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Role of neoadjuvant therapy in the management of pancreatic cancer: is the era of biomarker-directed therapy here?

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ABSTRACT

Pancreatic cancer is the 4th leading cause of cancer-related death. Complete surgical resection (CR0) is considered the only curative treatment. Most patients present with unresectable or borderline resectable disease. Many small phase I/II trials have tried to address the role of neoadjuvant treatment using chemotherapy with or without chemoradiation in the management of locally advanced disease. However, many of them looked at the rate of CR0 resection and the feasibility of such treatment. A trend for improved overall survival has been observed in the group of patients with borderline resectable disease who completed neoadjuvant treatment. A large proportion of patients progress while on treatment, sparing them from unnecessary surgery.

We searched the PubMed database (using the key words "pancreatic cancer," or "pancreatic neoplasm," or "pancreatic adenocarcinoma," and "neoadjuvant treatment," or "neoadjuvant chemotherapy," or "neoadjuvant radiation therapy," or "neoadjuvant chemoradiation," or "adjuvant therapy" [all fields] and "clinical trial" or "study") and abstracts presented at the American Society of Clinical Oncology meetings on gastrointestinal cancers. Here, we review the most recent papers that present results on neoadjuvant therapy in pancreatic cancer. All but one report used overall survival as an endpoint. Unfortunately, there are no valid biomarkers predicting tumour progression or recurrence, and response to treatment than can help to guide therapeutic choices.

Our recommendation is to consider neoadjuvant treatment in cases of borderline resectable disease. In patients with primary resectable tumours, surgery followed by adjuvant treatment and enrollment on adjuvant treatment studies would be appropriate.

KEY WORDS

Pancreatic cancer, neoadjuvant therapy, chemoradiation, borderline resectability, biomarkers

1. BACKGROUND

Pancreatic cancer (PCC) is one of the most difficult cancers to treat and the 4th leading cause of cancer-related death in North America. Despite surgical resection, radiation, and chemotherapy, more than 94% of people with PCC do not survive beyond 5 years. Estimates in 2013 suggested that 4700 people in Canada were diagnosed with PCC, with 4300 of them having died[1]. The lifetime probability of developing of PCC is about 1 in 72 for men and 1 in 69 for women[1].

Most PCC patients are diagnosed with metastatic disease at the time of presentation, with median survival duration being 4.5 months. Palliative chemotherapy with gemcitabine extends survival by 2 months, with only 18% of treated patients living more than 1 year. Compared with with gemcitabine as a single agent, recently introduced chemotherapy regimens such as FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin)[2] and gemcitabine with nab-paclitaxel[3] further improved overall survival (OS) by 4.3 and 2 months respectively.

Only small proportion of patients (15%–20%) are diagnosed with limited-stage PCC that is amenable to resection[4]. Only complete surgical resection (CR0) can be considered a curative modality, but most resections are reported to have microscopically positive margins (CR1), with a 74%–80% risk of recurrence[5,6]. Overall, 5-year post-resection survival is 7%–24%, with a median survival of about 1 year[7] given the small, but statistically significant, role of adjuvant chemotherapy. The limitation of adjuvant therapy is that it is often delayed because of prolonged recovery time. As well, a patient's tolerance to chemotherapy and radiation therapy in the postsurgical period is lower; only two thirds of all patients are able to complete scheduled treatment[8,9].

In contrast, the potential benefits of neoadjuvant therapy are early exposure of the patient to systemic therapy, treatment of micrometastatic disease, better tolerability, and reduced risk of seeding during

surgery. Also, patients who progress on therapy can avoid major surgery, with its associated morbidity and mortality. However, no clear recommendations have yet been made with respect neoadjuvant treatment in PCC. All information on this topic comes from small phase II trials or single-centre experiences. many of which have endpoints other than OS.

We searched the U.S. National Library of Medicine's PubMed database (key words were "pancreatic cancer," or "pancreatic neoplasm," or "pancreatic adenocarcinoma," and "neoadjuvant treatment," or "neoadjuvant chemotherapy," or "neoadjuvant radiation therapy," or "neoadjuvant chemoradiation," or "adjuvant therapy" [all fields] and "clinical trial" or "study") and abstracts presented at the American Society of Clinical Oncology (ASCO) meetings on gastrointestinal cancers. Here, we review papers published from 1988 onward that reported results of neoadjuvant therapy in PCC and prognostic or predictive markers to guide therapy.

2. DEFINITION OF RESECTABILITY

Per the American Hepato-Pancreato-Biliary Association, nonmetastatic pancreatic tumours can be divided into resectable, borderline resectable, and unresectable based on involvement of the superior mesenteric artery and vein, the portal vein, the celiac axis, and lymph nodes outside the resection area[10,11]. Surgical skills and techniques have significantly improved in recent years, and pancreatectomy with venous or portal vein resection (or both) is feasible. The morbidity and mortality of such a procedure is comparable to that of a standard Whipple procedure[7].

More objective criteria of resectability have been defined by the MD Anderson Cancer Center pancreatic cancer group[12]. By consensus, a tumour is considered primary resectable if there is "no distant metastases detected, no radiographic evidence of SMV [superior mesenteric vein] and portal vein abutment, distortion, tumour thrombus, or venous encasement, and clear fat planes around the celiac axis, hepatic artery, and CMA [celiac mesenteric artery]." Criteria for borderline resectability include "no distant metastases; venous involvement SMV/portal vein demonstrating tumour abutment with or without impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of nearby arteries, or short segment venous occlusion..., allowing for safe resection and reconstruction; gastrointestinal artery encasement up to the hepatic artery ... without extension to celiac axis; tumor abutment of the SMA not to exceed > 180 degrees of the circumference of the vessel wall." In apparently resectable tumours, staging laparoscopy is advised to be used selectively; in locally advanced unresectable cancer without evidence of distant metastatic disease, laparoscopy is suggested to rule out subclinical metastases and to guide treatment. Nevertheless, tumours that invade arterial structures are associated with significantly increased morbidity and mortality[13] and are considered inoperable[11]. No satisfactory treatment modality is available for this group of patients. Surgery with adjuvant therapy results in the best survival rate, ranging from 8 months to 14.5 months after treatment[14–16].

3. NEOADJUVANT THERAPY IN PRIMARY RESECTABLE TUMOURS

Many chemotherapy regimens have been used in the neoadjuvant treatment of primary resectable PCC: 5-fluorouacil, gemcitabine, mitomycin, paclitaxel, platin compounds, and combinations of chemotherapeutic agents with and without concurrent radiation. No large trial has been reported to date; many of published trials were phase II studies. Of those trials, reported primary endpoints were the rate of local recurrence or pathologic response (or both), safety, and—less likely—survival.

A small phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head reported results for 28 enrolled patients[17]. Of those 28, 93% had resectable disease on restaging. The rate of R0 was 80%, and pathologic tumour response and cytopathic effect were documented in 54% and 83% respectively. In the latter two groups, disease-free survival and OS were, respectively, 9.2 months [95% confidence interval (CI): 5.6 to 12.9 months] and 26.5 months (95% CI: 11.4 to 41.5 months), and 9 months (95% CI: 6.99 to 10.1 months) and 19.1 months (95% CI: 15 to 23.1 months). The authors also reported good tolerance, improved quality of life, and better nutrition status in those patients.

A trial using preoperative gemcitabine-based chemoradiation for patients with primary resectable adenocarcinoma of the pancreatic head reported disease progression or performance status decline (or both) in 13 patients of 86 involved in the trial (15%)[18]. Surgery was successfully performed in 64 patients (74%); the rest of the patients were found to have disease progression that precluded them from surgery. Median OS for all patients was 22.7 months, and 5-year survival was 27%. For the 64 patients who underwent surgery, median OS was 34 months.

The same chemotherapy, combined with concurrent chemoradiation using gemcitabine as a sensitizer, was used in another trial in the neoadjuvant setting to treat patients with stage I–II resectable pancreatic adenocarcinoma[19]. Of the 90 patients who entered the study, 79 completed chemotherapy and chemoradiation. Of 62 patients (78%) who went on to surgery, 52 (66%) underwent pancreaticoduodenectomy. The median OS for all 90 patients was 18.7 months; it was 18.7 months for those who completed neoadjuvant treatment and 31 months for those who underwent radical surgery.

The authors concluded that their approach did not improve survival beyond that seen with preoperative gemcitabine-based chemoradiation.

A small trial of neoadjuvant chemotherapy with paclitaxel and radiation, combined with intraoperative electron-beam radiation therapy, reported that the regimen was feasible[20]. Of 35 patients, 25 underwent laparotomy, with 5 being found to have unresectable disease. However, toxicities such as neutropenia, nausea, vomiting, fatigue, and anorexia were worse than those seen with 5-fluorouracil, and histologic response and survival were similar. Table I summarizes of the above-mentioned trials.

The only trial that compared neoadjuvant and adjuvant treatment head to head in primary resectable PCC reported results for 458 patients with nonmetastatic PCC who underwent resection and who received systemic therapy[21] (Table II). Most tumours in this group (79%) were T3/4, with evidence of lymph node involvement (64%). The rate of nodal positivity was lower in the neoadjuvant group (45% vs. 65%, $p = 0.011$), which also contained a higher proportion of individuals with extrapancreatic extension (86% vs. 77%). The patients receiving neoadjuvant treatment represented a small proportion of the overall cohort (8.5%). Most patients (64.1%) were treated with radiation therapy at some point, but most (94%) received adjuvant radiation. Median survival in the overall group was 19.5 months, with improved OS in the neoadjuvant group (median: 34 months vs. 19 months with adjuvant treatment, $p = 0.003$). On multivariate Cox regression analysis, neoadjuvant treatment was an independent predictor of improved survival (hazard ratio: 0.57; 95% CI: 0.37 to 0.89; $p = 0.013$).

Notably, neoadjuvant treatment has also been used in patients more than 75 years of age. Compared with their younger counterparts, older patients were less likely to complete therapy (72.4% vs. 89.5%, $p < 0.01$), and poor performance status was the most common reason for discontinuing treatment[22].

All studies reviewed—and published meta-analyses of phase I/II trials using neoadjuvant treatment in primary resectable PCC—reported progressive disease in the range of 17%–20% while on treatment[23–25].

4. NEOADJUVANT THERAPY IN LOCALLY ADVANCED PRIMARY UNRESECTABLE (BORDERLINE RESECTABLE) TUMOURS

A distinct group of patients with PCC has been recognized who still have localized disease, but in whom surgery is unfeasible because of resectability issues.

TABLE I Neoadjuvant therapy in primary resectable tumours

Treatment	*Study type*	*Pts (n)*	*Underwent surgery (%)*	*Response rate (%)*	*Survival (months)*		*5-Year overall survival (%)*
					Disease-free	*Overall*	
Gemcitabine–cisplatin	Phase II	28	93	54	9.2 (5.6–12.9) vs. 9 (6.99–10.1)	26.5 (11.4–41.5) vs. 19.1 (15–23.1)	—
Gemcitabine-based chemoradiation	Phase II	86	74	—	—	34 vs. 7 (p=0.001)	36 vs. 0
Gemcitabine–cisplatin → gemcitabine-based chemoradiation	Phase II	90	66	—	—	31 vs. 18.7 vs. 10.5 (p<0.001)[a]	—
Paclitaxel plus radiotherapy with or without intraoperative electron-beam RT	Phase II	35	20 pts	21	—	—	28 (3-year rate)

[a] Pancreaticoduodenectomy versus completed chemotherapy and chemoradiation versus no surgery.
Pts = patients; RT = radiation therapy.

TABLE II Neoadjuvant versus adjuvant systemic therapy for primary resectable tumours

Therapy type	*Patients*		*Involved lymph nodes (%)*	*Median OS (months)*	
	(n)	(%)		*In whole group*	*In extrapancreatic disease*
Neoadjuvant	39	8.5	45	34	31
Adjuvant	419	91.5	65	19	19
			p=0.011	p=0.003	p=0.018
Neoadjuvant therapy as independent predictor of improved survival: hazard ratio: 0.57; 95% confidence interval: 0.37 to 0.89; p=0.013					

OS = overall survival.

A number of chemotherapy regimens were studied in conjunction with radiation in the neoadjuvant setting to convert such tumours to resectability. Most of the studies were small and included 20–40 patients. A retrospective case review of 102 patients with PCC treated with surgical resection reported a lower local recurrence rate in the 42 patients treated with neoadjuvant chemotherapy and radiation (41%) than in the patients treated adjuvantly (5% vs. 34%, $p = 0.02$)[26]. No data on OS were reported. Another study of 41 patients treated with neoadjuvant chemoradiation using 5-fluorouracil and cisplatin reported that only 27 patients were able to complete treatment[27]. A major response was detected in 50% of specimens, with 1 complete response. Operative mortality was 2.8%. The rates of local recurrence and 2-year survival were 4% and 32% respectively. Many papers report disease progression during treatment and longer operative times and postoperative stays[28,29]. Limitations of those studies include a small sample size (28–39 patients), single-institution experience, and varying endpoints.

Outcomes of extended chemotherapy for 24 weeks in patients with borderline resectable tumours in the pancreatic head were reported at the 2014 ASCO gastrointestinal cancers meeting[30]. Of 64 patients, 39 (61%) met resectability criteria and underwent operative exploration; 31 (48%) were resected. The CR0 rate was 87%, and 3 patients (10%) experienced a complete pathologic response. No perioperative mortality was observed. Median OS in the 64 patients overall was 23.6 months; it was 15.4 months in unresectable patients. No data about the type of chemotherapy used in this study were provided.

Based on the experience with FOLFIRINOX in the metastatic setting[2], multiple institutions subsequently introduced the regimen into neoadjuvant treatment. In the metastatic setting, the objective response rate was 31.6% in the FOLFIRINOX group compared with 9.4% in the gemcitabine group, with a survival advantage of 4.3 months[2]. No data were published on stratification for response rate in primary tumour and metastases. Dr. Conroy kindly explained that the reported response was observed in both primary tumours and metastases (personal communication).

A small trial in 39 patients reported conversion to resectability in 7 patients after chemotherapy alone and in 3 more after the addition of radiation therapy[29]. The 1-year progression-free survival and OS were 83% (95% CI: 59% to 96%) and 100% (95% CI: 85% to 100%) respectively. Grade 3–4 toxicities were neutropenia (22%), febrile neutropenia (17%), thrombocytopenia, (11%), fatigue (11%), and diarrhea (11%). Interestingly, and despite a previously reported increased complication rate in the postoperative period in patients treated with stent insertion, 50% of patients received a biliary stent that did not interfere with treatment[31].

The most recent paper (published in *The Oncologist* in 2013) reported a greater than 20% rate of conversion to resectability, with R0 resection, in 5 of 22 patients who received FOLFIRINOX and chemoradiation treatment, followed by distant recurrence in 3 of the 5 within 5 months[32,33].

The use of FOLFIRINOX as neoadjuvant chemotherapy, with or without subsequent chemoradiation, has the best reported rates of conversion to resectability and R0 resection. These trials are the only ones to have reported no disease progression while patients were on treatment, although both were small and had different endpoints.

Another trial using FOLFIRINOX in the neoadjuvant setting followed it with gemcitabine- or capecitabine-based chemoradiation; however, disease progression was reported in 6 of 18 patients[34]. Despite the common occurrence of grades 3 and 4 toxicities that required multiple hospital admissions, 15 of the 18 patients completed treatment. The 12 patients who did not progress underwent CR0. Of those 12, 7 (58.3%) were alive at the time of the report, and 5 had no evidence of disease progression (median time from diagnosis: 22 months; range: 18–35 months). Deaths were recorded in 6 patients who did not complete all intended therapy (time from diagnosis: 6.9–17.5 months). The authors concluded that the treatment is safe and is associated with a favourable resection rate in this high-risk population.

At the ASCO 2014 gastrointestinal cancers meeting, an interesting abstract was presented on the use of neoadjuvant chemoradiotherapy with S-1 (an oral fluoropyrimidine) in primary unresectable PCC[35]. Of 28 patients, 25 completed treatment, and 24 underwent R0 resection with no operative or in-hospital mortality. The authors concluded that this regimen is promising for borderline resectable PCC with major arterial or portal system involvement. The critique of this study includes its small size and the absence of data on survival (Table III).

The largest report on effect of neoadjuvant treatment in borderline resectable PCC was presented at the ASCO 2014 gastrointestinal cancers meeting[36]. Of 2608 patients who underwent curative-intent surgery from 2001 to 2007, just 162 (6%) received neoadjuvant therapy. Those patients were 28% less likely to experience death at 1 year (hazard ratio: 0.72; 95% CI: 0.53 to 0.97; $p = 0.03$), and the investigators observed a trend toward a lower risk of death at 2 years (hazard ratio: 0.82; 95% CI: 0.66 to 1.01; $p = 0.07$). This population-based study was the first to suggest improved survival in patients with PCC treated with neoadjuvant therapy.

5. ARE ANY PREDICTIVE BIOMARKERS AVAILABLE?

A significant proportion of patients progress or develop distant metastasis while on treatment. Many study

TABLE III Neoadjuvant therapy in locally advanced, unresectable (borderline resectable) primary tumours

Treatment	*Pts (n)*	*Underwent surgery (%)*	*Pathologic response rate (%)*	*Recurrence rate (%)*	*Overall survival*
Chemoradiation with or without intraoperative radiation therapy (5FU–cisplatin or gemcitabine or DMS 9621)[a]	102	41	—	5 vs. 34 p=0.02	—
Chemoradiation (5FU–cisplatin)	41	67.5	50	4 (at 2 years)	32% (at 2 years)
Extended chemoradiation (gemcitabine–docetaxel or 5FU–capecitabine–oxaliplatin–irinotecan)	64	48	10	—	Median: 23.6 months vs. 15.4 months in unresected group[a]
FOLFIRINOX → chemoradiation	25	33	24	—	—
FOLFIRINOX → chemoradiation	22	5 pts[a]	27.3	—	—
FOLFIRINOX → chemoradiation (gemcitabine or capecitabine)	18	67	100[a]		Median from diagnosis: 22 months (range: 18–35 months)[a]
Chemoradiation (S-1)	28	24 pts	50	—	—
Gemcitabine–oxaliplatin → chemoradiation (gemcitabine)	39	10 pts			Median: 16.7 months[a]

[a] Pancreaticoduodenectomy versus completed chemotherapy and chemoradiation versus no surgery.
Pts = patients; 5FU = 5-flourouracil; FOLFIRINOX = leucovorin, 5FU, irinotecan, oxaliplatin.

patients who underwent neoadjuvant chemoradiation followed by surgery with curative intent demonstrated disease recurrence within a few months after treatment. The identification of markers that might predict response to treatment (and thus conversion to resectability) and potential for recurrence would be helpful in making decisions about management and avoiding unnecessary surgery[37].

Prognostic biomarkers are an intrinsic property of the tumour that indicate its aggressiveness and prognosticate clinical outcome. Many markers have been investigated for their possible correlation with the biologic behaviour of tumours or the prognosis of patients and their response to treatment.

As a prognostic biomarker leading to treatment optimization, *KRAS* was investigated in a retrospective study of 328 patients undergoing the Whipple procedure for PCC[38]. Median survival duration was 21 months for patients with *KRAS*-mutated tumours (95% CI: 10–40 months) and, at the time of the report, had not been reached for patients with *KRAS* wild-type tumours. Analysis showed that *KRAS* mutation was not a significant factor for OS.

Genetic alterations in three other commonly mutated genes—*TP53, CDKN2A,* and *SMAD4* (*DPC4*)—are associated with the malignant behaviour of PCC and might therefore be useful in making management decisions[39]. The presence of circulating tumour cells in the blood of patients with advanced or metastatic PCC was identified as an independent negative prognostic factor[40]. Detection of such cells before treatment was associated with inferior median progression-free survival [66.0 days (95% CI: 44.8 to 87.2 days) vs. 138 days (95% CI: 124.1 to 151.9 days) in the absence of circulating tumour cells]. A report on circulating tumour cells as a useful biomarker for staging or for identifying micrometastases at the time of diagnosis and as a tool for management decision-making was presented at the ASCO 2014 gastrointestinal cancers meeting[41]. Other biomarkers under investigation that might potentially be prognostic include Bax, Bcl-2, Ki-67, PD-ECGF, S100A4, and survivin, among others[37,42].

Reliable identification and validation of biomarkers predictive of chemotherapy response (so-called predictive biomarkers) might lead to individualized patient therapy[43]. Thus, in a phase II clinical trial of biomarker-directed treatment for localized PCC, the choice of adjuvant therapy was guided by the patient's STREET profile (*SPARC, TOPO1, RRM1, ENT1, ERCC1, TYMS*)[44]. The selected markers were related to commonly accepted chemotherapy regimens used in PCC treatment. The primary endpoint was increase in the surgical resection rate; secondary endpoints were OS and progression-free survival. Just 26 of the preplanned 100 patients were enrolled. It is hard to make a strong recommendation based on those numbers. Further studies are warranted.

6. DISCUSSION AND SUMMARY

The results of treatment for advanced PCC remain suboptimal. Surgery is the only curative modality if R0 resection is feasible. Unfortunately, even in that

group of patients, the 5-year survival rate is about 14%, with a median survival duration of 24 months[45]. In many institutions, the most common treatment today is either chemotherapy alone or combined with chemoradiation.

Numerous small phase I/II trials have reported on neoadjuvant therapy in this setting for two distinct groups of patients: those with primary resectable and with potentially or borderline resectable disease. All trials report that neoadjuvant therapy is well tolerated and feasible to administer[17,19,20,32,46], and patients receive earlier exposure to systemic therapy and treatment for micrometastatic disease. The downside of the approach is that surgery for nonresponders must be delayed, and if the lack of response continues, patients might progress to an unresectable state. However, patients who progress on treatment or who develop distant metastasis avoid extensive surgery that would not be curative in their circumstances, given that micrometastases are believed to be present at diagnosis in those patients[18–20]. On the other hand, only one trial reported improved survival in patients with resectable PCC who underwent neoadjuvant treatment (median OS: 34 months vs. 19 months; $p = 0.003$)[21]. Chemoradiation does not increase the operative risk, but it does make surgeries more technically demanding and requires a longer postsurgical stay[28].

In the treatment of borderline resectable disease, neoadjuvant therapy can downsize the tumour and enhance the rate of R0 resection[29,32,46]. When resectability is achieved, median OS appears to be comparable to that observed in primary resectable PCC[29,46,47]. The most promising chemotherapy regimen used in that setting is FOLFIRINOX, although that regimen is associated with potentially severe toxicities[32,46]. Randomized controlled trial data comparing the various chemotherapy regimens and the use of adjuvant or neoadjuvant treatment are lacking.

Despite the description of more than 1000 markers that are related to PCC and that could potentially predict clinical outcome, no identified biomarkers are being routinely used in clinical practice[42]. Further studies are warranted to compare neoadjuvant with adjuvant treatment approaches.

Our recommendation is to consider neoadjuvant chemotherapy in the setting of borderline resectable disease in carefully selected patients with good performance status. In the metastatic setting, FOLFIRINOX has been associated with the greatest response rate, and so that regimen is likely the best choice of chemotherapy. However, further study is needed.

In patients with primary resectable tumours, we recommend proceeding with surgery, followed by adjuvant therapy and enrolment on adjuvant treatment studies such as PA.6 or ACCORD 24 (phase III trials comparing 6 months of adjuvant gemcitabine or FOLFIRINOX in completely resected PCC) or Radiation Therapy Oncology Group 0848 (phase III trial evaluating the combination of erlotinib and chemoradiation in completely resected adenocarcinoma of the pancreatic head).

7. CONFLICT OF INTEREST DISCLOSURES

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8. REFERENCES

1. Canadian Cancer Society. Pancreatic Cancer Statistics [Web page]. Toronto, ON: Canadian Cancer Society; 2013. [Available at: http://www.cancer.ca/en/cancer-information/cancer-type/pancreatic/statistics/?region=on; cited February 2, 2014]
2. Conroy T, Desseigne F, Ychou M, *et al.* on behalf of the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011;364:1817–25.
3. Von Hoff DD, Ervin TJ, Arena FP, *et al.* Results of a randomized phase III trial (MPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone for patients with metastatic adenocarcinoma of the pancreas with PET and CA19-9 correlates [abstract 4005]. *J Clin Oncol* 2013;31:. [Available online at: http://meetinglibrary.asco.org/content/116827-132; cited June 1, 2014]
4. Canadian Cancer Society's Steering Committee. *Canadian Cancer Statistics 2010.* Toronto, ON: Canadian Cancer Society; 2010.
5. de Castro SM, Kuhlmann KF, van Heek NT, *et al.* Recurrent disease after microscopically radical (R0) resection of periampullary adenocarcinoma in patients without adjuvant therapy. *J Gastrointest Surg* 2004;8:775–84.
6. Rau BM, Moritz K, Schuschan S, Alsfasser G, Prall F, Klar E. R1 resection in pancreatic cancer has significant impact on long-term outcome in standardized pathology modified for routine use. *Surgery* 2012;152(suppl 1):S103–11.
7. Yekebas EF, Bogoevski D, Cataldegirmen G, *et al. 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;247:300–9.
8. Merkow RP, Bilimoria KY, Tomlinson JS, *et al.* Postoperative complications reduce adjuvant chemotherapy use in resectable pancreatic cancer. *Ann Surg* 2013;:[Epub ahead of print].
9. Sohn TA, Yeo CJ, Cameron JL, *et al.* Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators. *J Gastrointest Surg* 2000;4:567–79.
10. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma*. Ver. 2.2014. Fort Washington, PA: NCCN; 2014. [Current version available online at: http://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf (free registration required); cited June 13, 2014]
11. Fleming JB. Borderline resectable pancreatic cancer. Presented at: The International Society of Gastrointestinal Oncology 2012 Gastrointestinal Oncology Conference; Arlington, VA, U.S.A.; September 13–15, 2012. [Available online at: http://www.isgio.org/isgio2012/abstracts/2012AbstractsS2A5.pdf; cited May 31, 2014]

12. Callery MP, Chang KJ, Fishman EK, *et al.* Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. *Ann Surg Oncol* 2009;16:1727–33.
13. Mollberg N, Rahbari NN, Koch M, *et al.* Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011;254:882–93.
14. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. Gastrointestinal Tumor Study Group. *J Natl Cancer Inst* 1988;80:751–5.
15. Li CP, Chao Y, Chi KH, *et al.* Concurrent chemoradiotherapy treatment of locally advanced pancreatic cancer: gemcitabine versus 5-fluorouracil, a randomized controlled study. *Int J Radiat Oncol Biol Phys* 2003;57:98–104.
16. Willett CG, Del Castillo CF, Shih HA, *et al.* Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer. *Ann Surg* 2005;241:295–9.
17. Heinrich S, Pestalozzi BC, Schafer M, *et al.* Prospective phase II trial of neoadjuvant chemotherapy with gemcitabine and cisplatin for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:2526–31.
18. Evans DB, Varadhachary GR, Crane CH, *et al.* Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3496–502.
19. Varadhachary GR, Wolff RA, Crane CH, *et al.* Preoperative gemcitabine and cisplatin followed by gemcitabine-based chemoradiation for resectable adenocarcinoma of the pancreatic head. *J Clin Oncol* 2008;26:3487–95.
20. Pisters PW, Wolff RA, Janjan NA, *et al.* Preoperative paclitaxel and concurrent rapid-fractionation radiation for resectable pancreatic adenocarcinoma: toxicities, histologic response rates, and event-free outcome. *J Clin Oncol* 2002;20:2537–44.
21. Artinyan A, Anaya DA, McKenzie S, Ellenhorn JD, Kim J. Neoadjuvant therapy is associated with improved survival in resectable pancreatic adenocarcinoma. *Cancer* 2011;117:2044–9.
22. Miura JT, Krepline AN, Duelge KD, *et al.* Neoadjuvant therapy for pancreatic cancer in patients older than age 75 [abstract 287]. *J Clin Oncol* 2014;32(suppl 3):. [Available online at: http://meetinglibrary.asco.org/content/122914-143; cited June 1, 2014]
23. Gillen S, Schuster T, Meyer Zum Buschenfelde 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.
24. 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;150:466–73.
25. Andriulli A, Festa V, Botteri E, *et al.* Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. *Ann Surg Oncol* 2012;19:1644–62.
26. Greer SE, Pipas JM, Sutton JE, *et al.* Effect of neoadjuvant therapy on local recurrence after resection of pancreatic adenocarcinoma. *J Am Coll Surg* 2008;206:451–7.
27. Le Scodan R, Mornex F, Girard N, *et al.* Preoperative chemoradiation in potentially resectable pancreatic adenocarcinoma: feasibility, treatment effect evaluation and prognostic factors, analysis of the SFRO-FFCD 9704 trial and literature review. *Ann Oncol* 2009;20:1387–96.
28. Massucco P, Capussotti L, Magnino A, *et al.* Pancreatic resections after chemoradiotherapy for locally advanced ductal adenocarcinoma: analysis of perioperative outcome and survival. *Ann Surg Oncol* 2006;13:1201–8.
29. Leone F, Gatti M, Massucco P, *et al.* 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;119:277–84.
30. Rose JB, Rocha FG, Alseidi A, *et al.* Extended neoadjuvant chemotherapy for borderline resectable pancreatic cancer demonstrates promising postoperative outcomes and survival. *Ann Surg Oncol* 2014;21:1530–7.
31. Povoski SP, Karpeh MS Jr, Conlon KC, Blumgart LH, Brennan MF. Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. *Ann Surg* 1999;230:131–42.
32. Faris JE, Blaszkowsky LS, McDermott S, *et al.* FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. *Oncologist* 2013;18:543–8.
33. Boone BA, Steve J, Krasinskas AM, *et al.* Outcomes with FOLFIRINOX for borderline resectable and locally unresectable pancreatic cancer. *J Surg Oncol* 2013;108:236–41.
34. Christians KK, Tsai S, Mahmoud A, *et al.* Neoadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? *Oncologist* 2014;19:266–74.
35. Hattori M, Fujii T, Suenaga M, *et al.* Neoadjuvant chemoradiotherapy with S-1 in patients with borderline resectable pancreatic cancer [abstract 302]. *J Clin Oncol* 2014;32(suppl 3):. [Available online at: http://meetinglibrary.asco.org/content/122487-143; cited June 1, 2014]
36. Minter RM, Feng MUS, Al-Hawary K, *et al.* Effect of neoadjuvant chemoradiotherapy (NCRT) on survival in patients with borderline resectable (BR) pancreatic adenocarcinoma (PDA) with acceptable peri-operative morbidity [abstract 288]. *J Clin Oncol* 2014;32(suppl 3):. [Available online at: http://meetinglibrary.asco.org/content/122908-143; cited June 1, 2014]
37. Ansari D, Rosendahl A, Elebro J, Andersson R. Systematic review of immunohistochemical biomarkers to identify prognostic subgroups of patients with pancreatic cancer. *Br J Surg* 2011;98:1041–55.
38. Schultz NA, Roslind A, Christensen IJ, *et al. KRAS* mutations and relation to prognosis in patients operated for localized pancreatic cancer and other periampullary cancers [abstract e15618]. *J Clin Oncol* 2009;27:. [Available online at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/e15618; cited June 1, 2014]
39. Oshima M, Okano K, Muraki S, *et al.* Immunohistochemically detected expression of 3 major genes (*CDKN2A/p16, TP53,* and *SMAD4/DPC4*) strongly predicts survival in patients with resectable pancreatic cancer. *Ann Surg* 2013;258:336–46.
40. de Albuquerque A, Kubisch I, Stolzel U, *et al.* Prognostic and predictive value of circulating tumor cell analysis in colorectal cancer patients. *J Transl Med* 2012;10:222.

41. Ankeny JS, Hou S, Lin M, *et al.* Pancreatic circulating tumor cells as a diagnostic adjunct in pancreatic cancer [abstract 175]. *J Clin Oncol* 2014;32(suppl 3):. [Available online at: http://meeting.ascopubs.org/cgi/content/short/32/3_suppl/175?rss=1; cited June 1, 2014]
42. Jamieson NB, Carter CR, McKay CJ, Oien KA. Tissue biomarkers for prognosis in pancreatic ductal adenocarcinoma: a systematic review and meta-analysis. *Clin Cancer Res* 2011;17:3316–31.
43. Xu X, Strimpakos AS, Saif MW. Biomarkers and pharmacogenetics in pancreatic cancer. Highlights from the "2011 ASCO Annual Meeting." Chicago, IL, USA; June 3–7, 2011. *JOP* 2011;12:325–9.
44. Tsai S, Ritch PS, Erickson B, *et al.* Phase II clinical trial of biomarker-directed therapy for localized pancreatic cancer [abstract TPS4147]. *J Clin Oncol* 2013;31:. [Available online at: http://meetinglibrary.asco.org/content/114020-132; cited June 1, 2014]
45. Perysinakis I, Avlonitis S, Georgiadou D, Tsipras H, Margaris I. Five-year actual survival after pancreatoduodenectomy for pancreatic head cancer. *ANZ J Surg* 2013;:[Epub ahead of print].
46. 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.
47. Katz MH, Pisters PW, Evans DB, *et al.* Borderline resectable pancreatic cancer: the importance of this emerging stage of disease. *J Am Coll Surg* 2008;206:833–46.

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