

Current and emerging therapies for the treatment of pancreatic cancer

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Abstract: Pancreatic adenocarcinoma carries a dismal prognosis and remains a significant cause of cancer morbidity and mortality. Most patients survive less than 1 year; chemotherapeutic options prolong life minimally. The best chance for long-term survival is complete resection, which offers a 3-year survival of only 15%. Most patients who do undergo resection will go on to die of their disease. Research in chemotherapy for metastatic disease has made only modest progress and the standard of care remains the purine analog gemcitabine. For resectable pancreatic cancer, presumed micrometastases provide the rationale for adjuvant chemotherapy and chemoradiation (CRT) to supplement surgical management. Numerous randomized control trials, none definitive, of adjuvant chemotherapy and CRT have been conducted and are summarized in this review, along with recent developments in how unresectable disease can be subcategorized according to the potential for eventual curative resection. This review will also emphasize palliative care and discuss some avenues of research that show early promise.

Keywords: neoadjuvant therapy, palliative care adeno carcinoma, mortality

Introduction

Despite all efforts at developing effective therapy, pancreatic adenocarcinoma carries a dismal prognosis¹ and remains a significant cause of cancer morbidity and mortality. There is no screening test for this disease, and patients are generally only identified when already symptomatic with weight loss, back or abdominal pain, or obstructive jaundice. Most patients survive less than 1 year; chemotherapeutic options prolong life minimally. The best chance for long-term survival is complete resection, which offers a 3-year survival of only 15%.² Most patients who do undergo resection will go on to die of their disease³ (see Figure 1). Research in chemotherapy for metastatic disease has made only modest progress and the standard of diabetes mellitus care remains the purine analog gemcitabine.⁴

Well-established risk factors for pancreatic cancer include smoking and family history. There is a slight increased risk with some familial cancer syndromes, including Lynch syndrome⁵ and *BRCA2* mutations.⁶ Recently, obesity has been identified as a modifiable risk factor in the development of and mortality from pancreatic cancer.^{7–10} There are no screening recommendations for this disease.

In this article, we will review current treatments for pancreatic cancer. We will discuss adjuvant therapy and recent developments in how unresectable disease can be subcategorized according to the potential for eventual curative resection. Considering the bleak prognosis of this disease, an important challenge is maintaining quality of remaining life with multidisciplinary support. Therefore, we will emphasize palliative care.

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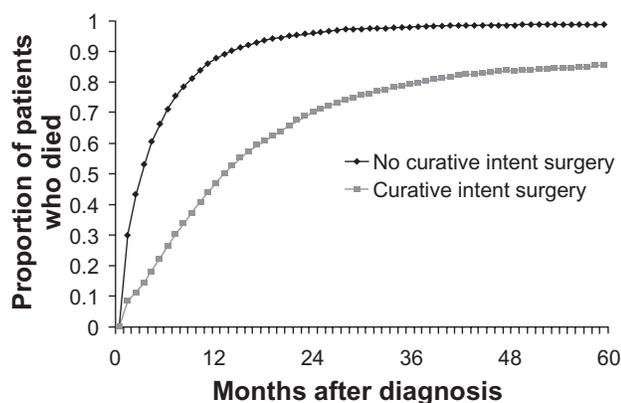


Figure 1 Survival of patients with pancreatic cancer categorized by the receipt of curative intent surgery. Copyright © 2007. Reproduced with permission from Shaib Y, Davila J, Naumann C, El-Serag H. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. *Am J Gastroenterol.* 2007;102(7):1377–1382.

Finally, we will discuss some avenues of research that show early promise as our understanding of the biology of this devastating disease improves.

Managing resectable disease

Surgical resection for treatment of localized pancreatic cancer is currently the best chance for cure. Unfortunately, up to

85%¹¹ of patients initially present in advanced or metastatic stages, and curative resection is only possible in roughly 13% of patients.¹ Even in patients who present with more favorable disease and undergo surgery with curative intent, there is a high rate of relapse,^{12,13} with high local recurrence rates of up to 50% following surgery alone¹⁴ leading to a 5-year survival rate of under 5%.¹ This aggressive recurrence pattern is highly suggestive of the presence of micrometastases at the time of surgery.¹¹ For resectable pancreatic cancer, presumed micrometastases provide the rationale for adjuvant chemotherapy and chemoradiation (CRT) to supplement surgical management. Numerous randomized control trials, none definitive, of adjuvant chemotherapy and CRT have been conducted, summarized in Table 1.

Adjuvant CRT and chemotherapy: regional differences

The earliest prospective randomized trial to suggest a survival benefit from the addition of postoperative CRT was the Gastro-Intestinal Study Group (GITSG) trial.¹⁵ Patients receiving bolus fluorouracil (5-FU) and a split course of 20 Gy radiation for 2 cycles after primary surgery followed by maintenance

Table 1 Randomized control trials of adjuvant chemotherapy and CRT

Study	Year	Chemo	RT	No. of patients	MOS	2-yr survival rate, %	P value
GITSG Kalsner ¹⁵	1985	5-FURT→5-FU	40 Gy	21	20	42	0.035
		Observation		22	11	15	
Bakkevoid et al ¹⁹	1993	AMF		30	23	43	0.009
		Observation		31	11	32	
EORTC Klinkenbijn et al ¹⁶	1999	5-FURT	60 Gy	60	17.1	37	0.099
		Observation		54	12.6	23	
ESPAC-1 Neoptolemos et al ¹⁸	2004	5-FURT	40 Gy	145	15.9	29	0.053
		Observation		144	17.9	41	
		5-FU/LV		147	20.1	40	
		Observation		142	15.5	30	
ROTG 9704 Regine et al ¹⁹	2006	All patients	50.4 Gy				0.15
		GEM→5-FURT→GEM		221	18.8		
		5-FU→5-FURT→5-FU		221	16.9		
		Pancreas head					
Kosuge et al ²¹	2006	GEM→5-FURT→GEM	50.4 Gy	187	20.6		0.033
		5-FU→5-FURT→5-FU		194	16.9		
		5-FU/CDDP		45	12.5		
CONKO-001 Oettle et al ²²	2007	Observation		44	15.8		0.94
		GEM		179	22.1	47.5	
Kosuge et al ²¹ /Ueno et al ²³ (abstract)	2007	Observation		175	20.2	42	0.06
		GEM		58	22.3	48.3	
ESPAC-3 Neoptolemos et al ²⁴	2009	5-FU/LV		60	18.4	39.8	0.29
		GEM		551	23.0		
		GEM		537	23.6		

Abbreviations: AMF, adriamycin/mitomycin CRT, chemoradiation; RT, radiation therapy; MOS, median survival overall; GITSG, Gastrointestinal Tumor Study Group; 5-FURT, fluorouracil and radiation; CDDP, cisplatin; EORTC, European Organization for Research and Treatment of Cancer; ESPAC, European Study Group For Pancreatic Cancer; 5-FU, fluorouracil; GEM, gemcitabine; LV, leucovorin; RTOG, Radiation Therapy Oncology Group; CONKO, German Study Group for Pancreatic Cancer.

5-FU were reported to have a median overall survival (OS) of 20 months compared with 11 months with surgery alone. Though this study had a small sample size, early termination, and suboptimal radiation dosing, it was still highly influential, making concurrent adjuvant CRT the standard of care in the United States. In Europe, however, the European Organization for Research and Treatment of Cancer (EORTC) conducted a similar study comparing postoperative radiation with continuous infusion of 5-FU without subsequent chemotherapy maintenance. The median duration of survival was 19.0 months for the observation group and 24.5 months in the treatment group but the study did not reach statistical significance (two-tailed test, $P = 0.208$).¹⁶ Thus, CRT did not become standard practice in Europe. However, the European study may have an inappropriate statistical design that biased against the detection of treatment effects. As a follow up to the positive GITSG study, a one-tailed rather than two-tailed test would have been appropriate and would have brought the results to significance ($P = 0.049$) in favor of CRT.¹⁷ This finding is even more robust considering that nearly 20% of the patients assigned to the CRT arm were not even treated, which would further bias the study against CRT.

Despite these criticisms, the debate continued. A second line of evidence has led most European clinicians to adopt chemotherapy rather than CRT as the current standard of care. The European Study Group for Pancreatic Cancer-1 (ESPAC-1) study showed a near-doubling of benefit for adjuvant chemotherapy with infusional 5-FU and leucovorin (LV), but no benefit with 5-FU and radiation. This trial had a 2×2 factorial design comparing CRT to observation and infusional 5-FU/LV to observation. The estimated 5-year survival rate was 10% among patients assigned to receive CRT and 20% among patients who did not receive CRT ($P = 0.05$).¹⁸ However, this study may have suffered from selection bias and an insufficient sample size for a 2×2 study design.¹⁹ In addition, there was an excessive rate of local recurrence in the CRT arm, suggesting the radiation schedule was suboptimal.²⁰

Outside the United States, adjuvant chemotherapy remains the focus of trials

Trials of adjuvant chemotherapy alone have continued subsequent to the EORTC and ESPAC-1 trials. A trial of 5-FU and cisplatin based in Japan showed no difference, and possibly harm in patients receiving this aggressive adjuvant chemotherapy regimen.²¹ The CONKO-001 trial of 368 patients showed a benefit in disease-free survival (DFS) for patients receiving gemcitabine compared with observation

(median DFS, 13.4 months vs 6.9 months), but only a small and insignificant difference in OS.²² A similar but smaller study in Japan did not reach statistical significance.²³ At the 2009 American Society of Clinical Oncology (ASCO) annual meeting, Neoptolemos et al²⁴ presented the results of ESPAC-3 trial in which patients were randomized 1:1 to adjuvant chemotherapy with 5-FU/LV bolus vs gemcitabine. The OS was 23.0 months vs 23.6 months ($P = 0.39$) in this large study, with the conclusion that gemcitabine is not superior to 5-FU in the adjuvant setting.²⁴ However, ESPAC-4, currently enrolling in Europe, is based on the assumption that gemcitabine is superior to 5-FU in the adjuvant therapy setting. ESPAC-4 will directly compare gemcitabine to a gemcitabine–capecitabine combination after resection of pancreatic cancer, again without radiation. Enrollment of more than 1,000 patients is planned. Unfortunately, there will be no comparison of adjuvant CRT to chemotherapy alone, maintaining the regional differences in both practice and clinical trials.

Can locally advanced disease be resected?

The most significant advance in treating locally advanced disease has been the recognition that treatment has potential to downstage tumors to allow secondary surgical manage-

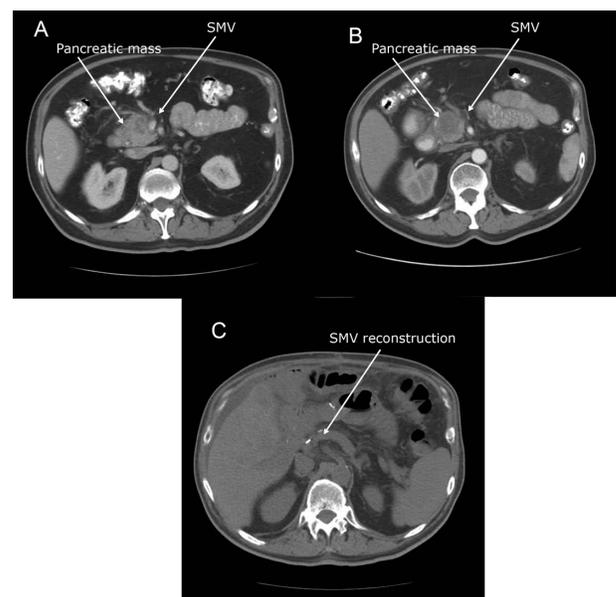


Figure 2 Downstaging with neoadjuvant therapy: 59-year-old man with a 2.2 × 1.8 cm pancreatic head mass found to be pancreatic adenocarcinoma on biopsy **A)** Pretreatment scan. Note severe SMV impingement, which fits criteria for borderline resectable disease **B)** Post-treatment scan. The patient was treated with neoadjuvant capecitabine 1500 mg po bid and concurrent radiation. The SMV is less confined; the pancreas mass remains similar in size. **C)** Post-operative scan. The patient underwent pancreaticoduodenectomy with jugular SMV reconstruction.

Table 2 Criteria for defining resectability status^{25,26}

	Resectable	Borderline resectable	Unresectable
Venous	Patent SMV and portal vein	Severe SMV impingement or reconstructable SMV occlusion	Unreconstructable SMV/portal occlusion Greater than 180° SMA encasement
Arterial	Clear fat plane around celiac A and SMA	Less than 180° abutment of SMA, reconstructable encasement of SMA Reconstructable abutment or encasement of hepatic artery	Greater than 180° SMA encasement Unreconstructable SMA involvement Any celiac abutment (head mass) Greater than 180° SMA encasement (body mass)
Aorta			Aortic invasion or encasement
Mets	No distant metastases		Distant metastases Metastases to LN beyond field of resection

ment²⁵ (see Figure 2). With this new paradigm of possibly downstaging tumors, locally advanced pancreatic cancer is categorized into 2 distinct groups: borderline resectable and unresectable, summarized in Table 2.^{25,26} Before these criteria were established, the standard of care for locally advanced disease had been concurrent CRT without expectation of making the disease resectable.^{27,28} These criteria allow borderline resectable disease with no vascular involvement to be distinguished from locally advanced unresectable disease with vascular involvement. Both these categories may benefit from neoadjuvant therapy, and secondary resection has emerged as an important therapeutic goal.

Early attempts at preoperative treatment using chemotherapy,²⁹ radiotherapy,³⁰ and CRT³¹ demonstrated that neoadjuvant treatment of previously inoperable pancreatic tumors may result in potentially curative secondary surgery. In this scenario, the chief objective of neoadjuvant therapy for borderline resectable patients is to induce a partial tumor response and, therefore, increase the likelihood of complete resection with negative margins. Additionally, exposure of the tumor to chemotherapeutic agents before resection allows for the sensitivity of the tumor to those agents to be assessed. Tumors that progress despite therapy

may be those with aggressive biology that would progress even if resected and treated adjuvantly. Those patients who progress during neoadjuvant treatment are, therefore, spared the morbidity and mortality of major surgery. On the other hand, patients with favorable responses to preoperative therapy as demonstrated by radiographic tumor regression and improvement in serum tumor marker levels may have the best chance for an R0 resection and a favorable long-term outcome.²⁵

Might neoadjuvant CRT improve resectability and survival?

Preoperative therapy for locally advanced pancreatic cancer has been the focus of multiple phase II trials. Several of these trials have demonstrated encouraging rates of secondary resection.^{32,33} The emergence of borderline resectable disease as a separate category in trials in 2002 (see Table 3) has opened the possibility of evaluating the role of neoadjuvant CRT. Previously, trials failed to distinguish borderline resectable from resectable or borderline unresectable disease. In the single study to address this subgroup, Brown et al³⁴ tested a combination of radiosensitizing agents with 50.4 Gy of radiation in 13 patients with borderline resectable disease. All patients underwent secondary surgery with intent for cure. Eighty-five percent (11 patients) had complete, or R0, resections, which led to a 2-year survival of 69% (n = 9) and 8 patients disease-free at 2 years.

In a phase II trial by Massucco et al³³ of neoadjuvant gemcitabine with 45 Gy radiation in borderline resectable and unresectable locally advanced disease, 8 patients who had unresectable disease responded favorably to neoadjuvant therapy and went on to resection. These patients had similar OS and DFS to those with initially resectable disease receiving the same regimen.³³ Like many previous trials, this study found margin status to be the most powerful predictor of survival. This trial is interesting for having used gemcitabine as a radiation sensitizer, albeit at only 50 mg/m² twice weekly,³³ far less than the full dose of gemcitabine, 1,000 mg/m² weekly, that has been shown to be of benefit in metastatic disease,⁴ and which would be hypothesized to better treat micrometastases.

Role of gemcitabine in CRT

Historically, 5-FU has been used as a radiation sensitizer in pancreatic cancer, even though it has been demonstrated to be inferior to gemcitabine for treating metastatic disease.⁴ The Massucco et al³³ trial, described above demonstrated the possibility of secondary surgical resection after CRT, is one

Table 3 Summary of studies for locally advanced pancreatic cancer

Study	Year	Chemo	Radiation	No. of patients	Resection rate, %	Borderline resection rate	Borderline resection rate	Median survival unresected	Median survival resected (borderline)
Weese et al ³²	1990	5-FU, MIT	50.4	15	67			7	
Jessup et al ²⁹	1993	5-FU	>45	16	13			8	20
Yeung et al ²⁰	1993	5-FU, MIT	50.4	26	38			8	
Kamthan et al ²¹	1997	5-FU, CDDP, STZ	54	35	14			15	31
White et al ²²	1999	5-FU, MIT or CDDP	45	25	20			10	
Bajetta et al ²³	1999	5-FU, Leu	50	32	16			10 overall	
Wanebo et al ²⁴	2000	5-FU, CDDP	45	14	64 (3 refused)			9	19
Kim et al ²⁵	2002	5-FU/GEM	45	87	1 (n = 1)			11	18
Rau et al ²⁶	2002	5-FU, CDDP	45	26	42			10	
Crane et al ¹⁴	2002	5-FU or GEM	30	114	2 vs 9			9 vs 10	
Aristu et al ²⁷	2003	5-FU or CDDP	45	47	19			10	23
Ammori et al ²⁸	2003	GEM	39.6	67	13	18	33%	12	18
Wilkowski et al ²⁸	2004	GEM, CDDP	45-50	47	42 (R0 27)			11	24 (for R0)
Sa Cunha et al ²⁹	2005	5-FU, CDDP	45	61	21			11	28
Delpero ³⁰	2006	5-FU, CDDP	45	26	58			21	Not reached
Adhoue et al ³¹	2006	5-FU CDDP	45-50.4	33	24			16	
Massuco et al ³³	2006	GEM	45	28	29%			10	721
Marti et al ⁴¹	2007	GEM, CDDP	45	26	15	3	100%	13	(12-62)
Budiharto et al ¹³	2008	GEM	45 or 54	5 vs 6	60 vs 33			20	(69% OS at 2 yrs)
Brown et al ³⁴	2008	Various 5-FU, cap/bev, or GEM	50.4			13	100		
Chauffert et al ⁴²	2008	5-FU/CDDP + GEM	60 Gy	59					
Tinkl et al ³²	2009	GEM, CDDP or 5-FU, MIT	3D55.8	120	32			25	52 (for R0)
Small et al ³⁸	2008	GEM	36	9.14	33%		7%*	3	33%

Notes: *One patient deemed unresectable underwent surgery after neoadjuvant treatment.

Abbreviations: 5-FU, fluorouracil; CDDP, cisplatin; GEM, gemcitabine; cap/bev, capecitabine/bevacizumab; MIT, mitomycin C treatment.

of a series of trials exploring the potential of gemcitabine as a radiation sensitizer. In the Munich Pancreas Trial, gemcitabine at a dose of 300 mg/m² was given on days 1, 15, and 29 with 5-FU continuous infusion and concurrent radiation (45–50 Gy) in 32 patients with locally advanced unresectable pancreatic cancer. They demonstrated an overall response rate (RR) of 62.5%. An impressive 37.5% of patients were found to be resectable after neoadjuvant treatment.³⁵

An number of phase I and II trials have explored full-dose gemcitabine given in conjunction with varying doses of radiotherapy^{36,37} and have shown encouraging RRs, allowing in some cases for secondary surgery for previously unresectable disease. In a single-arm trial of 41 patients, Small et al³⁸ have reported that full-dose gemcitabine with concurrent radiation (36 Gy) in nonmetastatic pancreatic cancer resulted in 3 of 9 cases of borderline resectable disease going on to secondary resection; 1 of 14 unresectable patients went on to resection. The 12-month survival rate in this study was 94% (95% confidence interval [CI]: 82%–100%) for primarily resectable disease, 76% (95% CI: 47%–100%) in secondary resection after neoadjuvant treatment, and 47% (95% CI: 19%–75%) for unresectable patients. Of 17 surgically resected patients, 16 showed negative margins at the time of resection,³⁶ suggesting that the CRT may have contributed to local control; however, the large overlap in CIs for these results raises the necessity of a larger scale study to confirm the benefit of full-dose gemcitabine with concurrent radiation.

Because of the theoretical importance of full-dose gemcitabine for treating micrometastatic disease and for improving RRs, some researchers argue for the use of gemcitabine before and after 5-FU-based CRT in a sandwich regimen, explored in the Radiation Therapy Oncology Group (RTOG) 97-04 trial. 5-FU was used as a radiosensitizer in both groups. Before and after CRT, patients received gemcitabine or 5-FU in a 1:1 ratio. OS was similar in both groups (18.8 months vs 16.9 months), but in subgroup analysis, patients with resectable pancreatic head mass had significant benefit on the gemcitabine arm (20.5 months vs 16.9 months, $P = 0.033$),³⁹ again suggesting the importance of gemcitabine in this disease.

Comparing CRT to chemotherapy: neoadjuvant intent

Although there have been no recent trials comparing adjuvant chemotherapy to CRT for resected pancreatic cancer, this comparison is being made in the setting of locally advanced pancreatic cancer.

Eastern Cooperative Oncology Group-4201 (ECOG-4201) is the first study that directly compared gemcitabine in combination with radiation therapy vs gemcitabine alone in patients with locally advanced pancreatic cancer. In the radiation arm, gemcitabine was given at a dose of 600 mg/m² weekly concurrent with radiation, and then followed by 5 cycles of full-dose gemcitabine. The concurrent CRT was found to be more myelosuppressive and was also associated with considerable gastrointestinal toxicity and fatigue. However, the addition of radiation therapy to gemcitabine significantly improved OS ($P = 0.034$) and tripled the survival rate at 24 months for patients with locally advanced pancreatic cancer.⁴⁰

Does more chemotherapy improve RRs to radiation?

In a small trial, Marti et al⁴¹ found that adding cisplatin to gemcitabine with 45 Gy concurrent radiation was well tolerated and allowed some patients with locally advanced pancreatic cancer to go on to resection. However, this benefit has not been borne out in phase III trials. The French 2000–2001 Fédération Francophone de la Cancérologie Digestive/Société Française de Radiothérapie Oncologie (FFCD/SFRO) study was a phase III trial comparing intensive induction CRT (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. This trial was a departure from the European approach of neoadjuvant chemotherapy alone. The intensive regimen unfortunately showed a significant decrease in OS from 13 to 8.6 months,⁴² possibly associated with toxicity of the aggressive chemotherapy. Although RR was not reported, there was similar tumor progression in both arms. The role of platinum agents in CRT for pancreatic cancer remains unsupported by evidence.

Who is resectable? radiologic staging

Although computed tomographic (CT) scans are the standard imaging modality at present, they are often unable to differentiate active pancreatic cancer from necrotic or fibrous tissue.⁴³ Therefore, they are ineffective at identifying which tumors have been adequately downstaged to allow resection. Indeed, there are reports of complete pathologic response to neoadjuvant therapy not appreciated on preoperative scans.⁴⁴ Thus, an important area of research is the development of advanced postprocessing techniques to increase the resolution of CT scanning for better restaging of disease,⁴⁵ an important unmet need at present. An alternate modality for clinical assessment is 2-deoxy-2-[¹⁸F]fluoro-D-glucose-positron

emission tomographic scanning, which in 1 small study has been used to quantify response to neoadjuvant treatment.⁴⁶ One approach to this dilemma is to err on the side of secondary surgery for curative intent, but this may increase the rate of futile surgery and subsequent complications.

The future of neoadjuvant therapy in borderline unresectable and resectable diseases

As the above definitions of resectability are incorporated into clinical trials and surgical technique and as criteria for assessment of margin status become standardized, the relative contributions of chemotherapy and radiation to the benefit neoadjuvant therapy will become more clear.¹⁴ Taken together, the trials conducted in locally advanced pancreatic cancer suggest that CRT is not only tolerable but also can downstage the disease, thus enabling secondary resection, possibly prolonging survival. The possibility of using full-dose gemcitabine as a radiation sensitizer is intriguing, but phase III trials have not yet been conducted with full-dose gemcitabine as a radiation sensitizer. Until such trials are available, a reasonable standard of care for locally advanced pancreatic cancer is the RTOG 97-04 sandwich approach with full-dose gemcitabine before and after CRT with 5-FU.³⁹

Metastatic disease: treating the patient not the disease

Once pancreatic cancer becomes metastatic, it is uniformly fatal. At this point, the goal of treatment shifts away from curative attempts and toward prolonging survival while maintaining good quality of life. Chemotherapy is an important component of palliative care but must be deployed as part of a multidisciplinary approach to treat pain, minimizing weight loss, and manage declines in functional status.

Pain control

Pain control in advanced pancreas cancer needs to be aggressive and comprehensive. The appropriate initial line of attack is long-acting narcotics supplemented by short-acting preparations for breakthrough pain. A key principle is to balance pain control against oversedation in order to maintain both comfortable and functional living. For patients who suffer from postprandial pain, multidisciplinary support is necessary. Postprandial pain may be alleviated by pancreatic enzyme replacement therapy (PERT), or celiac plexus block, both detailed below. Nutritional support is also important in staving off cachexia, which can interfere with pain management options like transdermal fentanyl.



Figure 3 **A)** CT image after injection of a small volume of dilute contrast agent through both needles, confirming correct distribution of injected contrast around the celiac axis (arrows) prior to alcohol injection. **B)** After injection of alcohol, darkened region (arrow) shows its distribution in the vicinity of the celiac plexus. Copyright © 2007. Reproduced with permission from Arellano RS. Image-guided pain management, Part I: celiac plexus block for palliative pain relief. *Radiology Rounds*, Vol 5. Boston, MA: Massachusetts General Hospital; 2007.

For patients who have localized cancer-related pain, often described as band-like and radiating from the epigastrium, an important palliative option is neurolytic celiac plexus block (NCPB). In this procedure, an analgesic, such as lidocaine and an anti-inflammatory or a neurolytic agent, can be introduced to the celiac plexus. At some centers, this procedure may be done endoscopically with endoscopic ultrasound guidance, but it can also be accomplished by fluoroscopic and CT guidance (see Figure 3). The approach may be made from either an anterior or a posterior approach based on anatomy and the patient's comfort.⁴⁷ Celiac plexus block may also be applied intraoperatively on initial surgical exploration with 50% ethanol or 6% phenol under direct visualization during laparotomy.⁴⁸ In a meta-analysis, partial or complete pain relief was achieved in 90% of patients via NCPB.⁴⁹ NCPB can decrease the subsequent onset pain even in patients without preexisting pain at the time of surgery.⁵⁰ Although the efficacy of this procedure is high, the duration or response is limited. As patients live longer, the efficacy of repeated NCPB diminishes, presumably due to disease metastasizing past the splanchnic bed,⁴⁷ and systemic analgesics become necessary to control pain.

PERT

Patients with pancreatic cancer may suffer from symptoms of pancreatic enzyme deficiency and malabsorption. The deficiency stems from both disease-related obstruction of the pancreatic duct and destruction of normal pancreatic parenchyma, as well as unwanted consequences from interventional or surgical procedures.⁵¹ The rate of malabsorption can be 85%–90% in patients with pancreatic carcinoma, even in those who have not had surgery.⁵² Malabsorption can lead to vitamin and mineral

deficiencies, particularly the fat-soluble vitamins A, D, E, and K. Symptoms of pancreatic enzyme deficiency include abdominal pain and distention, particularly postprandial, flatus, belching, diarrhea, steatorrhea, and weight loss.

To avoid symptoms and sequela of these deficiencies, it is important to provide pancreatic enzyme replacement therapy (PERT). A standard initial dose of replacement therapy is 50,000 IU of lipase with each meal. The dosage is then titrated to symptoms, leading eventually to a widely varying therapeutic range. PERT can be optimized with the addition of a proton-pump inhibitor, which increases intestinal pH and leads to decreased inactivation of prescribed PERT.⁵³

Nutritional status

Pancreatic cancer is associated with cachexia, which is in and of itself a significant systemic symptom. Weight loss of 5% or more has been associated with an increased rate of metastatic disease, which renders surgical resection moot.⁵⁴ It is not clear whether weight loss is causative since those with more tumor burden may lose more weight. Weight loss is, therefore, useful as a prognostic indicator⁵⁵ and has even been considered an end point in major trials.⁴

Cachexia has important implications for symptom management. Because many cachectic patients with pancreatic cancer swallow poorly or have significant nausea and vomiting, transdermal fentanyl is an attractive treatment option. Unfortunately, cachexia has been demonstrated to decrease absorption of the narcotic due to lack of subcutaneous fat.⁵⁶

For patients who have intractable nausea and vomiting on the basis of mechanical obstruction not amenable to endoscopic stenting, a gastric bypass surgery may be necessary to allow patients to continue to eat. A gastrojejunostomy with anastomosis between the jejunum and the anterior or posterior wall of the stomach can be performed to alleviate gastric outlet obstruction.⁵⁷

Hyperbilirubinemia

Clearance of gemcitabine depends on a functioning liver. Thus, biliary tract obstruction due to tumor or complications of surgery, which may lead to hyperbilirubinemia as evidenced by jaundice, pruritus, and even direct neurotoxicity,⁵⁸ can significantly delay optimal treatment. If the cancer is unresectable, biliary obstruction can often be relieved endoscopically by the placement of biliary stents.⁵⁹ Stenting can decompress the biliary passages and relieve symptoms in the setting of pancreatic cancer, with 60% of patients experiencing complete resolution of pain and 25% of patients

experiencing partial pain relief.⁵⁹ However, stenting can also lead to many infectious complications.⁶⁰ The main complication is stent occlusion, which accounts for the risk of cholangitis of approximately 7% in the setting of malignant biliary obstruction.⁶¹ Biliary stenting is also associated with up to a 10% postprocedure incidence of cholecystitis.⁶²

To reduce the risk of stent occlusion and subsequent infectious complications, plastic stents, if used for malignant biliary obstruction, must be changed regularly. A more occlusion-resistant alternative to plastic stents is metal stents, which are, therefore, the intervention of choice in patients with malignant distal obstructive jaundice due to pancreatic carcinoma.⁶³ Plastic stents should only be used in the palliative setting in patients with short predicted survival, who are not expected to require the patency benefits of metal stents. Historically, the surgical literature has reported postoperative infectious complications associated with preoperative stenting for patients undergoing pancreaticoduodenectomy.^{64–66} However, a Cochrane database review found no significant increased risk of infectious complications in this group,⁶⁷ so there is no known rationale for avoiding this important palliative procedure.

In some cases, palliative surgery to bypass the biliary obstruction may be possible if endoscopic stenting is not feasible. Patency rates appear to be superior with surgical as opposed to endoscopic interventions, but at the cost of surgical morbidity.⁶³ In addition, patients found to have unresectable disease at the time of laparotomy may benefit from a surgical biliary bypass with an hepaticojejunostomy, a procedure to anastomose the hepatic duct to the jejunum to relieve obstruction.⁵⁷

Chemotherapy for metastatic disease

The primary intent of chemotherapy for metastatic pancreatic cancer is to relieve symptoms while prolonging survival. By causing tumor regression, chemotherapy may relieve the symptoms of biliary obstruction, reduce ascites, and contribute to resolving pain. Mallinson et al⁶⁸ published the first randomized, controlled trial to demonstrate a survival benefit with systemic chemotherapy in 1980. Patients with unresectable disease (diagnosed at laparotomy) were treated with 5-FU, methotrexate, vincristine, and cyclophosphamide. Chemotherapy treatment was associated with a significant improvement in OS of 44 weeks compared with only 9 weeks with best supportive care (BSC).⁶⁸ Several other combination regimens were then studied with promising results in phase II trials, but upon phase III evaluation, resulted in only modest

improvements in progression-free survival (PFS) with no advantage in OS.^{69,70} This pattern of improvement in PFS without an OS benefit is common in subsequent trials in pancreatic cancer as well.

The next advancement in the treatment of metastatic disease was the establishment of single-agent gemcitabine as standard of care in the late 1990s. Burris et al⁴ conducted the pivotal trial. They compared weekly gemcitabine bolus of 1,000 mg/m² to weekly 5-FU bolus. Due to the palliative nature of chemotherapy at this stage, a clinical benefit response (CBR) scale, a composite score for pain, was used as the primary end point. A significant 23.8% of patients receiving gemcitabine had a CBR vs only 4.8% of patients in the 5-FU arm with a significant benefit in OS of 5.65 months vs 4.41 months, with few adverse events associated with the gemcitabine chemotherapy.⁴

Previous efforts to improve on chemotherapy were made using 5-FU as the basis for chemotherapy regimens, with little success; even a meta-analysis of 5-FU combination regimens showed no benefit of 5-FU-based combination therapy compared with 5-FU alone.⁷¹ For the past several years, researchers have

been duplicating this experience by adding different chemotherapies to a gemcitabine backbone, again with limited success.

Efforts to improve upon gemcitabine: phase II promise does not predict success in phase III

Although single-agent gemcitabine demonstrated its superiority over 5-FU in metastatic pancreatic cancer, the benefits were still modest.⁴ A number of trials have tried to improve the efficacy of gemcitabine by adding a number of other agents (see Table 4). Other efforts have been made to improve the efficacy of gemcitabine itself. In phase I studies, gemcitabine at a concentration of 20 μmol/L was found to maximize the rate of active gemcitabine triphosphate formation. This correlates to a fixed dose rate (FDR) of 10 mg/m²/min.⁷² A phase II trial of FDR gemcitabine was also promising. OS on the FDR gemcitabine arm was associated with a significant improvement in OS of 8 months vs 5 months with standard dosing.⁷³ Despite this encouraging data from a phase II trial, there was no benefit observed when FDR gemcitabine was evaluated as

Table 4 Phase III studies comparing addition to gemcitabine therapy

Study	Chemo	Year	No. of patients	RR, %	PFS, mo	OS, mo	1-year survival, %
E2297 Berlin et al ¹³³	GEM	2002	322	5.6	2.2	5.4	14
	GEM + 5-FU			6.9	3.4 (P = 0.022)	6.7 (P = 0.09)	20
Reiss et al ¹³⁴	GEM	2005	466			6.2	22
	GEM + 5-FU/leuk					5.85 (P = 0.68)	21 (P = 0.68)
Herrmann et al ⁸⁶	GEM	2007	319	7.8		7.2	30
	GEM + cap			10.0		8.4 (P = 0.234)	32
Cunningham et al ¹³⁵	GEM	2005	533	7		6.0	19
	GEM + cap			14 (P = 0.008)		7.4 (P = 0.26)	26
Heinemann et al ¹³⁶	GEM	2006	190	8.2	3.1	6.0	
	GEM + cis			10.2	5.3 (P = 0.053)	7.5 (P = 0.15)	
E6201 Poplin et al ⁷⁴	GEM	2009	824	6	2.6	4.9	16
	FDR GEM			10 (P = 0.11)	3.5 (P = 0.04)	6.2 (P = 0.04)	22
	GEM Ox			9	2.7 (P = 0.1)	5.7 (P = 0.22)	21
GERCOR/GISCAD	GEM	2005	313	17.3	3.7	7.1	27.8
	GEM Ox			26.8	5.8 (P = 0.04)	9.0 (P = 0.13)	34.7 (P = 0.22)
Louvet et al ⁷⁶	GEM	2004	342	4.4	3.0	6.6 (P = 0.789)	
	GEM + iri			16.1 (P < 0.001)	3.5 (P = 0.352)	6.3 (P = 0.789)	20
Strathopoulos et al ¹³⁷	GEM	2006	130	10	2.9	6.5	21.8
	GEM + iri			15 (P = 0.387)	2.8	6.4 (P = 0.97)	24.3 (P = 0.666)
Abou-Alfa et al ¹³⁸	GEM	2006	349	5.1	3.8	6.2	21
	GEM + exa			6.8	3.7	6.7 (P = 0.52)	23 (P = 0.52)
Reni et al ¹³⁹	GEM	2005	104	8.5	3.3		21.3
	PEFG			38.5	5.4 (P = 0.0033)		38.5 (P = 0.11)
Oettle et al ¹⁴⁰	GEM	2005	565	7.1	3.3	6.3	20.1
	GEM + pemetrexed			14.8 (P = 0.004)	3.9 (P = 0.11)	6.2 (P = 0.85)	21.4

Abbreviations: RR, response rate; PFS, progression-free survival; OS, overall survival; GEM, gemcitabine; 5-FU, fluorouracil; Leuk, leukemia; cap, capecitabine; cis, cisplatin; FDR, fixed dose rate; GERCOR, French Multidisciplinary Clinical Research Group in Oncology; GISCAD, Italian Group for the Study of Gastrointestinal Tract Cancer; GEMOx, gemcitabine plus oxaliplatin; iri, irinotecan; exa, exatecan.

one of the arms of ECOG-6201, a large phase III trial that also looked at the combination of gemcitabine plus oxaliplatin.⁷⁴ Although FDR gemcitabine was associated with the longest OS (6.2 months), this outcome did not meet criteria for superiority, nor did the doublet of gemcitabine with the platinum, another area where multiple efforts have been made.

Efforts adding a platinum

There has been promising phase II data for adding a platinum to gemcitabine. For example, the French Multidisciplinary Clinical Research Group in Oncology (GERCOR) showed promising results with oxaliplatin combined with gemcitabine.⁷⁵ When conducted in a phase III trial, however, despite improvements in RRs and PFS, OS was not statistically different.^{74,76} ECOG-6201, a larger trial, was designed to test 2 promising approaches against standard single-agent gemcitabine in 832 patients with advanced pancreatic carcinoma. Disappointingly, the addition of oxaliplatin increased neither OS nor PFS significantly when compared with standard gemcitabine.⁷⁴ Many authors consider this the definitive trial of platinum combinations, although interest in the combination continues.

Data presented at 2009 ASCO, including the Gruppo Italiano Pancreas-1 (GIP-1) trial of gemcitabine combined with cisplatin vs gemcitabine alone in locally advanced and metastatic pancreatic cancer, failed to demonstrate any OS benefit or benefit in RR to adding the platinum.⁷⁷

Many explanations for this consistent shortcoming among phase III trials of gemcitabine with a platinum drug have been proposed. Some postulate that this may be due to second-line therapy crossovers, or that combination therapy candidates need to be carefully selected for good performance status.^{76,78}

Do meta-analyses shed light on the role of a platinum analog?

In the metastatic setting, till date, the only first-line phase III combination chemotherapy trial to show benefit over single-agent gemcitabine was the addition of erlotinib.⁷⁹ Despite promising results with the addition of a platinum agent in the phase II setting, when conducted in a phase III trial, despite improvements in RRs and PFS, OS is not statistically different.^{74,76} A number of meta-analyses have been undertaken in an effort to tease out the benefit of combination therapy.⁸⁰ Heinemann et al⁸¹ pooled the results of the GERCOR/Italian Group for the Study of Gastrointestinal Tract Cancer (GISCAD) intergroup study comparing gemcitabine plus oxaliplatin to gemcitabine and a German multicenter trial comparing gemcitabine plus cisplatin vs gemcitabine and

concluded that a platinum analog significantly improved PFS and OS as compared with single-agent gemcitabine in advanced pancreatic cancer in patients with a good performance status,⁸¹ similar to other pooled analyses.⁸⁰ These meta-analyses raise interesting questions, but are not comprehensive enough to dictate standard of care. For example, 2 phase III trials not included in the Heinemann analysis did not show an advantage when cisplatin was combined with gemcitabine.^{82,83} Also discouragingly, a different meta-analysis showed no significant improvement in survival when using cisplatin in combination with gemcitabine.⁸⁴

Efforts adding capecitabine

Another notable example of the difference in results between phase II and III trials in pancreatic cancer are trials of capecitabine, which shows activity comparable with gemcitabine in phase II trials.⁸⁵ In the phase III setting, however (see Table 4), there was no statistically significant difference between the gemcitabine plus capecitabine arm compared with the gemcitabine arm.⁸⁶ Interestingly, in a post hoc analysis, patients in this study with a Karnofsky Performance score (PS) of >90 had a significantly improved OS of 10.1 months vs 7.4 months, suggesting again that the subset of patients with excellent PS may benefit from combination therapy.⁸⁰ The positive phase II results may stem in part from better PS in phase II trial participants than in larger trials.

Targeting the EGFR pathway: statistical significance does not mean clinical relevance

Of all molecularly targeted agents studied in phase III trials, only erlotinib, targeting the human epidermal growth factor receptor 1 (HER-1/EGFR), has demonstrated statistical significant improvement over gemcitabine alone. However, the clinical benefit of this addition is uninspiring. In a phase III randomized trial, erlotinib with gemcitabine was associated with statistically significant 1-year survival advantage of 23% vs 17%; PFS of 3.75 months vs 3.55 months; and OS of 6.24 months vs 5.91 months. This was approved by the US Food and Drug Administration (FDA) due to all of these end points achieving statistical significance, a feat that could not be demonstrated in cytotoxic agents above. Clinically, however, the addition of erlotinib manifests a median benefit of only 0.33 months, or about 10 days.⁷⁹

The most common toxicity of anti-EGFR agents is an acne-like rash, which may vary in severity. Interestingly, in a review of both cetuximab and erlotinib in a variety of solid tumors, multiple studies demonstrate a correlation between

efficacy and severity of the acneiform rash. In a phase II study of cetuximab and gemcitabine for pancreatic cancer, not only the presence of the rash but also the severity of it was associated with longer survival.⁸⁷

Second-line therapy: an area of great need

Currently, there is a lack of proven therapy in the second-line, a great unmet need as most patients do not have a good response to first-line therapy. The only established second-line regimen after failure of first-line gemcitabine in the metastatic setting is 5-FU with oxaliplatin. In the CONKO-003 trial, a phase III trial of oxaliplatin and 5-FU with folinic acid vs BSC, patients who received second-line therapy were noted to have an OS of 40 weeks compared with 34.4 weeks after initiation of second-line chemotherapy ($P = 0.0312$).⁸⁸ It is notable that in this study, after 46 of 165 patients were randomized, the BSC arm was closed due to participating centers deciding that BSC alone was no longer acceptable. This benefit, although statistically significant, is small and points to the dire need for more investigation.

Directions of current research

A number of genetic alterations have been shown to occur in pancreatic cancer. Commonly mutated genes include the oncogenes *K-ras* (75%–100%), *HER2/neu* (about 65%), *p16^{Ink4a}* (>90%), *notch1*, *Akt-2*, and *COX-2* and also the tumor suppressor genes *p53* (45%–75%), *DPC4* (approximately 50%), *FHIT* (70%), and *BRCA2*. Despite this diversity of mutations, none of these genes is currently being targeted in clinical practice.⁸⁹ The promise of targeted therapies nevertheless continue to hold great interest in this disease, and other approaches, such as

concentrating the role of the tumor stroma, overcoming resistance mechanisms to chemotherapy, and recruiting immune defenses, show early promise and are highlighted below.

Targeted therapies: efforts to improve on the best available

The tyrosine kinase inhibitor erlotinib is the first and only molecularly targeted therapy approved by the FDA for first-line treatment of advanced pancreatic cancer in combination with gemcitabine.⁷⁹ As this is currently FDA approved, it is discussed above. Several investigators have sought to build upon the benefit of erlotinib. A phase I trial was conducted of erlotinib CRT with gemcitabine followed by maintenance erlotinib for locally advanced pancreatic cancer.⁹⁰ A retrospective study of single-agent erlotinib as second-line therapy showed no observed responses.⁹¹ Second-line erlotinib with capecitabine in gemcitabine refractory pancreatic cancer showed a modest median survival time of 6.5 months and a RR of 10%.⁹²

Cetuximab: limited activity

A monoclonal antibody against HER1/EGFR, cetuximab, has been demonstrated to have activity in pancreatic cancer when combined with gemcitabine.⁸⁷ This combination is being tested in the phase III setting, but unfortunately, preliminary reports suggest that this trial will likely fail to significantly improve OS time⁹³ (see Table 5). Nongemcitabine-based first-line therapy with cetuximab has also been studied. An ECOG phase II trial with randomization between irinotecan and docetaxel vs irinotecan and docetaxel plus cetuximab demonstrated modest improvements in clinical response with an OS time of 7.4 months with cetuximab vs 6.5 months without.⁹⁴

Table 5 Phase III trials of molecularly targeted agents for advanced and metastatic pancreatic cancer

Author	Chemo	Year	No. of patients	RR, %	PFS (mo)	OS (mo)	1-year survival (%)
Bramhall et al ¹⁴¹	Marimastat	2001	414	3	2.9	4	14–20
	GEM			26	4.9 ($P = 0.0001$)	5.6 ($P = 0.19$)	19
Bramhall et al ¹⁴²	GEM	2002	239	16	3.2	5.5	17
	GEM + marimastat			11	3.1 ($P = 0.68$)	5.4 ($P = 0.95$)	18
Moore et al ¹⁴³	Talomastat	2003	277	1	1.68	3.74	10
	GEM			5	3.5 ($P < 0.001$)	6.59	25
Van Cutsem et al ¹⁴⁴	GEM	2007	688	8	3.6 ($P = 0.72$)	6.1	24
	GEM + tafarnib			6	3.7	6.4 ($P = 0.75$)	27
Philip ⁹³ S0205	Cetuximab	2007		7	3.5	6.5	
				7	3 ($P = 0.058$)	6.0 ($P = 0.14$)	
Kindler et al ⁹⁶ CALGB 8030	Bevacizumab	2007		11	4.7	5.8	
				10	4.9 ($P = 0.99$)	6.1 ($P = 0.78$)	

Abbreviations: RR, response rate; PFS, progression-free survival; OS, overall survival; GEM, gemcitabine.

Targeting the vascular epithelial growth factor may be inactive in pancreatic cancer

The vascular epithelial growth factor (VEGF) and its receptors are attractive targets for antineoplastic therapy, particularly as they have a theoretical benefit in improving chemotherapy delivery to tumor. In a phase II trial, the anti-VEGF monoclonal antibody bevacizumab demonstrated activity in advanced pancreatic cancer with a RR of 21% and a median survival time of 8.8 months.⁹⁵ Yet again, these phase II results were not borne out in the phase III setting. The Cancer and Leukemia Group B (CALGB) 8030, a phase III, trial showed disappointing results for OS and was terminated early.⁹⁶ Sorafenib, a multikinase inhibitor against VEGFR, platelet-derived growth factor receptor, Kit, and Flt-3, was demonstrated to have no activity in combination with gemcitabine in phase II trial,⁹⁷ although it is being investigated in the second-line setting.⁹⁸

Secreted protein acid rich in cysteine (SPARC): the stroma as the target

The role of the pancreatic cancer stroma is an area of active research regarding the pathogenesis of the disease and its vigorous resistance to chemotherapy.^{99,100} Pancreatic adenocarcinoma is characterized by a strong desmoplastic reaction, which may promote the malignant phenotype.^{101,102} Pancreatic stellate cells (PSC) have been shown to produce substances that aid in the invasion of pancreatic cancer. The level of paracrine secreted protein acidic and rich in cysteine (SPARC) from PSC has been demonstrated to be inversely proportional to survival.¹⁰¹ This makes SPARC in the PSCs an attractive adjunct target. Nab-paclitaxel uses endogenous albumin pathways via binding of the albumin to SPARC. In a phase II trial as first-line therapy in metastatic pancreatic cancer, nab-paclitaxel and gemcitabine were given on days 1, 8, and 15 of a 28-day cycle. One patient had a complete response to therapy, 12 patients (24%) had partial response (PR), and 20 patients (41%) had stable disease (SD). Median PFS increased from 4.8 months for SPARC-negative patients to 6.2 months for SPARC-positive patients.¹⁰³ In a proof-of-principle parallel study in mouse xenografts, researchers demonstrated that nab-paclitaxel depleted the stroma surrounding pancreatic tumors and thus was able to facilitate delivery of gemcitabine more effectively. Those treated with the combination had a gemcitabine concentration in tumors that was 3.7-fold higher than that seen

with gemcitabine alone.¹⁰⁴ SPARC is, therefore, emerging as an important biomarker of response to nab-paclitaxel chemotherapy in this disease.

CP-4126: gemcitabine evolved

The human equilibrative nucleoside transporter 1 and human concentrative nucleoside transporter 1 and 3 are responsible for gemcitabine uptake into tumor cells. Lack of these transporters denotes a poorer prognosis with adjuvant treatment and predicts for resistance to therapy.¹⁰⁵ A promising new nucleoside analog that bypasses this mechanism has shown some benefit in refractory solid tumors in phase I trials, including stabilization of disease in some patients with pancreatic cancer. Though a derivative of gemcitabine, CP-4126 does not require nucleoside transporters.¹⁰⁶ This agent is currently entering phase II trials.

Vaccine trials: new techniques hold promise

In 2002, dendritic cells derived from peripheral blood monocytes were transfected with human tumor antigen mucin (MUC1) to be used as a vaccine for advanced breast, pancreatic, or papillary cancer. In this phase I trial, it was demonstrated that immune responses could be induced in 4 of 10 patients, but only 1 patient with a response had observed benefit. Despite lack of efficacy, treatment was regarded as safe.¹⁰⁷ The same year, a phase I/II trial using dl1520, a gene-deleted replication-selective adenovirus that targets malignant cells, was delivered by endoscopic ultrasound in combination with gemcitabine in locally advanced pancreatic cancer. Though this was also deemed safe with only small elevations of pancreatic enzymes and no pancreatitis, the effect was modest with 20% RR and another 38% SD.¹⁰⁸ One complete remission of liver metastasis of pancreatic cancer refractory to gemcitabine was reported.¹⁰⁹ Encouragingly, a recent phase I trial with peptide vaccine for VEGFR2 using the epitope peptide VGFR2-169 in combination of gemcitabine shows promising results in advanced pancreatic cancer. The control rate was 67% with a OS of 8.7 months with 1 PR and 11 patients (61%) with SD.¹¹⁰ Clearly, this is an evolving field in which more study is needed, and trials are ongoing, including a trial of endoscopically-guided intratumoral injections, as intratumoral injections have been demonstrated to generate an enhanced systemic tumor-specific immune response in a preclinical model.¹¹¹

Summary

Despite improved surgical outcomes and advances in chemotherapy and radiation therapy, overall 5-year survival of pancreatic cancer is approximately 5%.¹¹² Although complete surgical resection offers the only chance for long-term survival, the majority of patients who undergo surgery with curative intent will eventually succumb to the disease.³

A multidisciplinary approach with CRT holds the promise of downstaging a locally advanced cancer and sterilizing the perivascular neoplastic tissue and even distant micrometastatic disease and results in a survival advantage as compared with unresected patients. Although the optimal regimen has not been identified, there is strong phase II evidence that full-dose gemcitabine can be tolerated in combination with adequate radiation, and this dose is theoretically most likely to address micrometastatic disease outside of the radiation field. There appears to be a trend toward higher RRs with gemcitabine-based CRT that must be confirmed in multicenter trials.^{38,113–115}

In metastatic disease, chemotherapy is an important component of a multidisciplinary approach to palliative care, which must be supported by pain management and nutrition. Gemcitabine has been considered the standard treatment for patients with advanced pancreatic cancer ever since Burris et al⁴ demonstrated a modest, yet statistically significant, improvement in OS and a significant clinical benefit for gemcitabine chemotherapy compared with 5-FU. However, single-agent gemcitabine in multiple trials consistently only achieves median OS figures of approximately 6 months, a finding that clearly indicates the need for the development of new treatment strategies.¹¹⁶ Phase I and phase II trials of a variety of gemcitabine-based combinations have demonstrated promising activity. Invariably, when these have been evaluated in randomized phase III trials compared with single-agent gemcitabine, the results have been disappointing.

The conclusive results of ECOG-6201 establish that adding oxaliplatin to gemcitabine is not an appropriate standard of care for patients with advanced pancreatic cancer.⁷⁴ Some meta-analyses, however, have found that overall RRs were significantly improved by gemcitabine-based combination therapy with a platinum^{80,81} or fluoropyrimidine,⁸⁰ particularly in patients with good performance status. Other combination therapies have shown promise in improving the RR, eg, a phase III study of the combination of irinotecan with gemcitabine vs gemcitabine in patients with advanced or metastatic pancreatic cancer, with a primary end point of survival, a statistically significant improvement in RR was found although the primary end point of survival was not reached.¹¹⁷ Similarly,

the GERCOR trial demonstrated an improved RR with the addition of oxaliplatin to gemcitabine,⁷⁶ a benefit not seen in the larger ECOG trial.⁷⁴

The possibility of improved RR with combination therapy, however, does raise the question: would combination therapy be worth examining in the neoadjuvant setting, where RR dictates the possibility of future resection?

In future trials, it will be important to stratify patients by modern criteria for resectability to elucidate the benefit of our therapies. Most neoadjuvant trials have grouped together: patients with borderline resectable, resectable, and borderline unresectable disease. Most chemotherapy trials have treated as one group: patients with unresectable locally advanced disease, recurrent disease, and metastatic disease. There is increasing evidence that the prognosis is different in these stages of disease,¹¹⁸ although micrometastasis may already present in most patients. We are doing the research process and our patients a disservice if we do not stratify the patients in our trials by modern criteria. Trials of innovative technology, such as vaccines, should pay particular attention to the characteristics of patients' disease.

Some of the most interesting current research seeks to differentiate which patients will respond to therapy. As evidenced by the relatively low RRs with gemcitabine, better biological markers to help predict response are urgently needed if we are to make progress in this disease.

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