *vs* Gemcitabine alone but no study had resection as an endpoint. In a meta-analysis by Andriulli and others exploring the effects of Gemcitabine-based

Table 3 Studies on neoadjuvant chemotherapy for locally advanced pancreatic cancer

Ref.	Study type	CT regimen	Staging system	LAPC (*n*)	Res rate (%)	R0 resections/total resections	ORR	OS median
Lee *et al*[51]	Prospective non-randomized	Gemcitabine + capecitabine	NCCN	18 BR 25 UR	61 BR 24 UR	9/11 BR 5/6 UR	NR	23.1 mo (cumulative)
			APBCC	33 BR 10 UR	46 BR 20 UR	13/15 BR 1/2 UR	NR	
Sahora *et al*[52]	Prospective phase Ⅱ	NeoGEMTAX	NR	12 BR 13 UR	32	7/8	NR	16 mo (resected patients)
FARIS[1] *et al*[54]	Single centre, retrospective	FOLFIRINOX	NCNN	22	NR	22.7	27.3% (CT alone)	NR
Hosein[1] *et al*[39]	Prospective phase Ⅱ	FOLFIRINOX	NR	14 BR 4UR	55.5	7/8	NR	16 mo (resected patients)

[1]Some patients had CRT. ORR: Overall response rate; OS: Overall survival; NR: Not reported; NeoGEMTAX: Gemcitabine + docetaxel; FOLFIRINOX: 5-Fluorouracil + leucovorin + oxaliplatin + irinotecan; GEM: Gemcitabine; GEM FDR: Gemcitabine fixed dose ratio; NCCN: National comprehensive cancer network; APBCC: Asan pancreaticobiliary cancer center.

neoadjuvant therapy for pancreatic cancer, the reported of 1 and 2 year survival rates are 54.2% and 27% for patients with LAPC, respectively, with a complete/partial response ratio of 27% (95%CI: 18-38)[50]. A recent report by Lee *et al*[51] studied 43 patients affected by both LAPC (25) and BRPC (18), as defined by the NCCN criteria. The patients were treated with a combination of Gemcitabine and Capecitabine and the authors reported a 18.6% radiological response rate and a stable disease rate of 69.8%. In the LAPC group, 24% underwent surgical resection with 83.3% having R0 resections. In the BRPC group, 61% underwent resection with 81.8% having R0 resections. Sahora and collaborators, in a prospective study on 13 LAPC patients and 12 BRPC patients treated by neoadjuvant Gemcitabine and docetaxel chemotherapy, reported an overall resection rate of 32% with 87.5% having R0 resections and a median survival time of 16 mo for resected patients (95%CI: 8-24 mo) *vs* 12 mo for unresected patients[51]. An overview of these studies is given in Table 3.

FOLFIRINOX-based chemotherapy

Based on the work of Conroy *et al*[33] reporting on the results of a phase Ⅲ study on the efficacy of FOLFIRINOX chemotherapy on both LAPC and metastatic pancreatic cancer, this study compared FOLFIRINOX with Gemcitabine alone and showed the significant superiority of FOLFIRINOX in Overall Survival (OS), Progression Free Survival (PFR) and Overall Response Rate. Notably, as for the Gemcitabine-based studies, LAPC showed the same response rate as metastatic pancreatic cancer. Retrospective and registry analyses data on neoadjuvant FOLFIRINOX are currently available and show mostly consistent results for both metastatic pancreatic cancer and LAPC[33,53-55]. A recent retrospective study published by Hosein *et al*[39] on 18 patients with LAPC (4 BRPC and 14 UR, as defined using the AHPBA/SSO/SSAT criteria for resectability definition) report a 38.8% post-treatment radiologic resectability with a 62.5% rate of R0 resections and a 1 year progression free survival (PFS) rate as high as 83%; the 1 year overall survival rate was 100%. They did not find any statistically significant difference in survival rates between the R0 and R1 resected patients. Moreover, several dosage adjustments of chemotherapic were required during treatment, although this procedure did not seem to interfere with the overall results[39]. A more recent study from Marthey on a preliminary prospective database with FOLFIRINOX in 53 LAPC patients showed an 83% disease control rate with a 30% response rate and a final 32% resectability rate although some of the responding patients underwent external beam radiotherapy as a continuation of the treatment schedule[56]. The preliminary result of this study is that FOLFIRINOX is effective at controlling pancreatic cancer with an overall response rate higher than 30%. This finding forecasts more focused phase Ⅲ clinical trials on this subject.

Neoadjuvant chemoradiotherapy

Evidence to support the use of neoadjuvant chemoradiotherapy (CRT) for LAPC is limited but rapidly increasing. The theoretical hypothesis that CRT is based on is that while chemotherapy provides control for a micro-disseminated disease and also acts as a radiation sensitizer, radiotherapy (RT) may have a huge impact on the local control of the disease. Since the mid-1980s, studies have been published on the treatment of LAPC by 5-FU-based CRT protocols that were shown to prolong survival when compared with radiation alone[57].

The next step was the use of Gemcitabine as a chemotherapic drug instead of 5-FU, with some evidence of a higher efficacy on both local response and overall survival[57]. In a recent meta-analysis from Gillen *et al*[40] 111 trials including as many as 4394 pancreatic cancer patients were evaluated[47]. The authors found an overall response rate of 42% for LAPC and overall disease control for 77% of LAPC patients. Laparotomies was performed in 47% of initially UR patients and, among these patients, 33% were resected; 79% had R0 resections. The overall reported median survival duration was 10.2 mo while for the 33% of resected patients, the median survival duration was 20.5 mo. Similar results were found by other systematic reviews[39,48,58-60]. A recent multi-institutional phase Ⅱ study on GEMOX-based CRT by Kim *et al*[61] clearly reports on the efficacy of their CRT protocol. This is the first prospective trial where resectability is a clear end-

point, including resectable pancreatic cancer, BRPC, and UR with a clear definition according to NCCN criteria. The study enrolled 68 patients (23 resectable, 39 BRPC and 6 UR). Sixty-six patients completed the protocol and were evaluated for surgery and 48 underwent laparotomies with 84% having R0 resections. In particular, 13 out of 19 eligible patients from the BRPC group had a post-CRT R0 resection. The median OS was 18.2 mo (95%CI: 13-26.9 mo) with the best performance for the initially resectable patients (26.5 mo). The resected patients from the BRPC pre-treatment group had a median OS of 18.4 mo.

The evidence that about 30% of LAPC patients develop systemic metastases during the early cycles of treatment[40] indicates the need for some early systemic control of the disease. To this end, some researchers treated LAPC patients with upfront chemotherapy followed by CRT. The presumed advantage of such a treatment schedule is that the early therapeutic approach may use not only RT-sensitizing drugs such as 5-FU and Gemcitabine or Capecitabine but rather drugs that are more effective against cancer. On the other hand, this approach may select patient who did not progress, thus avoiding the additional toxicity of unnecessary Radiotherapy (RT). Two retrospective and two prospective studies on this issue showed promising results. Huguet *et al*[62] used an upfront administration of Gemcitabine followed by Gemcitabine-based CRT for 71% of patients who did not progress. The authors recorded a 15 mo median OS with a 10.8 mo median PFS that was significantly better than the median OS and PFS of patients treated by Gemcitabine-based CT only in the same study. These data completely consist with those reported by Krishnan[63], who retrospectively analyzed the effect on 323 LAPC patients who had received primary CRT (247 patients) or induction Gemcitabine-based CT followed by Gemcitabine-based CRT (76 patients). They found that there was a strongly statistically significant improvement in both OS and PFS in the CT-CRT group when compared with patients in the CT-alone group ($P < 0.001$ in both cases).

Last year, data from one phase Ⅱ and one phase Ⅲ prospective trials on CT followed by CRT became available. Mukherjee *et al*[64] treated 114 patients (the SCALOP study) with induction Gemcitabine/Capecitabine-based chemotherapy. The 74 patients who were not progressing were randomized to undergo a course of external beam RT given with Capecitabine (36 patients) or Gemcitabine (36 patients) administered concomitantly. In the setting of a strong survival advantage for CRT patients *vs* CT alone, the authors reported a better performance in both OF and DFS for the Capecitabine group, which showed a median OS of 15.2 mo and a DFS of 12 mo *vs* 13.4 mo (OS) and 10.4 mo (DFS) for the Gemcitabine-based CRT patients ($P < 0.001$).

Leone *et al*[65] published results of upfront GEMOX CT followed by Gemcitabine-based CRT; this study is the only one to include surgery as an option while also reporting on the resectability rate. The authors enrolled 39 patients with both BRPC (15 patients) and LAPC (24 patients) as defined by the NCCN criteria and applied an induction GEMOX-based CT and then a restaging; non-progressing patients then underwent a 50.5 Gy fractioned RT with concomitant Gemcitabine infusion on a twice-weekly base standard dose. The study reports that 94.9% of patients maintained at least a stable disease with no complete responses and 10.2% were partial responses; 15 patients were deemed resectable at the end of the treatment (38.4%) and, of these, 14 were operated on (one patient refused) with nine R0 resections (64.2%). The overall median PFS was 10.2 mo with 40% DFS at 1 year and 12% DFS at 2 years. The DFS was significantly longer for resected patients ($P < 0.000001$). The overall median OS was 16.7 mo while it was 27.8 mo for BRPC and 13.3 mo for LAPC (Table 4). These data substantially confirm that BRPC and LAPC patients converted to resectability may have a significant survival advantage and even a chance for a cure by an appropriate multimodal treatment.

NEOADJUVANT TREATMENT FOR RESECTABLE PANCREATIC CANCER

The impressive initial results obtained by neoadjuvant treatment for LAPC lead one to consider applying neoadjuvant strategies even to resectable pancreatic cancer. In a prospective phase Ⅱ trial giving GEMOX CT to 28 patients, Heinrich *et al*[66] showed that neoadjuvant treatment did not affect resectability rates with a good tolerance profile since the same author began, in 2011, a randomized multicentric phase Ⅲ study tht gave adjuvant Gemcitabine *vs* neoadjuvant GEMOX to resectable pancreatic cancer patients (NEOPAC study). This study is still continuing[67]. Tujima *et al*[68] reported on 34 patients with resectable pancreatic cancer randomized to receive standard upfront resection (21 patients) or two cycles of neoadjuvant therapy with Gemcitabine and oral S-1. They found no difference in resectability rates between the two groups and a statistically significant difference in the 1 and 2 years survival rates for treated patients that decreased over time to become consistent with that of the untreated patient survival rates at 3 years. More recent papers including neoadjuvant CRT are available. The study from Sho *et al*[69] compared 61 resectable (22 patients) or borderline resectable (39 patients) pancreatic cancer patients treated by a Gemcitabine-based 50 Gy fractionated course of RCT with 71 pancreatic cancer patients treated by upfront resection. The study presents some potential biases from the lack of pre-neoadjuvant Chemoradiotherapy (nCRT) histological confirmation of the diagnosis for some patients and the administration of adjuvant CT to some others. Otherwise, they report no difference in the resection rates between the groups and a statistically significant reduction in post-operative pancreatic fistulas ($P = 0.045$) and length of hospital stay ($P = 0.0173$) for nCRT patients *vs* upfront surgery. Moreover,

Table 4 Studies on neoadjuvant chemoradiotherapy for locally advanced pancreatic cancer

Ref.	Study type	CT regimen	RT	Staging System	LAPC (*n*)	Resection rate (%)	R0 resections/ total resections	ORR (%)	OS median (mo)
Shinchi *et al*[57]	Prospective randomized trial	5-FU concurrent infusion	External beam RT (50.4 Gy/28 fractions) *vs* no RT	NR	31	NR	NR	31	13.2 *vs* 6.4
Tinkl *et al*[60]	Prospective study	Gemcitabine	Three dimensional conformal 55.8 Gy tumor 50.4 Gy nodes	NR	120	31.6	35/38	NR	25
Kim *et al*[61]	Phase Ⅰ study	Gemcitabine + oxaliplatin	Concurrent external beam RT 27 Gy/15 fractions	NCCN	38	28.9	7/11	15.7	12.5 (all patients)
Huguet *et al*[62]	Phase Ⅱ and Ⅲ trial	Upfront CT: FOLFUGEM, GEMOX, Gemcitabine *vs* GEMOX 167 patients	External beam RT (55 Gy/30 fractions) 72 patients	NR	167	NR	NR	NR	13.1
Krishnan *et al*[63]	Prospective non-randomized trial	Chemoradiation (247 patients) Upfront GEM CT followed by CRT 5-FU, GEM, CAPE (76 patients)	30 Gy (220 patients) or 55 Gy (27 patients) 30 Gy (64 patients) or 55 Gy (12 patients)	MDACC	323	NR	NR	NR	9.1
Mukerjee *et al*[64]	Open label, randomized, phase Ⅱ trial	Upfront CT GEM or CAPE CRT GEM or CAPE	58 Gy/30 fractions	NR	74 38 GEM 36 CAPE	NR	NR	20.2	15.2 (GEM) *vs* 13.4 (CAPE)
Leone *et al*[65]	Prospective non-randomized trial	Upfront CT GEMOX CRT GEM	50.4 Gy	NCCN	39 15 BR 24 UR	28.2	11/11	NR	16.7 27.8 BR 13.3 UR
Polistina *et al*[76]	Prospective non-randomized trial	Upfront GEM CT GEM CRT	SBRT 30 Gy/3 fractions	MDACC	23 UR	8	2/3	69.5	10.6

NR: Not reported; RT: Radiotherapy; CT: Chemotherapy; CRT: Chemoradiotherapy; LAPC: Locally advanced pancreatic cancer; ORR: Overall response rate; OS: Overall Survival; GEM: Gemcitabine; CAPE: Capecitabine; FOLFUGEM: Leucovorin + gemcitabine + 5-fluorouracil; GEMOX: Gemcitabine + Oxaliplatin; NCCN: National comprehensive cancer network; MDACC: MD Anderson Cancer Center; BR: Borderline resectable; UR: Unresectable; SBRT: Stereotactic body radiotherapy.

there was a statistically significant reduction on nodal metastases in nCRT patients ($P = 0.0001$) and an R0 resection rate that was statistically higher in nCRT patients *vs* upfront surgery patients (92% *vs* 56%; $P < 0.0001$); no data on OS and DFS are reported.

In the most recently published study of Van Buren *et al*[70] in a phase Ⅱ trial, the effects of induction fixed dose rate Gemcitabine followed by 30 Gy RT as neoadjuvant treatment of potentially resectable pancreatic cancer were examined. They enrolled 59 patients, of which 29 had BRPC. They report a 72.8% resection rate with a toxicity similar to other reported series and an R0 resection rate of 88% of resected patients (95%CI: 75-96) and a median OS of 16.8 mo (19.7 mo for resected patients).

Neoadjuvant therapy for resectable pancreatic cancer is an upcoming issue to be explored since it appears to have no significant toxicity nor shows a reduction in surgical resections. Conversely, from preliminary results, neoadjuvant therapy appears to reduce post-operative complications and hospital stay durations and also increase the rate of R0 resections. Further large randomized studies are necessary to confirm its usefulness and to assess the best treatment planning and schedule. An overview of studies is given in Table 5.

CONCLUSION

Pancreatic cancer remains a highly lethal disease in spite of all surgical, oncological, and technological progress of the last 30 years. Over this period, the prognosis of virtually all solid cancers has significantly increased; the prognosis for pancreatic cancer has remained almost the same. Pancreatic cancer patients had an overall 3% 5 year survival rate in the 1970s compared with the 5%-6% survival rate they have nowadays. In the last decade, LAPC has been recognized as an autonomous pathological entity; surgeons and oncologists have begun to try to standardize specific therapeutic strategies according to the evidence that only the achievement of surgical resection with negative margins may give a chance for a cure. The evidence that R0 resection rates are higher after neoadjuvant therapies highlights the need for research in this specific field. Based on a literature review on the issue, it appears that there are several critical points that still remain unresolved. First of all, there is a need for an univocal classification system that clearly distinguishes

Table 5 Studies on neoadjuvant chemotherapy for potentially resectable pancreatic cancer

Ref.	Study type	CT regimen	Patients (*n*)	Resection rate (%)	R0 resections rate (%)	OS median (mo)
Heinrich *et al*[66]	Prospective non-randomized phase Ⅱ	Gemcitabine + cisplatin	28	93	80	26.5
Tajima *et al*[68]	Pilot study	S1 *vs* upfront surgery	34 (total) 13 (S1) *vs* 21 (upfront surgery)	100	84.6 *vs* 85.7	2 yr 55.6% *vs* 29.6%
Sho *et al*[69]	Single centre	GEM CRT (external beam 50 to 54 Gy)	61	97	92	NR
Van Buren *et al*[70]	Prospective phase Ⅱ trial	FDR GEM + bevacizumab induction GEM + bevacizumab Accelerated RT 30 Gy/10 fractions	59	72.8	38/43 (88.3%)	16. 8 (overall) 19.7 (resected patients)

CT: Chemotherapy; OS: Overall survival; NR: Not reported; GEM: Gemcitabine; CRT: Chemoradiotherapy.

between borderline resectable and UR pancreatic cancer; the currently available systems do not allow for this distinction and tumors deemed "resectable" by the MDACC are deemed "unresectable" by the NCCN classification. This situation is somewhat misleading in objectively interpreting data from various groups of researchers.

Most of the studies are retrospective and done on series collected before the rise of LAPC as an independent entity, therefore the classification was done "ex-post" and this may be a further bias. Very few studies report on resectability rates or even have resection as a study endpoint; the data are mostly extracted from a larger series of patients including mostly metastatic pancreatic cancer. These studies are of great significance as they show the potentialities of treatment but are non-specific and therefore potentially highly biased.

Nonetheless, an encouraging level of evidence suggests that patients undergoing neoadjuvant therapies for LAPC have a better prognosis than patients treated by upfront surgery or adjuvant therapy alone. At the same time, it appears that even patients with LAPC may have a chance for cure if down-staged to have an R0 resection, thereby achieving survival curves identical to those of primarily resectable patients. Such evidence currently suggests that even initially resectable pancreatic cancer can benefit from a neoadjuvant treatment, but this hypothesis is yet to be confirmed.

We are convinced that there is an enormous need for high-quality, randomized prospective studies that include a better selection of patients and searches for better strategies for each patient.

LOOKING FORWARD

As a future perspective, there are new advances in the field of chemotherapy agents and newer RT technologies such as Intensity Modulated Radiotherapy or Stereotactic Body Radiotherapy.

There are recently closed and ongoing trials on metastatic pancreatic cancer testing the efficacy of combined Gemcitabine and the Epidermal Growth Factor Receptor antibodies Cetuximab and Erlotinib[71,72]. However, at the present time, the results are not encouraging. Preliminary results on the use of Gemcitabine and the Vascular Endothelial Growth Factor inhibitor Axitinib did not improve outcomes in a published series[73] and the anti-HER2 drug Trastuzumab associated with Capecitabine did not seem to improve patient outcomes[74].

Recently, interest has been rising about a tumoral cytoplasmic protein involved in intracellular transport and RNA inclusion of Gemcitabine metabolites: the Intratumoral Human Equilibrative Nucleoside Transporter-1, whose presence seems to be related to responses to Gemcitabine therapy[75], but which still lacks a standard definition of a proper tissutal concentration of the molecule.

Stereotactic Body Radiotherapy has been tested in some non-randomized studies. Polistina *et al*[76] treated 24 patients with intraoperatively proven UR LAPC with a 3 wk Gemcitabine CT followed by 30 Gy SBRT in three consecutive fractions and concomitant Gemcitabine at a standard dose. They report a 33% radiologic conversion to resectability and 8% R0 resections (with three patients refusing reoperation) and minimal treatment toxicity (no grade 3 or 4 events) with a 20 mo median survival time for resected patients and one histological complete tumor response. Similar toxicity and response rate results have been published by other groups[77].

SBRT CRT is a promising tool as it hypothetically adds the benefits of systemic CT to the local control of disease as obtained with more focused delivery of radiation to the tumor bed. There is less risk to nearby organs and a subsequent decreased toxicity. However, there is a strong need for prospective, randomized trials to confirm these preliminary results.

REFERENCES

1 **Silvestrini R**. Il carcinoma pancreatico: epidemiologia e fattori di rischio. Basi scientifiche per linee guida. Available from: URL: http://www.iss.it/lgac/docu/cont.php?id=171&lang=1&tipo=32
2 **Griffin JF**, Smalley SR, Jewell W, Paradelo JC, Reymond RD, Hassanein RE, Evans RG. Patterns of failure after curative resection of pancreatic carcinoma. *Cancer* 1990; **66**: 56-61 [PMID: 2354408 DOI: 10.1002/1097-0142(19900701)66]
3 **Sohn TA**, Yeo CJ, Cameron JL, Koniaris L, Kaushal S,

Abrams RA, Sauter PK, Coleman J, Hruban RH, Lillemoe KD. Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000; **4**: 567-579 [PMID: 11307091 DOI: 10.1016/S1091-255X(00)80105-5]

4 **Zakharova OP**, Karmazanovsky GG, Egorov VI. Pancreatic adenocarcinoma: Outstanding problems. *World J Gastrointest Surg* 2012; **4**: 104-113 [PMID: 22655124 DOI: 10.4240/wjgs.v4.i5.104]

5 **Varadhachary GR**, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, Lee JE, Pisters PW, Evans DB, Wolff RA. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006; **13**: 1035-1046 [PMID: 16865597 DOI: 10.1245/ASO.2006.08.011]

6 **Vauthey JN**, Dixon E. AHPBA/SSO/SSAT Consensus Conference on Resectable and Borderline Resectable Pancreatic Cancer: rationale and overview of the conference. *Ann Surg Oncol* 2009; **16**: 1725-1726 [PMID: 19396495 DOI: 10.1245/s10434-009-0409-5]

7 **Kang CM**, Hwang HK, Choi SH, Lee WJ. Controversial issues of neoadjuvant treatment in borderline resectable pancreatic cancer. *Surg Oncol* 2013; **22**: 123-131 [PMID: 23518243 DOI: 10.1016/j.suronc.2013.02.007]

8 **Fuhrman GM**, Charnsangavej C, Abbruzzese JL, Cleary KR, Martin RG, Fenoglio CJ, Evans DB. Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. *Am J Surg* 1994; **167**: 104-11; discussion 111-3 [PMID: 7906097 DOI: 10.1016/0002-9610(94)90060-4]

9 **Takeshita K**, Furui S, Takada K. Multidetector row helical CT of the pancreas: value of three-dimensional images, two-dimensional reformations, and contrast-enhanced multiphasic imaging. *J Hepatobiliary Pancreat Surg* 2002; **9**: 576-582 [PMID: 12541043 DOI: 10.1007/s005340200077]

10 **Catalano C**, Laghi A, Fraioli F, Pediconi F, Napoli A, Danti M, Reitano I, Passariello R. Pancreatic carcinoma: the role of high-resolution multislice spiral CT in the diagnosis and assessment of resectability. *Eur Radiol* 2003; **13**: 149-156 [PMID: 12541123]

11 **Freeny PC**. Pancreatic carcinoma: imaging update 2001. *Dig Dis* 2001; **19**: 37-46 [PMID: 11385250 DOI: 10.1159/000050652]

12 **Conlon KC**, Dougherty E, Klimstra DS, Coit DG, Turnbull AD, Brennan MF. The value of minimal access surgery in the staging of patients with potentially resectable peripancreatic malignancy. *Ann Surg* 1996; **223**: 134-140 [PMID: 8597506 DOI: 10.1097/00000658-199602000-00004]

13 **Yoshida T**, Matsumoto T, Morii Y, Ishio T, Kitano S, Yamada Y, Mori H. Staging with helical computed tomography and laparoscopy in pancreatic head cancer. *Hepatogastroenterology* 2002; **49**: 1428-1431 [PMID: 12239959]

14 **Schima W**, Ba-Ssalamah A, Kölblinger C, Kulinna-Cosentini C, Puespoek A, Götzinger P. Pancreatic adenocarcinoma. *Eur Radiol* 2007; **17**: 638-649 [PMID: 17021700 DOI: 10.1007/s00330-006-0435-7]

15 **Reddy KR**, Levi J, Livingstone A, Jeffers L, Molina E, Kligerman S, Bernstein D, Kodali VP, Schiff ER. Experience with staging laparoscopy in pancreatic malignancy. *Gastrointest Endosc* 1999; **49**: 498-503 [PMID: 10202066 DOI: 10.1016/S0016-5107(99)70050-7]

16 **Brandwein SL**, Farrell JJ, Centeno BA, Brugge WR. Detection and tumor staging of malignancy in cystic, intraductal, and solid tumors of the pancreas by EUS. *Gastrointest Endosc* 2001; **53**: 722-727 [PMID: 11375578 DOI: 10.1067/mge.2001.114783]

17 **Miller FH**, Rini NJ, Keppke AL. MRI of adenocarcinoma of the pancreas. *AJR Am J Roentgenol* 2006; **187**: W365-W374 [PMID: 16985107 DOI: 10.2214/AJR.05.0875]

18 **Kahl S**, Glasbrenner B, Zimmermann S, Malfertheiner P. Endoscopic ultrasound in pancreatic diseases. *Dig Dis* 2002; **20**: 120-126 [PMID: 12566614 DOI: 10.1159/000067481]

19 **Wang Y**, Gao J, Li Z, Jin Z, Gong Y, Man X. Diagnostic value of mucins (MUC1, MUC2 and MUC5AC) expression profile in endoscopic ultrasound-guided fine-needle aspiration specimens of the pancreas. *Int J Cancer* 2007; **121**: 2716-2722 [PMID: 17708554 DOI: 10.1002/ijc.22997]

20 **Ahmad NA**, Lewis JD, Siegelman ES, Rosato EF, Ginsberg GG, Kochman ML. Role of endoscopic ultrasound and magnetic resonance imaging in the preoperative staging of pancreatic adenocarcinoma. *Am J Gastroenterol* 2000; **95**: 1926-1931 [PMID: 10950037 DOI: 10.1111/j.1572-0241.2000.02245.x]

21 **Catheline JM**, Turner R, Rizk N, Barrat C, Champault G. The use of diagnostic laparoscopy supported by laparoscopic ultrasonography in the assessment of pancreatic cancer. *Surg Endosc* 1999; **13**: 239-245 [PMID: 10064755]

22 **Jimenez RE**, Warshaw AL, Fernandez-Del Castillo C. Laparoscopy and peritoneal cytology in the staging of pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2000; **7**: 15-20 [PMID: 10982586 DOI: 10.1007/s005340050148]

23 **John TG**, Wright A, Allan PL, Redhead DN, Paterson-Brown S, Carter DC, Garden OJ. Laparoscopy with laparoscopic ultrasonography in the TNM staging of pancreatic carcinoma. *World J Surg* 1999; **23**: 870-881 [PMID: 10449813 DOI: 10.1007/s002689900592]

24 **Schachter PP**, Avni Y, Shimonov M, Gvirtz G, Rosen A, Czerniak A. The impact of laparoscopy and laparoscopic ultrasonography on the management of pancreatic cancer. *Arch Surg* 2000; **135**: 1303-1307 [PMID: 11074885 DOI: 10.1001/archsurg.135.11.1303]

25 **Lim KH**, Chung E, Khan A, Cao D, Linehan D, Ben-Josef E, Wang-Gillam A. Neoadjuvant therapy of pancreatic cancer: the emerging paradigm? *Oncologist* 2012; **17**: 192-200 [PMID: 22250057 DOI: 10.1634/theoncologist.2011-0268]

26 **Moore GE**, Sako Y, Thomas LB. Radical pancreatoduodenectomy with resection and reanastomosis of the superior mesenteric vein. *Surgery* 1951; **30**: 550-553 [PMID: 14866700]

27 **Siriwardana HP**, Siriwardena AK. Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer. *Br J Surg* 2006; **93**: 662-673 [PMID: 16703621 DOI: 10.1002/bjs.5368]

28 **Glanemann M**, Shi B, Liang F, Sun XG, Bahra M, Jacob D, Neumann U, Neuhaus P. Surgical strategies for treatment of malignant pancreatic tumors: extended, standard or local surgery? *World J Surg Oncol* 2008; **6**: 123 [PMID: 19014474 DOI: 10.1186/1477-7819-6-123]

29 **Talamonti M**. Borderline resectable pancreatic cancer: a new classification for an old challenge. *Ann Surg Oncol* 2006; **13**: 1019-1020 [PMID: 16865593 DOI: 10.1245/ASO.2006.02.902]

30 **Bold RJ**, Charnsangavej C, Cleary KR, Jennings M, Madray A, Leach SD, Abbruzzese JL, Pisters PW, Lee JE, Evans DB. Major vascular resection as part of pancreaticoduodenectomy for cancer: radiologic, intraoperative, and pathologic analysis. *J Gastrointest Surg* 1999; **3**: 233-243 [PMID: 10481116 DOI: 10.1016/S1091-255X(99)80065-1]

31 **Yekebas EF**, Bogoevski D, Cataldegirmen G, Kunze C, Marx A, Vashist YK, Schurr PG, Liebl L, Thieltges S, Gawad KA, Schneider C, Izbicki JR. En bloc vascular resection for locally advanced pancreatic malignancies infiltrating major blood vessels: perioperative outcome and long-term survival in 136 patients. *Ann Surg* 2008; **247**: 300-309 [PMID: 18216537 DOI: 10.1097/SLA.0b013e31815aab22]

32 **Nakao A**, Takeda S, Inoue S, Nomoto S, Kanazumi N, Sugimoto H, Fujii T. Indications and techniques of extended resection for pancreatic cancer. *World J Surg* 2006; **30**: 976-982; discussion 983-984 [PMID: 16736324]

33 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M. FOLFIRINOX *vs* gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**:

1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]
34 **Assifi MM**, Lu X, Eibl G, Reber HA, Li G, Hines OJ. Neoadjuvant therapy in pancreatic adenocarcinoma: a meta-analysis of phase II trials. *Surgery* 2011; **150**: 466-473 [PMID: 21878232 DOI: 10.1016/j.surg.2011.07.006]
35 **Herreros-Villanueva M**, Hijona E, Cosme A, Bujanda L. Adjuvant and neoadjuvant treatment in pancreatic cancer. *World J Gastroenterol* 2012; **18**: 1565-1572 [PMID: 22529684 DOI: 10.3748/wjg.v18.i14.1565]
36 **Tucker ON**, Rela M. Controversies in the management of borderline resectable proximal pancreatic adenocarcinoma with vascular involvement. *HPB Surg* 2008; **2008**: 839503 [PMID: 19283083 DOI: 10.1155/2008/839503]
37 **Al-Haddad M**, Martin JK, Nguyen J, Pungpapong S, Raimondo M, Woodward T, Kim G, Noh K, Wallace MB. Vascular resection and reconstruction for pancreatic malignancy: a single center survival study. *J Gastrointest Surg* 2007; **11**: 1168-1174 [PMID: 17632763]
38 **Satoi S**, Yanagimoto H, Toyokawa H, Takahashi K, Matsui Y, Kitade H, Mergental H, Tanigawa N, Takai S, Kwon AH. Surgical results after preoperative chemoradiation therapy for patients with pancreatic cancer. *Pancreas* 2009; **38**: 282-288 [PMID: 19142173 DOI: 10.1097/MPA.0b013e31819438c3]
39 **Hosein PJ**, Macintyre J, Kawamura C, Maldonado JC, Ernani V, Loaiza-Bonilla A, Narayanan G, Ribeiro A, Portelance L, Merchan JR, Levi JU, Rocha-Lima CM. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer* 2012; **12**: 199 [PMID: 22642850 DOI: 10.1186/1471-2407-12-199]
40 **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 [PMID: 20422030 DOI: 10.1371/journal.pmed.1000267]
41 **Chandler NM**, Canete JJ, Stuart KE, Callery MP. Preoperative chemoradiation in resectable pancreatic cancer. *J Hepatobiliary Pancreat Surg* 2003; **10**: 61-66 [PMID: 12918459]
42 **Evans DB**. Preoperative chemoradiation for resectable and locally advanced adenocarcinoma of the pancreas. *J Gastrointest Surg* 2001; **5**: 2-5 [PMID: 11370617]
43 **Russo S**, Chabot J, Saif MW. Resectable pancreatic cancer: is surgery the best first step? *JOP* 2012; **13**: 151-154 [PMID: 22406588]
44 **Abbott DE**, Tzeng CW, Merkow RP, Cantor SB, Chang GJ, Katz MH, Bentrem DJ, Bilimoria KY, Crane CH, Varadhachary GR, Abbruzzese JL, Wolff RA, Lee JE, Evans DB, Fleming JB. The cost-effectiveness of neoadjuvant chemoradiation is superior to a surgery-first approach in the treatment of pancreatic head adenocarcinoma. *Ann Surg Oncol* 2013; **20** Suppl 3: S500-S508 [PMID: 23397153 DOI: 10.1245/s10434-013-2882-0]
45 **Louvet C**, Labianca R, Hammel P, Lledo G, Zampino MG, André T, Zaniboni A, Ducreux M, Aitini E, Taïeb J, Faroux R, Lepere C, de Gramont A. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol* 2005; **23**: 3509-3516 [PMID: 15908661]
46 **Rocha Lima CM**, Green MR, Rotche R, Miller WH, Jeffrey GM, Cisar LA, Morganti A, Orlando N, Gruia G, Miller LL. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol* 2004; **22**: 3776-3783 [PMID: 15365074]
47 **Poplin E**, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, Alberts S, O'Dwyer P, Haller D, Catalano P, Cella D, Benson AB. Phase III, randomized study of gemcitabine and oxaliplatin *vs* gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2009; **27**: 3778-3785 [PMID: 19581537 DOI: 10.1200/JCO.2008.20.9007]
48 **Laurence JM**, Tran PD, Morarji K, Eslick GD, Lam VW, Sandroussi C. A systematic review and meta-analysis of survival and surgical outcomes following neoadjuvant chemoradiotherapy for pancreatic cancer. *J Gastrointest Surg* 2011; **15**: 2059-2069 [PMID: 21913045 DOI: 10.1007/s11605-011-1659-7]
49 **Kindler HL**, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol* 2010; **28**: 3617-3622 [PMID: 20606091 DOI: 10.1200/JCO.2010.28.1386]
50 **Andriulli A**, Festa V, Botteri E, Valvano MR, Koch M, Bassi C, Maisonneuve P, Sebastiano PD. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. *Ann Surg Oncol* 2012; **19**: 1644-1662 [PMID: 22012027 DOI: 10.1245/s10434-011-2110-8]
51 **Lee JL**, Kim SC, Kim JH, Lee SS, Kim TW, Park do H, Seo DW, Lee SK, Kim MH, Kim JH, Park JH, Shin SH, Han DJ. Prospective efficacy and safety study of neoadjuvant gemcitabine with capecitabine combination chemotherapy for borderline-resectable or unresectable locally advanced pancreatic adenocarcinoma. *Surgery* 2012; **152**: 851-862 [PMID: 22682078 DOI: 10.1016/j.surg.2012.03.010]
52 **Sahora K**, Kuehrer I, Schindl M, Koelblinger C, Goetzinger P, Gnant M. NeoGemTax: gemcitabine and docetaxel as neoadjuvant treatment for locally advanced nonmetastasized pancreatic cancer. *World J Surg* 2011; **35**: 1580-1589 [PMID: 21523499 DOI: 10.1007/s00268-011-1113-8]
53 **Gunturu KS**, Yao X, Cong X, Thumar JR, Hochster HS, Stein SM, Lacy J. FOLFIRINOX for locally advanced and metastatic pancreatic cancer: single institution retrospective review of efficacy and toxicity. *Med Oncol* 2013; **30**: 361 [PMID: 23271209 DOI: 10.1007/s12032-012-0361-2]
54 **Faris JE**, Blaszkowsky LS, McDermott S, Guimaraes AR, Szymonifka J, Huynh MA, Ferrone CR, Wargo JA, Allen JN, Dias LE, Kwak EL, Lillemoe KD, Thayer SP, Murphy JE, Zhu AX, Sahani DV, Wo JY, Clark JW, Fernandez-del Castillo C, Ryan DP, Hong TS. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist* 2013; **18**: 543-548 [PMID: 23657686 DOI: 10.1634/theoncologist.2012-0435]
55 **Peddi PF**, Lubner S, McWilliams R, Tan BR, Picus J, Sorscher SM, Suresh R, Lockhart AC, Wang J, Menias C, Gao F, Linehan D, Wang-Gillam A. Multi-institutional experience with FOLFIRINOX in pancreatic adenocarcinoma. *JOP* 2012; **13**: 497-501 [PMID: 22964956 DOI: 10.6092/1590-8577/913]
56 **Marthey L**, Sa-Cunha A, Blanc JF, Cueff A, Francois E, Trouilloud I, Malka D, Bachet J, Coriat R, Taieb J. FOLFIRINOX for locally advanced pancreatic adenocarcinoma, results of an AGEO multicentric prospective study. *Ann Oncol* 2012; **23** (suppl 9): ix238 (abstract 716P)
57 **Shinchi H**, Takao S, Noma H, Matsuo Y, Mataki Y, Mori S, Aikou T. Length and quality of survival after external-beam radiotherapy with concurrent continuous 5-fluorouracil infusion for locally unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys* 2002; **53**: 146-150 [PMID: 12007953]
58 **Zhu CP**, Shi J, Chen YX, Xie WF, Lin Y. Gemcitabine in the chemoradiotherapy for locally advanced pancreatic cancer: a meta-analysis. *Radiother Oncol* 2011; **99**: 108-113 [PMID: 21571383 DOI: 10.1016/j.radonc.2011.04.001]
59 **Morganti AG**, Massaccesi M, La Torre G, Caravatta L, Piscopo A, Tambaro R, Sofo L, Sallustio G, Ingrosso M, Macchia G, Deodato F, Picardi V, Ippolito E, Cellini N, Valentini V. A systematic review of resectability and survival after concur-

rent chemoradiation in primarily unresectable pancreatic cancer. *Ann Surg Oncol* 2010; **17**: 194-205 [PMID: 19856029 DOI: 10.1245/s10434-009-0762-4]

60 **Tinkl D**, Grabenbauer GG, Golcher H, Meyer T, Papadopoulos T, Hohenberger W, Sauer R, Brunner TB. Downstaging of pancreatic carcinoma after neoadjuvant chemoradiation. *Strahlenther Onkol* 2009; **185**: 557-566 [PMID: 19756421 DOI: 10.1007/s00066-009-1977-9]

61 **Kim EJ**, Ben-Josef E, Herman JM, Bekaii-Saab T, Dawson LA, Griffith KA, Francis IR, Greenson JK, Simeone DM, Lawrence TS, Laheru D, Wolfgang CL, Williams T, Bloomston M, Moore MJ, Wei A, Zalupski MM. A multi-institutional phase 2 study of neoadjuvant gemcitabine and oxaliplatin with radiation therapy in patients with pancreatic cancer. *Cancer* 2013; **119**: 2692-2700 [PMID: 23720019 DOI: 10.1002/cncr.28117]

62 **Huguet F**, André T, Hammel P, Artru P, Balosso J, Selle F, Deniaud-Alexandre E, Ruszniewski P, Touboul E, Labianca R, de Gramont A, Louvet C. Impact of chemoradiotherapy after disease control with chemotherapy in locally advanced pancreatic adenocarcinoma in GERCOR phase II and III studies. *J Clin Oncol* 2007; **25**: 326-331 [PMID: 17235048]

63 **Krishnan S**, Rana V, Janjan NA, Varadhachary GR, Abbruzzese JL, Das P, Delclos ME, Gould MS, Evans DB, Wolff RA, Crane CH. Induction chemotherapy selects patients with locally advanced, unresectable pancreatic cancer for optimal benefit from consolidative chemoradiation therapy. *Cancer* 2007; **110**: 47-55 [PMID: 17538975]

64 **Mukherjee S**, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, Crosby T, Jephcott C, Roy R, Radhakrishna G, McDonald A, Ray R, Joseph G, Staffurth J, Abrams RA, Griffiths G, Maughan T. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* 2013; **14**: 317-326 [PMID: 23474363 DOI: 10.1016/S1470-2045(13)70021-4]

65 **Leone F**, Gatti M, Massucco P, Colombi F, Sperti E, Campanella D, Regge D, Gabriele P, Capussotti L, Aglietta M. Induction gemcitabine and oxaliplatin therapy followed by a twice-weekly infusion of gemcitabine and concurrent external-beam radiation for neoadjuvant treatment of locally advanced pancreatic cancer: a single institutional experience. *Cancer* 2013; **119**: 277-284 [PMID: 22778019 DOI: 10.1002/cncr.27736]

66 **Heinrich S**, Pestalozzi BC, Schäfer M, Weber A, Bauerfeind P, Knuth A, Clavien PA. Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008; **26**: 2526-2531 [PMID: 18487569 DOI: 10.1200/JCO.2007.15.5556]

67 **Heinrich S**, Pestalozzi B, Lesurtel M, Berrevoet F, Laurent S, Delpero JR, Raoul JL, Bachellier P, Dufour P, Moehler M, Weber A, Lang H, Rogiers X, Clavien PA. Adjuvant gemcitabine *vs* NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable pancreatic cancer: a randomized multicenter phase III study (NEOPAC study). *BMC Cancer* 2011; **11**: 346 [PMID: 21831266 DOI: 10.1186/1471-2407-11-346]

68 **Tajima H**, Ohta T, Kitagawa H, Okamoto K, Sakai S, Makino I, Kinoshita J, Furukawa H, Nakamura K, Hayashi H, Oyama K, Inokuchi M, Nakagawara H, Fujita H, Takamura H, Ninomiya I, Fushida S, Tani T, Fujimura T, Ikeda H, Kitamura S. Pilot study of neoadjuvant chemotherapy with gemcitabine and oral S-1 for resectable pancreatic cancer. *Exp Ther Med* 2012; **3**: 787-792 [PMID: 22969969]

69 **Sho M**, Akahori T, Tanaka T, Kinoshita S, Tamamoto T, Nomi T, Yamato I, Hokuto D, Yasuda S, Kawaguchi C, Nishiofuku H, Marugami N, Enomonoto Y, Kasai T, Hasegawa M, Kichikawa K, Nakajima Y. Pathological and clinical impact of neoadjuvant chemoradiotherapy using full-dose gemcitabine and concurrent radiation for resectable pancreatic cancer. *J Hepatobiliary Pancreat Sci* 2013; **20**: 197-205 [PMID: 22766692 DOI: 10.1007/s00534-012-0532-8]

70 **Van Buren G**, Ramanathan RK, Krasinskas AM, Smith RP, Abood GJ, Bahary N, Lembersky BC, Shuai Y, Potter DM, Bartlett DL, Zureikat AH, Zeh HJ, James Moser A. Phase II study of induction fixed-dose rate gemcitabine and bevacizumab followed by 30 Gy radiotherapy as preoperative treatment for potentially resectable pancreatic adenocarcinoma. *Ann Surg Oncol* 2013; **20**: 3787-3793 [PMID: 23904005 DOI: 10.1245/s10434-013-3161-9]

71 **Kullmann F**, Hollerbach S, Dollinger MM, Harder J, Fuchs M, Messmann H, Trojan J, Gäbele E, Hinke A, Hollerbach C, Endlicher E. Cetuximab plus gemcitabine/oxaliplatin (GEMOXCET) in first-line metastatic pancreatic cancer: a multicentre phase II study. *Br J Cancer* 2009; **100**: 1032-1036 [PMID: 19293797]

72 **Safran H**, Iannitti D, Ramanathan R, Schwartz JD, Steinhoff M, Nauman C, Hesketh P, Rathore R, Wolff R, Tantravahi U, Hughes TM, Maia C, Pasquariello T, Goldstein L, King T, Tsai JY, Kennedy T. Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress HER-2/neu. *Cancer Invest* 2004; **22**: 706-712 [PMID: 15581051]

73 **Kindler HL**, Ioka T, Richel DJ, Bennouna J, Létourneau R, Okusaka T, Funakoshi A, Furuse J, Park YS, Ohkawa S, Springett GM, Wasan HS, Trask PC, Bycott P, Ricart AD, Kim S, Van Cutsem E. Axitinib plus gemcitabine *vs* placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol* 2011; **12**: 256-262 [PMID: 21306953 DOI: 10.1016/S1470-2045(11)70004-3]

74 **Harder J**, Ihorst G, Heinemann V, Hofheinz R, Moehler M, Buechler P, Kloeppel G, Röcken C, Bitzer M, Boeck S, Endlicher E, Reinacher-Schick A, Schmoor C, Geissler M. Multicentre phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer. *Br J Cancer* 2012; **106**: 1033-1038 [PMID: 22374460 DOI: 10.1038/bjc.2012.18]

75 **Murata Y**, Hamada T, Kishiwada M, Ohsawa I, Mizuno S, Usui M, Sakurai H, Tabata M, Ii N, Inoue H, Shiraishi T, Isaji S. Human equilibrative nucleoside transporter 1 expression is a strong independent prognostic factor in UICC T3-T4 pancreatic cancer patients treated with preoperative gemcitabine-based chemoradiotherapy. *J Hepatobiliary Pancreat Sci* 2012; **19**: 413-425 [PMID: 21898089 DOI: 10.1007/s00534-011-0440-3]

76 **Polistina F**, Costantin G, Casamassima F, Francescon P, Guglielmi R, Panizzoni G, Febbraro A, Ambrosino G. Unresectable locally advanced pancreatic cancer: a multimodal treatment using neoadjuvant chemoradiotherapy (gemcitabine plus stereotactic radiosurgery) and subsequent surgical exploration. *Ann Surg Oncol* 2010; **17**: 2092-2101 [PMID: 20224860 DOI: 10.1245/s10434-010-1019-y]

77 **Tozzi A**, Comito T, Alongi F, Navarria P, Iftode C, Mancosu P, Reggiori G, Clerici E, Rimassa L, Zerbi A, Fogliata A, Cozzi L, Tomatis S, Scorsetti M. SBRT in unresectable advanced pancreatic cancer: preliminary results of a mono-institutional experience. *Radiat Oncol* 2013; **8**: 148 [PMID: 23799996]

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