

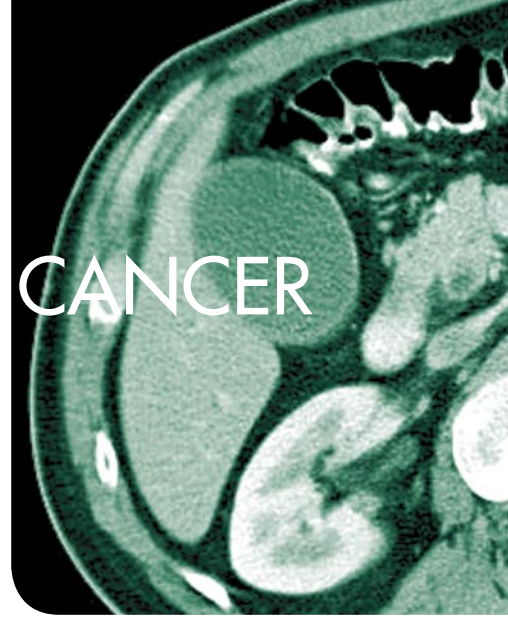
## DISCOURSE

Emerging trends and recommendations

# RESECTABLE PANCREATIC CANCER

## Looking forward to a new era

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### Top-line summary

Pancreatic cancer is the fourth leading cause of cancer-related death in the western world and the second leading cause of death from gastrointestinal cancers. An estimated 3500 new cases and 3400 deaths from pancreatic cancer will occur in Canada in 2006.<sup>1</sup> Overall 5-year survival is < 5%;<sup>2</sup> the poor prognosis is due to high rates of advanced disease at presentation, low rates of surgical resectability, and the aggressive biological behaviour of this cancer, including high likelihood of distant micrometastases. Surgical resection is the cornerstone of potential cure, but incorporation of other treatment modalities is essential to maximize survival. A recent trend towards improved outcomes has been attributed to an increased proportion of patients undergoing surgery in specialized, high-volume treatment centres and greater use of adjuvant therapy — although the latter remains controversial. Significant improvement in survival of patients with pancreatic cancer will require better understanding of the molecular biology behind this malignancy combined with novel treatment modalities.

Determining the extent of disease at distant sites (e.g. liver, peritoneal and omental metastases) as well as local extension and involvement of adjacent critical structures (celiac axis and tributaries, portal and/or superior mesenteric vein and superior mesenteric artery) identifies the approximately 10% to 20% of patients eligible for surgical resection and is thus the focus of preoperative diagnostic imaging.

Optimized preoperative staging would better detect resectable lesions while sparing other patients the morbidity, mortality, and expense of unnecessary surgery. Pancreatic adenocarcinoma is often considered to be systemic disease, as occult metastases present at the time of surgery often result in relapse and cancer-related mortality in the first few months following pancreatectomy.

Approximately 80% of pancreatic cancer patients are deemed to have unresectable disease at diagnosis. Depending on the stage, primary management generally consists of a combination of chemotherapy, radiation and/or palliative surgery. In those with locally advanced unresectable disease, combined-modality treatment provides a survival benefit over either radiation or chemotherapy alone.<sup>3-5</sup> In those with metastatic disease, the nucleoside analog gemcitabine achieves relief of tumour-related symptoms although significant tumour response remains dismal.<sup>6</sup> Ongoing randomized trials are evalu-

ating the role of fluorouracil and other cytotoxic treatment regimens. Targeted therapies to vascular endothelial growth factor A (VEGF-A) and epidermal growth factor receptor (EGFR) also hold promise for treatment of advanced pancreatic cancer.

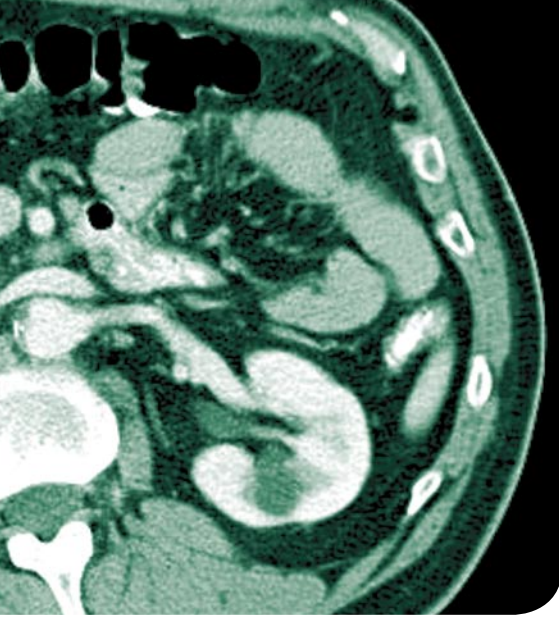
### PREOPERATIVE ASSESSMENT TECHNIQUES

#### Computed tomography

A computed tomography (CT) scan performed with a current-generation multidetector scanner using dual-phase contrast enhancement and thin cuts (3–5 mm) through the pancreas is the single best study — and perhaps the only study required — to diagnose and clinically stage pancreatic cancer. Adenocarcinoma of the pancreas typically appears as a hypoattenuated lesion relative to normal parenchyma. Dilation of the pancreatic duct and/or common bile duct may be associated with obstruction of these structures secondary to tumours in the head of the pancreas. Peripancreatic lymph nodes, peritoneal disease and ascites can suggest regional or distant metastases. Nevertheless, CT typically underestimates the extent of disease: out of all patients whose CTs show resectable disease only about 75% are truly oper-

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able.<sup>12,13</sup> The chief unexpected findings at surgery are subcentimetre hepatic or peritoneal metastases. Less commonly, regional lymphadenopathy and/or locally advanced tumour with vascular involvement preclude curative resection. Features associated with unresectability seen on CT include tumour contiguous with the portal vein, superior mesenteric artery and/or vein, hepatic artery, or celiac axis with > 50% involvement of the vessel circumference.<sup>14</sup> When this finding has been documented, CT yields a positive predictive value of 95% and a negative predictive value of 93% for unresectability of these vessels. Periportal collaterals or dilated peripancreatic veins suggest portal vein occlusion and a high likelihood of unresectability.<sup>15</sup> CT now readily documents vascular anomalies previously identified by angiography. CT angiography may achieve further progress in assessing vascular involvement.

### ERCP

Endoscopic retrograde cholangiopancreatography (ERCP, injection of contrast into the biliary tree and pancreatic duct via endoscopic access) has traditionally played a prominent role in the preoperative assessment of patients with suspected pancreatic malignancy because of its ability to image and define the anatomy of these structures. But associated complications such as perforation, bleeding and pancreatitis have made less invasive techniques, including CT, endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP), preferable. When pancreatic cancer is suspected but imaging stud-

ies show no discrete mass, ERCP can document a pancreatic duct stricture, biliary duct stricture or both, known as the double duct sign. While preoperative endobiliary stenting is avoided if possible (see below), ERCP plays a major role in stent insertion for symptomatic patients who cannot undergo immediate surgery for bypass or resection and for palliation in inoperable cases.

### Magnetic resonance

Magnetic resonance imaging (MRI) may be useful for differentiating inflammatory from neoplastic pancreatic lesions and may be more accurate than CT for assessing resectability.<sup>16-19</sup> Pancreatic adenocarcinomas are usually characterized by low signal intensity on T1- and T2-weighted images and enhance poorly on post-gadolinium images. Although MRI has a role in the diagnosis and staging of pancreatic

tumours, it does not confer enough significant advantages over CT to justify its increased cost except in patients with contrast allergy or renal insufficiency. The future role of MRI may be expanding through better anatomic definition of the biliary tree and pancreatic duct with magnetic resonance cholangiopancreatography (MRCP) and of the vascular anatomy through dynamic MRI.

### Endoscopic ultrasound

EUS incorporates realtime ultrasound from within the lumen of the stomach and duodenum, and is extremely sensitive and specific for evaluating small tumours (< 2–3 cm)<sup>20</sup> — but efficacy is highly operator-dependent. While EUS is purported to provide accurate assessment of local invasion and nodal metastases, vascular involvement (particularly the SMA and SMV) remains difficult to

## Serum tumour markers

High levels of cancer antigen (CA) 19-9, a small carbohydrate found in circulating blood, indicate possible pancreatic cancer with a sensitivity of 77% and specificity of 87%.<sup>7</sup> Levels may also be elevated in jaundiced patients without cancer or in other malignancies (e.g. gastric or hepatobiliary). CA 19-9 can be particularly useful when findings on diagnostic imaging are equivocal. In patients with suspected pancreatic cancer, addition of CA 19-9 enhanced the positive predictive value of preoperative CT or ultrasound from 71% and 62%, respectively, to 100% using a CA 19-9 cutoff level greater than 100 U/mL.<sup>8</sup>

Serum CA 19-9 may prove to be an important determinant in predicting resectability and long-term outcomes following therapy.

- In a recent study, 51 patients with resectable pancreatic cancer based on preoperative clinical and radiologic assessment all underwent laparotomy. Mean serum CA 19-9 was 68.8 U/mL in 18 (36%) patients with resectable disease and 622 U/mL in 33 (64%) found to be unresectable.<sup>9</sup> Patients with postoperative CA 19-9 values within normal range 3–6 months after surgery had longer disease-free and median survival.<sup>10</sup>
- In a trial monitoring responses to treatment of patients with inoperable cancer, those whose CA 19-9 declined by  $\geq 20\%$  had a significantly greater average survival compared with matched counterparts whose CA 19-9 did not decline by at least 20%.<sup>11</sup> CA 19-9 was the most important determinant in predicting survival in this study.

Because high serum levels appear to correlate with advanced tumours, unresectable disease should be suspected whenever high levels are documented.

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discern. Further, EUS cannot evaluate distant metastases. It currently plays a role in identifying neoplasms not imaged by other modalities, in clarifying locoregional spread when CT or MRI are equivocal, and in providing access for fine needle aspiration (FNA) when histologic diagnosis is required for unresectable disease or in patients being considered for neoadjuvant therapy.

## FDG PET

Positron emission tomography (PET) utilizes a radioactive-labeled glucose analog (18-fluorodeoxyglucose, FDG) that is actively taken up by the cell and phosphorylated for glycolysis. As phosphorylated FDG cannot be metabolized it becomes trapped within the cell and is detected by a positron emission scanner, and qualitative and quantitative evaluations describe uptake activity in a region of interest. Hypermetabolic cells in chronic pancreatitis and other inflammatory processes may limit the specificity of this test. The inability to resolve anatomic structures also precludes accurate diagnosis and staging of many pancreatic cancers.<sup>21,22</sup> In patients with unresectable disease, FDG avidity on PET correlates with aggressiveness of the tumour and may independently predict survival.<sup>23,24</sup> Potential areas of progress are lymph node staging, assessing response to neoadjuvant therapy and detection of metastatic or recurrent disease. Multimodal PET CT may prove to be superior, combining a metabolic assay with anatomic definition.

## Staging laparoscopy and laparoscopic ultrasound

Laparoscopy is most beneficial when unresectability appears likely but cannot be confirmed in less invasive ways. While laparoscopy cannot easily examine the pancreas itself because of its retroperitoneal position, up to 20% of patients deemed resectable by CT criteria have small (< 1 cm) liver and/or peritoneal metastases detected by laparoscopy combined with ultrasound.<sup>25,26</sup> Positive peritoneal cytology can identify advanced disease in the absence of visible metastases and is highly specific in predicting unresectability and poor survival.<sup>26,27</sup> Detecting small metastases missed by other diagnostic tests avoids

the morbidity of an unnecessary laparotomy.

## Preoperative biliary drainage

Endoscopic or percutaneous transhepatic biliary drainage, (i.e. stents) have been extensively studied. In addition to several retrospective single-institution studies,<sup>28-30</sup> 5 randomized controlled trials (RCTs)<sup>31-35</sup> and 2 meta-analyses<sup>36,37</sup> have evaluated this issue (Table 1). Although jaundice predisposes to coagulopathy, malabsorption and malnutrition, clinical studies show that stents appear to increase the incidence of perioperative infection, likely secondary to bacterial contamination after instrumentation of the biliary tree. Endobiliary stents are now used selectively for symptomatic jaundice (e.g. cholangitis and/or pruritus), when surgery will be delayed longer than 2 weeks (i.e. to enable neoadjuvant therapy), and for palliation of patients with unresectable cancers.

## SURGICAL MANAGEMENT

Concentrated experience — in a limited number of surgeons who routinely perform pancreatic resections in high-volume institutions — is associated with lower perioperative mortality, decreased length of hospital stay, lower hospital costs and better long-term

outcomes.<sup>38-45</sup> In this setting, perioperative mortality is < 5% with perioperative morbidity of 30% to 40% and median hospital length of stay of 8–13 days. While surgery offers the only potential chance for long-term survival, only 10% to 20% of patients are candidates for operative management and 5-year survival rates after curative resections remain dismal (10% to 25%), with median survival of 10–20 months.<sup>38,44,46,47</sup> Nodal status is the most important prognostic factor, while other significant predictors of outcome include tumour involvement at the resection margins, tumour differentiation, tumour size and intraoperative blood loss.

## Standard vs pylorus-preserving pancreaticoduodenectomy

Classic pancreaticoduodenectomy (PD) includes distal gastrectomy to decrease acid production, thereby minimizing risk for postoperative ulcer disease and also improving oncologic clearance (i.e. enhancing resection margins, particularly in the retroperitoneum), but postgastrectomy syndromes can be problematic. Two randomized trials and numerous retrospective reports showed pylorus-preserving pancreaticoduodenectomy (PPPD) to be equivalent to PD with regards to postoperative gastrointestinal function, tumour

**TABLE 1. Effect of preoperative biliary drainage (PBD) before pancreatic cancer resection**

Randomized controlled trials	
Pitt HA et al, 1985 <sup>33</sup>	↑ length of stay
Lai EC et al, 1994 <sup>35</sup>	improved liver function tests
Smith RC et al, 1985 <sup>34</sup>	↑ PBD morbidity ↓ surgical morbidity
McPherson GA et al, 1984 <sup>32</sup>	↑ PBD morbidity ↑ surgical morbidity
Hatfield AR et al, 1982 <sup>31</sup>	↑ PBD morbidity
Meta-analyses	
Salch MM et al, 2002 <sup>36</sup>	no beneficial or adverse effect
Sewnath ME et al, 2002 <sup>37</sup>	↑ surgical morbidity

**TABLE 2. Surgical morbidity and mortality in RCTs of prophylactic octreotide for patients with benign and malignant disease undergoing pancreatic resection**

Study	dose	n	pancreatic fistula		overall morbidity		overall mortality	
			placebo	octreotide	placebo	octreotide	placebo	octreotide
Buchler M et al, 1992 <sup>57</sup>	100 mcg tid x 7 days	246	38%	18%*	55%	32%*	5.8%	3.2%
Pederzoli P et al, 1994 <sup>58</sup>	100 mcg tid x 7 days	252	19%	9%*	29%	16%*	3.8%	1.6%
Montorsi M et al, 1995 <sup>59</sup>	100 mcg tid x 7 days	218	20%	9%*	36%	22%*	5.6%	8.1%
Friess H et al, 1995 <sup>60</sup>	100 mcg tid x 7 days	247	22%	10%*	30%	16%*	0.8%	4.6%
Lowy AM et al, 1997 <sup>61</sup>	150 mcg q 8 h x 6 days	110	6%	12%*	25%	30%*	0	2%
Yeo CJ et al, 2000 <sup>62</sup>	250 mcg q 8 h x 7 days	211	11%	9%*	34%	40%*	0	1%

\*  $p < 0.05$  compared with placebo control group

recurrence and survival. One RCT of 77 patients reported shorter operative time (404 vs 476 minutes,  $p = 0.04$ ), reduced blood loss (1453 vs 2096 mL,  $p = 0.03$ ), fewer blood transfusions (2.1 vs 3.6 units,  $p = 0.05$ ) and lower surgical morbidity with PPPD although length of intensive care and hospital stay were equivalent.<sup>48</sup> No differences were seen in gastric emptying, tumour recurrence or survival after a median followup of 1.1 years. Another RCT with 31 patients was underpowered to show a significant difference in perioperative parameters (operative time, blood loss, blood transfusion, morbidity or mortality) or gastric emptying.<sup>49</sup>

### Extended PD resections

Modifications of standard PD have been developed in an attempt to improve outcomes. Total pancreatectomy removes the entire gland involved by malignancy and avoids a pancreatojejunal anastomosis. It provides no impact on prognosis, however, and patients must cope with exocrine insufficiency and diabetes, which is often difficult to manage.<sup>50</sup> In fact, total pancreatectomy was associated with worse median survival (7.9 months compared to 17.2 months) in a contemporary cohort of patients undergoing standard PD — such that the authors questioned the value of this operation. Total pancreatectomy is therefore now reserved for those patients in whom it is necessary to completely remove the tumour

because of extension into the body or tail of the pancreas.

Some surgeons consider tumour invasion into the superior mesenteric portal vein (SMPV) confluence to be a contraindication to PD because perioperative morbidity (from extensive autonomic neurectomy) and mortality are generally higher, and major vessel involvement appears to be associated with worse outcome even after resection.<sup>51</sup> A positive margin after resection is associated with tumour recurrence, however, so en bloc resection of the SMPV confluence may facilitate complete resection when tumour is adherent to the lateral or posterior wall of the confluence. Vein resection can be performed safely, and histologic evaluation suggests that vein involvement does not necessarily imply aggressive tumour behaviour but is merely a function of tumour location.<sup>52</sup> Patients who require vein resection during PD for isolated tumour extension to the SMPV confluence have similar survival (22–23.4 months) to those who undergo standard PD (20–26.5 months),<sup>53,54</sup> and likely have superior survival compared to patients with locally advanced disease treated nonoperatively. Therefore, selective vein resection is commonly incorporated with PD in potentially curative resections with SMPV involvement in the absence of tumour extension into the celiac axis or superior mesenteric artery.

The presence of regional nodal metastases is the most significant adverse

prognostic factor in potentially curable pancreatic cancer. The role of extended lymphadenectomy (LAD) in patients with resectable disease was studied in hopes that it modifies the natural history of this malignancy. While extended resections may enhance resectability rates, this does not appear to translate into better survival. In a small RCT comparing standard PD to extended LAD, operative time (372 vs 297 min), number of patients (35 vs 38) and units of blood transfused (1.95 vs 2.07), length of hospital stay (22.7 vs 19.3 days), surgical morbidity (9 vs 11 patients), and perioperative mortality (2 patients in each group) as well as overall median survival (335 days, 95% CI 252–418 vs 500 days, 95% CI 353–647 days) were similar between the 2 groups.<sup>55</sup> Extent of resection did not correlate with the ability to achieve complete oncologic clearance (29 vs 32 patients) or with local control. Post hoc subgroup analysis showed better survival in patients with positive nodes undergoing extensive LAD. A subsequent trial that randomized 294 patients found extended retroperitoneal LAD to be associated with longer hospital stay (14.3 vs 11.3 days,  $p = 0.003$ ), increased rates of pancreatic fistula (13% vs 6%,  $p = 0.05$ ), delayed gastric emptying (16% vs 6%,  $p = 0.006$ ), and higher overall complication rates (43% vs 29%,  $p = 0.01$ ).<sup>56</sup> Perioperative mortality (4% vs 2%) and median survival (28 vs 30 months) did not differ between the

2 groups; thus extended LAD was associated with increased morbidity and similar mortality with no improvement in survival.

## Role of prophylactic octreotide after pancreatic resection

Pancreatic fistulae related to exocrine pancreatic secretions complicate 5% to 35% of pancreatic resections and may progress to serious life-threatening complications associated with sepsis and hemorrhage. A number of randomized prospective trials have addressed the potential of octreotide to reduce the rate of pancreatic anastomotic leaks and associated complications (Table 2, page 13). These studies used varying doses of octreotide and definitions of pancreatic anastomotic leak (clinical vs radiographic vs transient elevation in drain fluid amylase), and included a variety of pancreatic resections for both benign and malignant disease. As they did not consistently demonstrate reduction in pancreatic anastomotic leak, overall morbidity or mortality after pancreatic resection, routine use of octreotide remains controversial — its use is recommended in high-risk pancreatic anastomoses (soft gland, small pancreatic duct) and when pancreatic leak rates are expected to exceed 10%.<sup>63</sup>

## ADJUVANT THERAPY FOR RESECTED PANCREATIC CANCER

Long-term survival is unusual despite complete surgical resection of localized pancreatic cancer, with survival typically measured in months. Local failure occurs in 50% to 80% of cases, suggesting a possible role for radiation, and systemic chemotherapy and/or immunotherapy may eradicate distant failure from microscopic metastatic disease.<sup>64,65</sup> Table 3 (page 16) shows 4 randomized trials reporting the impact of postoperative adjuvant therapy in patients with resected pancreatic cancer. While the first RCT to evaluate adjuvant chemoradiation (CRT) conducted by the Gastrointestinal Tumour Study Group (GITSG) showed significant improvement in survival,<sup>66</sup> subsequent large Phase III trials completed by the European Organization for Research and Treatment of Cancer (EORTC)<sup>67</sup> and European Study Group for Pancreatic

Cancer (ESPAC)<sup>68</sup> failed to show a survival benefit.

The GITSG trial<sup>66</sup> randomized patients after potentially curative resection to no further treatment (n = 22) or adjuvant CRT (n = 21). Adjuvant therapy consisted of radiation therapy (RT, 40 Gy administered as two 2-week courses separated by a 2-week break after the first 10 treatments) with concurrent bolus fluorouracil (500 mg/m<sup>2</sup> weekly for 2 years or until recurrence). Although the difference in median survival (20 months in the treated group vs 11 months in the untreated group) was statistically significant, 24% of patients received adjuvant therapy later than the optimal interval of 10 weeks after surgery. The study was widely criticized for a number of reasons. The small sample size (n = 43) and prolonged accrual time (8 years) led to its early termination. Compared with current treatment regimens, the RT dose was relatively low and a more continuous RT schedule (i.e. no 2-week break) is now commonly used. Further, continuous infusion fluorouracil combined with radiotherapy has proved superior in the adjuvant therapy of other gastrointestinal cancers. This study did not definitively determine the advantage conferred by adjuvant CRT and whether any benefit was attributable to CRT, chemotherapy alone or radiotherapy alone. Despite these limitations, many U.S. centres adopted variations of this combination protocol. After retrospective studies confirmed the GITSG results, investigators at Johns Hopkins proceeded to a prospective case control study of 3 different treatment regimens administered to selected patients after surgery.<sup>69</sup> Participants received either no adjuvant treatment, standard CRT (40–45 Gy EBRT + bolus fluorouracil for 4 months) or intensive CRT (50–57 Gy EBRT + hepatic RT + continuous infusion fluorouracil and leucovorin for 4 months). Standard CRT compared to no treatment showed a survival advantage (median survival 21 vs 13.5 months). The intensively-treated group had median survival of 17.5 months, not significantly different from the control group — bringing into question the value of CRT. Between 1984 and 1999, 333 patients from a

consecutive series of 616 who had resection for pancreatic cancer at Johns Hopkins received adjuvant CRT and maintenance chemotherapy.<sup>77</sup> Even with this selection bias, median survival was only 19 months in the treated patients.

The Norwegian Pancreatic Cancer Trial (NPCT)<sup>71</sup> randomized post-resection patients with pancreatic or periampullary cancer to no further treatment (n = 31) or adjuvant chemotherapy (n = 30) consisting of doxorubicin, mitomycin C and fluorouracil. Median survival was 23 months in the treated group vs 11 months in the untreated group, but the survival benefit did not persist with long-term followup.

After these 2 trials, the EORTC studied a relatively large patient population (n = 207) with resectable pancreatic and periampullary cancers,<sup>67</sup> randomizing patients to surgery alone or postoperative CRT. RT (40 Gy) was divided into a split course of 2-week blocks of 20 Gy with an interval break of 2 weeks. Chemotherapy of fluorouracil infusion (25 mg/kg/day) started the same day as RT, without fluorouracil maintenance. This regimen was well tolerated, but 20% of patients in the treatment arm did not receive the assigned treatment because of postoperative complications or patient refusal. Analysis specific to primary tumour site in the head of pancreas (n = 114) favoured a survival benefit of 17.1 months median survival in those treated vs 12.6 months with observation. This was not statistically significant, however, perhaps due to the small size of the subset. Adjuvant CRT, while safe and well tolerated, did not appear to produce a survival benefit. A new EORTC randomized Phase II–III study (40013-22011) will compare gemcitabine followed by gemcitabine + concomitant RT (50.4 Gy) vs gemcitabine alone after curative PD for pancreatic cancer.

A multicentre study involving 61 centres in 11 European countries was organized to determine whether adjuvant CRT was superior to surgery alone.<sup>68,72</sup> Eligible patients had complete macroscopic resection of histologically-proven ductal pancreatic adenocarcinoma. They were stratified by centre and resection margin (positive

vs negative). The study consisted of a 2 x 2 factorial design with random assignment to chemotherapy vs no chemotherapy and to radiotherapy vs no radiotherapy. While 541 patients were enrolled, only 285 entered into the full 2 x 2 randomization; 188 patients who had received prior non-standardized chemoradiation were randomized to chemotherapy or no chemotherapy and another 68 patients previously treated with chemotherapy were randomized to chemoradiation or no chemoradiation. Chemotherapy consisted of fluorouracil + leucovorin given on 5 consecutive days for 6 cycles at 18-day intervals. RT was a split course of 20 Gy over 2 weeks followed by a 2-week break and then another 20 Gy over 2 weeks, similar to the GITSG trial. Median survival was not different for the subset of 285 patients randomized to the 2 x 2 factorial design. Analysis of the nonfactorial population showed a survival benefit for those receiving adjuvant chemotherapy (median survival 19.7 vs 14.0 months,  $p < 0.001$ ). An updated analysis confirmed the survival advantage with adjuvant chemotherapy and an apparent detrimental effect of adjuvant CRT (median survival 15.9) compared with patients who did not receive any treatment (median survival 17.9 months). These findings suggested that adjuvant RT was of no benefit while adjuvant cytotoxic chemotherapy was potentially beneficial and warranted further study. Two major concerns raised were that RT was delivered in 2 courses separated by a 2-week break with no central review or quality control for planning and administration of RT, and that bolus rather than infusional fluorouracil was used. Lack of standardization related to pathologic margin assessment was another major concern, particularly given the high rate of local relapse (62%) reported. This group's next trial, ESPAC-3, was to compare postoperative fluorouracil + leucovorin vs gemcitabine vs observation after potentially curative pancreatic resection. After the results of the ESPAC 1 trial, the surgery-alone arm was eliminated, leaving randomization to either gemcitabine or fluorouracil. RT is not included in any of the treatment arms in this trial.

The largest randomized trial to date is the American Intergroup trial (RTOG 9704) reported in abstract form at ASCO in June 2006.<sup>73</sup> This Phase III study randomized 538 patients to systemic fluorouracil or gemcitabine given pre- and post-fluorouracil-based CRT for resected pancreatic adenocarcinoma. Patients were stratified by nodal involvement, tumour diameter and status of the surgical resection margin. Pre-CRT chemotherapy consisted of 3 weeks of fluorouracil infusion or gemcitabine, with identical CRT for both arms, followed by another 12 weeks of fluorouracil or gemcitabine post-CRT. RT was given as 50.4 Gy with continuous fluorouracil. In patients with pancreatic head tumours ( $n = 380$ ), median survival was 18.8 months (31% 3-year survival) in those treated with gemcitabine compared with 16.7 months (21% 3-year survival) for those treated with fluorouracil ( $p = 0.047$ ).

### Targeted therapies and other agents

As patients continue to relapse at distant sites in the liver and other peritoneal surfaces, more effective systemic therapy is required. With the development of new chemotherapy drugs effective against gastrointestinal cancers, a new era for adjuvant therapy trials has emerged. In addition to standard cytotoxic systemic chemotherapy, recognition of the importance of VEGF, the VEGF receptor system and EGFR in pancreatic cancer has provided additional targets for treatment. ECOG-E2204, the next Intergroup Phase III study, randomizes patients with completely resected pancreatic carcinoma to bevacizumab (a monoclonal IgG antibody to VEGF) vs cetuximab (a monoclonal antibody to EGFR), both in combination with gemcitabine + capecitabine (an oral prodrug of fluorouracil) + RT. The Phase II American College of Surgeons Oncology Group (ACOSOG) 5041 study will compare preoperative gemcitabine vs bevacizumab before pancreatectomy followed by postoperative capecitabine + bevacizumab + 50.4 Gy RT. Preliminary results for both studies are anticipated sometime in 2007.

Interest in adjuvant therapy remains considerable despite the ill-defined role of postoperative CRT. Another approach is combining CRT with interferon-alpha. The Virginia Mason Medical Center reported on 43 patients treated with 50.4 Gy RT (25 fractions over 5 weeks) combined with fluorouracil + cisplatin + interferon.<sup>74</sup> While significant gastrointestinal toxicity was observed, with 42% of patients requiring hospitalization during CRT, all completed treatment, and therapy incurred no deaths. After a mean followup of 32 months, 67% of patients were alive and median followup had not been reached. ACOSOG is currently evaluating this regimen in a large multicentre Phase II trial (ACOSOG-Z0 5031).

### Rationale for neoadjuvant therapy

Multimodality therapy is presumed to be superior to surgery alone. Among the many potential advantages of neoadjuvant therapy are that it:

- avoids treatment delay in presumed metastatic occult disease
- improves patient selection by excluding those with rapidly progressive disease — avoiding the morbidity of surgery
- guarantees delivery of neoadjuvant therapy regardless of morbidity and mortality associated with postoperative recovery
- may enhance efficacy through delivery of RT to well-oxygenated tissues as opposed to relatively hypoxic tissues devascularized by surgery
- may enhance resectability and reduce the incidence of positive resection margins (particularly in the retroperitoneum)
- may prevent implantation and dissemination of tumour cells during surgery

Potential barriers to preoperative CRT for pancreatic cancer include the fact that confirmation of histology (allowing exclusion of other periampullary cancers usually associated with better survival) is possible only after resection, the requirement for FNA of a potentially resectable pancreatic neoplasm, and the need for preoperative biliary drainage in jaundiced patients. Further, as patients are restaged after neo-

adjuvant CRT a subgroup with disease progression is excluded, leaving an inherently biased population that goes on to resection with a better prognosis than the original group as a whole. Because clinically meaningful downstaging with preoperative CRT has not been observed, there has been a general lack of acceptance among surgeons for this approach.

Investigators at MD Anderson Cancer Center (MDACC) have reported some of the most encouraging neoadjuvant CRT results. In a study of 86 patients treated with neoadjuvant gemcitabine and 30 Gy RT given in 10 fractions, median survival for resected patients was 34.7 months.<sup>75</sup> Although 43% required hospitalization, there was no treatment-related mortality. The resectability rate was 74%, and 2 surgical specimens (3%) exhibited complete pathologic response. The current MDACC protocol incorporates gemcitabine + cisplatin followed by gemcitabine-based CRT (30 Gy) before preoperative restaging. While several groups have embarked on neoadjuvant therapy protocols, RCTs are needed to validate this treatment strategy, which should otherwise be regarded as investigational.

## Evolution of radiation technology


Conformal beam radiotherapy enables more RT to be delivered to targeted areas, allowing dose escalation while reducing overall field size. Respiratory motion in the target field, however, can affect the target volume. Image-guided RT takes motion artifact into account and defines a target field before radiation delivery, allowing for positional corrections. Intensity-modulated radiation therapy (IMRT) delivers RT more precisely by breaking the traditional large radiation ports into a number of smaller field segments or pencil beams, improving dose distribution to the target area while reducing exposure to surrounding structures at risk.

## TOWARDS A NEW ERA

Cure rates remain poor despite technical advances in the operative management of patients with pancreatic cancer, extended resections and existing

**TABLE 3. Survival after potentially curative pancreatic resection in prospective RCTs of adjuvant chemotherapy and radiation**

Study	n	median survival (months)		
		surgery	surgery + chemotherapy + radiation therapy	p value
GITSG, Kalser MH et al, 1985 <sup>66</sup>	43	11	20	0.03
NPCT, Hakevold KE et al, 1992 <sup>71</sup>	61	11.4	23	
EORTC, Klinkenbijl JH et al, 1999 <sup>55</sup>	114 (pancreas)	12.6	17.1	0.099
ESPAC-1, Neoptolemos JP et al, 2001 <sup>67</sup> and 2004 <sup>66</sup>	541	15.5	16.1	0.24
RTOG 9704, Regine WF et al, 2006 <sup>73</sup>	538	16.7	18.8	0.047

adjuvant therapies. While significant improvement in surgical technique is not anticipated, understanding pancreatic cancer at the molecular level, strategies for early detection, and combined-modality adjuvant treatment hold promise for progression to a new era in the treatment of potentially resectable pancreatic cancer. 

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### Disclosure

Dr. Ruo reports no potential conflicts of interest relevant to this article.

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