

# Updates and Controversies in the Treatment of Pancreatic Cancer

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**Abstract:** Despite the many advances in oncology over the last few decades, almost all patients with pancreatic cancer eventually die of the disease. Recent advances, however, have led to the development of more effective therapies. In pancreatic cancer, as in many other malignancies, significant progress in the understanding of important molecular processes associated with the development and progression of the disease is helping tailor more effective treatment strategies. Molecularly targeted agents are offering hope for their potential role in helping translate the improved activity of combination chemotherapy into improved survival. This article summarizes the data from studies that established standards of care and others that created controversy, and reviews novel treatment strategies for this intractable disease.

There were approximately 31,860 new cases of pancreatic carcinoma diagnosed in 2004 in the United States. With 31,270 deaths in the same year, pancreatic cancer is the fourth leading cause of cancer death in the United States.<sup>1</sup> Reasons for the high rate of mortality with adenocarcinomas of the pancreas include the advanced stage of disease at the time of diagnosis for more than 90% of patients,<sup>2</sup> lack of effective screening tests, and lack of effective treatment options. For instance, among patients who undergo potentially curative surgical resection, 78% and 61.5% will have local and hepatic recurrences, respectively.<sup>3</sup> These rates are reflected in a 5-year overall survival rate of less than 5% across stages.<sup>4</sup> Thus, pancreatic cancer is a formidable challenge.

Over 95% of pancreatic malignancies are adenocarcinomas,<sup>5</sup> and they are the focus of this review. Risk factors for pancreatic cancer are poorly understood. Smoking is consistently identified as a modifiable risk factor, with approximately 30% of all cancers of the pancreas linked to it.<sup>6,7</sup> Chronic pancreatitis is associated with a 10- to 15-fold increase in the risk of developing pancreatic cancer.<sup>8</sup> Hereditary pancreatitis and other familial syndromes involving the pancreas lend themselves to a 50- to 70-fold increase in pancreatic cancer risk.<sup>9</sup> Although there have been studies looking into race, diabetes, alcohol consumption, and even *Helicobacter pylori* infection as risk factors in the development of pancreatic cancer, their roles remain controversial. Thus, the role of cancer prevention is currently limited to education regarding tobacco use.

## Keywords

Pancreatic cancer, targeted agents, chemotherapy.

## Diagnosis and Staging

The clinical presentation of this disease is commonly vague, usually with abdominal or back pain. Patients may present with new-onset diabetes and/or acute pancreatitis. As most tumors arise in the head of the pancreas, some patients present with clinical jaundice as well.

In the last decade, significant advances have been made in the imaging and staging of pancreatic cancer. The principal staging modalities include helical computed tomography (CT) scans and endoscopic ultrasound (EUS). Helical or spiral CT scans are useful and generally accurate in assessing the pancreas and its surrounding structures, liver metastatic disease, and retroperitoneal lymph nodes<sup>10</sup>; more than 90% of pancreatic carcinomas deemed unresectable by CT are unresectable at operation.<sup>11</sup> CT scanning can also be utilized to facilitate fine-needle aspiration. EUS, an endoscopic procedure that utilizes an endoscope with an ultrasound transducer at its tip, can provide high-resolution images of regional lymph nodes and surrounding vessel involvement, as well as facilitate fine-needle biopsies.<sup>12</sup> However, the procedure is highly operator-dependent and is less accurate than CT scanning for evaluating overall resectability. EUS combined with endoscopic retrograde cholangiopancreatography (ERCP) are useful for both fine-needle biopsies and biliary stenting, if needed; ERCP by itself has no proven role in staging pancreatic cancer. Functional positron-emission tomography scanning is not useful in the staging of the primary tumor but may detect metastatic disease.<sup>13</sup> Standard magnetic resonance imaging is less accurate for identifying vessel disease compared to CT; however, magnetic resonance cholangiopancreatography (MRCP) has proven to be superior to CT, ERCP, or ultrasound in determining extrahepatic spread, lymph node involvement, and vascular invasion.<sup>14</sup> Laparoscopy may reveal small (<1 cm) peritoneal or liver metastases that cannot be seen by standard imaging modalities, and upstage approximately 10–40% of all patients depending on the location of their mass.<sup>15</sup>

Staging of pancreatic cancer is based on tumor-node-metastasis (TNM) criteria, which apply to both pathologic and clinical staging at the same time, given the very small percentage of patients undergoing surgical resection.<sup>16</sup> Stage I cancers are confined to the pancreas itself. Stage II disease may extend beyond the pancreas but involves neither the celiac axis nor the superior mesenteric artery. Stages I and II represent localized resectable cancer. When the mass involves the celiac axis or the superior mesenteric artery, the patient has stage III cancer or locally advanced disease. Finally, stage IV represents metastatic disease.

The sialylated Lewis blood group antigen CA 19-9 is the best available tumor marker for pancreatic cancer and

is elevated in approximately 80% of patients with the disease.<sup>17</sup> When measured levels are higher than 200 U/mL in combination with a suspicious mass in the pancreas, the diagnosis of a malignancy has an accuracy rate of 95%.<sup>17</sup> Serum levels above 750 U/mL are associated with a high probability of locally advanced or metastatic disease.<sup>18</sup> CA 19-9 should be used only to support the diagnosis and staging of pancreatic cancer and to help monitor for recurrence or response to treatment. While CA 19-9 is a useful predictor of pancreatic malignancy, age and jaundice were found to be better predictors than CA 19-9 alone. Patients over age 50 with jaundice or with CA 19-9 concentrations greater than 150 U/mL should undergo resection with a curative intent for suspected malignancy.<sup>19</sup>

There has been much research into uncovering biomarkers for identifying pancreatic cancer at an earlier stage. Investigational proteomic approaches, laser desorption ionization, and mass spectrometry are being utilized to identify novel proteins from both pancreatic secretions and serum. As an example, proteomics and gene expression profiling have yielded the discovery of a number of consistently overexpressed proteins and genes, the most promising of which is the *MIC-1* gene.<sup>20</sup> This gene, which is related to the transforming growth factor beta family, has proven itself to be a superior correlate to advanced-stage pancreatic cancer when compared to CA 19-9.

## The Genetics of Pancreatic Cancer

### Oncogenes

One of the most consistently found genetic mutations occurring in pancreatic cancer is that involving *K-ras*.<sup>21</sup> The mutated oncogene is present in about 90% of adenocarcinomas of the pancreas. Upregulation of this gene in tissue culture experiments has led to tumorigenesis and increased S-phase stimulation.<sup>22</sup> Another oncogene with possible involvement in the pathogenesis of pancreatic cancer is *HER2/neu*, which is found in 17–58% of all tumors.<sup>23</sup>

### Tumor Suppressor Genes

Mutations of the *TP53* gene have consistently been identified in 40–80% of all pancreatic adenocarcinomas.<sup>24</sup> *TP53* mutations have been shown to promote chromosomal instability, thus contributing to the development and progression of the cancer.<sup>25</sup>

Mutations of the *p16* gene have been associated with decreased survival in patients with pancreatic cancer. Mutations resulting in the absence of its expression lead to the inactivation of Rb1, an important protein in cell-cycle inhibition.<sup>24,26</sup> Inactivation of the Rb1/p16 pathway is reported to be present in 98% of all pancreatic carcinomas.

Other tumor suppressor genes that may be important in understanding the molecular biology of pancreatic cancer are *DPC4*, *TGF-B*, and *BRCA-2*.

### Localized Disease

Patients with resectable disease represent less than 10% of all pancreatic cancer patients. The mainstay in managing localized pancreatic cancer is surgical resection with curative intent. Radical resection procedures include pancreaticoduodenectomy (Whipple procedure), distal pancreatectomy, and total pancreatectomy. The Whipple procedure remains the most common surgical technique performed in patients with tumors of the pancreatic head, neck, and uncinate process, with a reported 5-year survival rate of approximately 15%.<sup>27</sup> Distal pancreatectomy is indicated for patients with tumors of the body and tail and has a reported 5-year survival rate of less than 15%.<sup>28</sup> There is strong evidence suggesting that surgical outcomes including mortality rate and 3-year survival improve at centers designated as high-volume.<sup>29</sup> Birkmeyer and coauthors looked at 10,507 US patients with resected pancreatic cancer and found that very low-volume hospitals (<1 procedure performed per year) had a reported 16.2% mortality rate and a 25% 3-year survival rate while high-volume hospitals (>16 procedures performed per year) had a reported 3.9% mortality rate and a 37% 3-year survival rate. Low- and moderate-volume hospitals had intermediate mortality and 3-year survival rates.<sup>29</sup>

The role of adjuvant therapy is continuously being redefined. An initial analysis of 100,313 US patients with pancreatic cancer in the National Cancer Database revealed that 9,044 patients (9%) had a pancreatectomy with only about 40% receiving adjuvant therapy (6.5% radiation alone, 5.1% chemotherapy alone, and 28.3% chemoradiation).<sup>30</sup> Five-year survival was 23.3% for the observation-alone arm and ranged between 13–17% in the other arms. However, numerous studies over the last three decades have consistently shown an advantage to adjuvant therapy versus observation alone (Table 1). Nonetheless, there is no universally accepted standard approach to date, with current options including combined modality therapy in the United States and chemotherapy alone in Europe.

### The Role of Chemoradiation

Evidence suggests that combining 5-fluorouracil (5-FU) with radiation can enhance response and improve local control.<sup>31</sup> In the late 1980s, the Gastrointestinal Tumor Study Group (GITSG) published the results of a study comparing observation alone with adjuvant chemotherapy (bolus 5-FU) and split-course radiation followed by 2 years of maintenance 5-FU.<sup>32,33</sup> This randomized study was terminated early because of low accrual and a large survival difference favoring the treatment arm (median survival 20 vs 11 months for observation arm). Based on the results of this study, adjuvant chemoradiation became the standard of care in the United States. In contrast, the

**Table 1.** Results of Randomized Trials of Adjuvant Therapy for Pancreatic Cancer

Study	Treatment	n	Median Survival (months)	Disease-Free Survival (months)
GITSG <sup>32</sup>	Observation	22	11	-
	CRT	21	20 (P=.035)	-
Bakkevold et al <sup>35</sup>	Observation	30	11	-
	5-FU/D/MMC	31	23 (P=.02)	-
EORTC <sup>34</sup>	Observation	54	12.6	-
	CRT	60	17.1 (P=.099)	-
Takada et al <sup>36</sup>	Observation	81	18.0%	-
	5-FU/ MMC	77	11.5% (P=NS)*	-
ESPAC-1 <sup>38</sup>	No CRT	144	17.9	-
	CRT	145	15.9 (P=.05)	-
ESPAC-1 <sup>38</sup>	No Chemotherapy	142	15.5	-
	Chemotherapy	147	20.1 (P=.009)	-
CONKO-001 <sup>37</sup>	Observation	182	-	7.46
	Gemcitabine	186	-	14.21 (P<.001)

\* Disease-free survival at 5 years.

5-FU = 5-fluorouracil; CRT = chemoradiation therapy; D = doxorubicin; EORTC= European Organization for Research and Treatment of Cancer; ESPAC-1 = European Study Group for Pancreatic Cancer; GITSG = Gastrointestinal Tumor Study Group; MMC = mitomycin C.

European Organization for Research and Treatment of Cancer (EORTC) looked at split-dose radiation combined with infusional 5-FU (without follow-up chemotherapy) and found no significant difference in survival compared to observation alone.<sup>34</sup>

### ***The Role of Chemotherapy***

Two randomized studies looking at the role of adjuvant chemotherapy (5-FU in combination with mitomycin C with or without the addition of doxorubicin) found no significant advantage over observation alone.<sup>35,36</sup> Recently the Charité Onkologie—Clinical Studies in GI Cancers (CONKO-001) trial, presented at the 2005 American Society of Clinical Oncology (ASCO) meeting, demonstrated the most convincing evidence to date for the use of adjuvant therapy over observation.<sup>37</sup> Unlike other studies of adjuvant therapy in pancreatic cancer, this randomized European trial was very well powered and looked at 6 months of standard gemcitabine therapy versus observation alone. The study showed a statistically significant disease-free survival advantage of 14.21 months in the gemcitabine arm compared to only 7.46 months in the observation arm. Survival analysis is still underway with a definite trend favoring the chemotherapy arm. All patients, whether they were N0 or N1, R0 or R1, seem to have benefited significantly from gemcitabine in the adjuvant setting.

### ***Chemotherapy Versus Chemoradiation***

The European Study Group for Pancreatic Cancer-1 (ESPAC-1) trial tried to address the question of chemotherapy alone or in combination with radiation. This large multicenter study had a 2 × 2 factorial with four randomization schemes including observation, chemoradiation, chemotherapy alone, and chemoradiation-followed-by-chemotherapy arms.<sup>38</sup> Because of the small sample size in each group, the final analysis included two options: chemoradiation versus no chemoradiation and chemotherapy versus no chemotherapy. The results of this large trial showed a significant impact on median survival in the chemotherapy-alone group compared to the no-chemotherapy groups (20.1 vs 15.5 months;  $P=.009$ ). The estimated 2- and 5-year survival rates for the chemotherapy versus no-chemotherapy groups were 40% versus 21% and 30% versus 8%, respectively. Conversely, no benefit was seen in the chemoradiation arm, which, surprisingly, performed worse than the no-chemoradiation arm (median survival, 15.9 vs 17.9 months;  $P=.05$ ). The estimated 2- and 5-year survival rates for the chemoradiation versus no-chemoradiation groups were 10% versus 29% and 20% versus 41%, respectively. The study, however, had a high rate of nonadherence with a large number of patients not completing the full number of treatment pro-

tol cycles; in addition there was a lack of quality control of the radiotherapy techniques. The study also lacked the power to perform statistical comparisons between the four treatment groups and instead analyzed pooled data.

Stocken and colleagues performed a meta-analysis of randomized adjuvant therapy trials, including ESPAC-1 (2 × 2 factorial design and the other two random assignment options; N=550), GITSG, EORTC, and the Norwegian and Japanese studies, with a total of 939 patients analyzed. The results of this meta-analysis were consistent with the results from ESPAC-1, confirming the benefit of adjuvant chemotherapy for patients with resected pancreatic cancer. Again, patients receiving chemoradiotherapy did worse than the control group. Subgroup analysis estimated that chemoradiation was more effective than chemotherapy (5-FU) in patients with positive-margin tumors.

### ***Neoadjuvant Therapy***

The rationale for neoadjuvant therapy in pancreatic cancer is to reduce tumor bulk. This has proven useful in the local control of the disease, but it does not affect overall survival. Preoperative radiation therapy is done with the expectation that, by altering the vascularity of the tumor, it may decrease the ability of the tumor cells to disseminate during subsequent laparotomy.<sup>40</sup> When looking at the role of radiation therapy, there was no difference between surgery alone or surgery preceded by radiation therapy in terms of overall survival and resectability rates.<sup>41</sup> Furthermore, there was no difference in overall survival between surgery alone or surgery preceded by 5-FU combined with radiotherapy<sup>42</sup> or 5-FU with mitomycin combined with radiotherapy<sup>43</sup> despite a decrease in locoregional recurrence rates from 21% to 10%.

### ***Locally Advanced Disease***

Patients with locally advanced cancer of the pancreas compose an intermediate group. They are unresectable but show no evidence of metastatic disease. Therapeutic options for this group of patients include external beam radiation therapy (EBRT) with 5-FU chemotherapy. With the exception of one trial, conventional EBRT combined with 5-FU has been shown to improve survival in patients with locally advanced cancer of the pancreas (Table 2).<sup>44-48</sup> The Eastern Cooperative Oncology Group study failed to show any difference when comparing 5-FU alone with EBRT in combination with 5-FU. More recently, a retrospective analysis evaluated the role of chemoradiation in patients with locally advanced disease. The results of this study showed that 21% of all patients were downstaged to resectability. In addition, the patients who achieved resectability had significantly prolonged survival compared to those who were not downstaged (28 vs 11 months).<sup>49</sup>

**Table 2.** Results of Randomized Trials for Locally Advanced Pancreatic Cancer

Study	Treatment	n	Median Survival (months)	18-Month Survival Rates
Mayo Clinic <sup>44</sup>	EBRT	32	6.3	6%
	EBRT+5-FU	32	10.4	13%
GITSG <sup>45</sup>	EBRT (60 Gy/10 wk)	25	5.3	5%
	EBRT (40 Gy/6 wk)+5-FU	83	8.4	20%
	EBRT (60 Gy/10 wk)+5-FU	86	11.4	20%
GITSG <sup>46</sup>	EBRT (60 Gy/6 wk)+5-FU+SMF	73	8.5	15%
	EBRT (40 Gy/4 wk)+D	70	7.6	17%
GITSG <sup>47</sup>	EBRT (54 Gy/6 wk)+5-FU+SMF	22	9.7	18%
	SMF	21	7.4	0%
ECOG <sup>48</sup>	EBRT (40 Gy/4 wk)+5-FU	47	8.3	11%
	5-FU	44	8.2	21%

5-FU = 5-fluorouracil; D = doxorubicin; EBRT = external beam radiation therapy; ECOG = Eastern Cooperative Oncology Group; GITSG = Gastrointestinal Tumor Study Group; SMF = streptozocin, mitomycin-C, and 5-FU.

## Metastatic Disease

Therapeutic strategies in the metastatic setting have fallen short of their goals of prolonging survival, although some progress has been made in improving patient quality of life. Metastatic disease tends to be relatively chemoresistant.

### The Role of Chemotherapy

Gemcitabine therapy is currently considered the standard of care in treating patients with advanced pancreatic cancer. The phase III advanced pancreatic cancer study that led to the approval of gemcitabine compared it with the previous standard, 5-FU, using the clinical benefit response (CBR; a composite of pain, daily analgesic use, weight, and performance status assessments) as a primary endpoint.<sup>50</sup> Gemcitabine showed a 24% CBR compared to 5% in patients receiving 5-FU ( $P=.0022$ ); there was also a modest difference in median survival (5.7 vs 4.4 months, respectively;  $P=.0025$ ). The 1-year survival rate improved 18% with gemcitabine versus 2% with 5-FU.

Since the establishment of gemcitabine as a standard of care in this malignancy, several large phase III studies have evaluated it in combination with various chemotherapeutic agents (Table 3), including 5-FU, cisplatin, irinotecan, pemetrexed, and exatecan.<sup>51-57</sup> These studies have shown no added benefit (survival or CBR) versus gemcitabine alone. One noteworthy study is a phase III trial conducted by Louvet and coworkers<sup>58</sup> (N=326) looking at the combination of gemcitabine plus oxaliplatin versus gemcitabine alone. Although there was an obvious trend toward improved survival with gemcitabine plus oxaliplatin (9 vs 7.1 months;  $P=.13$ ), the difference was not statistically significant. However, there was a statistically significant improvement in CBR with gemcitabine/oxaliplatin (38.2% vs 26.9%;  $P=.03$ ). A potentially con-

founding factor in this study was the use of a fixed-dose-rate infusion (10 mg/m<sup>2</sup>/min) of gemcitabine in the combination arm versus a standard 30-minute infusion in the control arm. An earlier phase II randomized study showed an improvement in median survival with fixed-dose-rate versus standard 30-minute infusion of gemcitabine in patients with metastatic pancreatic cancer.<sup>59</sup>

### The Role of Targeted Therapy

Although earlier studies with biologic agents such as tipifarnib (a farnesyl transferase inhibitor)<sup>60</sup> and marimastat (a matrix metalloproteinase inhibitor)<sup>61</sup> failed to show any improvement over gemcitabine alone, recent strategies incorporating agents that target growth factors or their receptors have shown some promise.

**The Epidermal Growth Factor Receptor** Epidermal growth factor and its receptor (EGFR) regulate cell division, repair, and survival, and may have a role in the processes of angiogenesis and metastasis.<sup>62</sup> EGFR is widely expressed in pancreatic cancer (up to 95% of all cases).<sup>63</sup> Agents that block EGFR activity are postulated to enhance the antitumor effects of chemotherapy and radiotherapy, as well as initiating multiple antitumor mechanisms by themselves.<sup>62</sup> The primary methods for targeting EGFR are monoclonal antibodies and small-molecule tyrosine kinase inhibitors. One strategy is to target the intracellular adenosine triphosphate pocket of the tyrosine kinase binding domain of the receptor, thereby preventing phosphorylation and leading to disruption of the signal transduction cascade. This inhibition is thought to arrest cell proliferation (G1 arrest) and promote apoptosis. Several agents in development have used this strategy including the oral agents erlotinib (Tarceva, Genentech) and gefitinib (Iressa, AstraZeneca). The National Cancer Insti-

**Table 3.** Results of Phase III Randomized Trials for the Treatment of Advanced Pancreatic Cancer

Study	Treatment	n	Median Survival (months)	1-Year Survival Rate
ECOG <sup>51</sup>	Gemcitabine	162	5.4	<20%
	Gemcitabine+5-FU	160	6.7 ( <i>P</i> =.09)	<20%
Rocha Lima et al <sup>52</sup>	Gemcitabine	169	6.6	-
	Gemcitabine+irinotecan	173	6.3 ( <i>P</i> =.789)	-
Heinemann et al <sup>53</sup>	Gemcitabine	100	3.0	-
	Gemcitabine+cisplatin	98	7.6 ( <i>P</i> =.120)	-
Oettle et al <sup>54</sup>	Gemcitabine	282	6.3	21.4%
	Gemcitabine+pemetrexed	283	6.2 ( <i>P</i> =.8477)	22.1%
Cheverton et al <sup>55</sup>	Gemcitabine	170	6.5	22.1%
	Exatecan	169	5.0 ( <i>P</i> =.0993)	17.9%
O'Reilly et al <sup>56</sup>	Gemcitabine	174	6.2	-
	Gemcitabine+exatecan	175	6.7 ( <i>P</i> =.52)	-
Colucci et al <sup>57</sup>	Gemcitabine	54	5.0	-
	Gemcitabine+cisplatin	53	6.0 ( <i>P</i> =.43)	-
Louvet et al <sup>58</sup>	Gemcitabine	156	7.1	27.8%
	Gemcitabine+oxaliplatin	157	9.0 ( <i>P</i> =.13)	34.7%
Bramhall et al <sup>61</sup>	Gemcitabine	119	5.5	17%
	Gemcitabine+marimastat	120	5.5 ( <i>P</i> =.950)	18%
Van Cutsem et al <sup>60</sup>	Gemcitabine	347	6.1	24%
	Gemcitabine+tipifarnib	341	6.4 ( <i>P</i> =.750)	27%
Moore et al <sup>64</sup>	Gemcitabine	284	5.91	17%
	Gemcitabine+erlotinib	285	6.37 ( <i>P</i> =.025)	24%

ECOG = Eastern Cooperative Oncology Group; 5-FU = 5-fluorouracil.

tute of Canada (NCIC) conducted a large phase III study looking at the benefit of adding erlotinib to gemcitabine versus gemcitabine alone.<sup>64</sup> The results of this study, presented at the 2005 ASCO meeting, showed a small but statistically significant improvement in median overall survival (6.37 vs 5.91 months; *P*=.025) and progression-free survival (3.75 vs 3.55 months; *P*=.003) with erlotinib. The drug was well tolerated with only a modest increase in toxicity with the erlotinib arm, mainly rash and diarrhea. Another strategy involves targeting the extracellular binding domain of EGFR through a monoclonal antibody. Cetuximab (Erbix, ImClone/Bristol-Meyers Squibb) is a chimeric anti-EGFR monoclonal antibody that was combined with gemcitabine in a recent phase II study.<sup>65</sup> The study showed promising results with a 75.5% tumor control rate (12.2% responders and 63.4% with stable disease), a median survival of 7.1 months, and a 1-year survival rate of 31.7%.

**The Vascular Endothelial Growth Factor** The vascular endothelial growth factor (VEGF) stimulates tumor angiogenesis, which is essential for tumor growth. VEGF inhibition may prevent the growth of new tumor blood

vessels by normalizing tumor vasculature structure and function and decreasing intratumoral fluid pressure, ultimately leading to vascular regression.<sup>66</sup> Bevacizumab (Avastin, Genentech) is a humanized monoclonal antibody that targets VEGF, preventing it from binding to its own receptors, thus resulting in an antiangiogenic effect.<sup>67</sup> When added to standard chemotherapy, bevacizumab improved all efficacy parameters in patients with malignancies of the colon and the lung in several recent large phase III studies.<sup>68-70</sup> A recent phase II study of gemcitabine and bevacizumab for advanced pancreatic cancer showed very promising results, with a 67% tumor control rate (19% responders and 48% with stable disease), a median survival of 8.7 months, and a 1-year survival rate of 29%.<sup>71</sup>

## Conclusions

Despite the many advances in the field of oncology, treating cancer of the pancreas remains a formidable challenge. Strategies to detect the cancer earlier would certainly impact survival but are a far reach for now. Clinical investigation into chemotherapy and targeted agents will hopefully lead to improved disease outcomes.

Surgical resection remains the only proven modality for achieving long-term survival, but unfortunately more than 85% of patients who undergo surgery die from recurrent disease. There is evidence that regionalization of care—by referring patients to high-volume centers—would immediately improve survival for patients with localized disease. Adjuvant therapy seems to impact survival, but the debate continues over a standard of care. Most of the available studies are small, underpowered, and inconclusive, with the exception of one large well-designed phase III study suggesting a benefit from adjuvant gemcitabine based on disease-free survival (CONKO-001) and some data supporting the use of 5-FU (ESPAC-1). All patients with R0 resected pancreatic cancer should be considered for adjuvant therapy with gemcitabine or 5-FU. Patients with R1 resection should receive either gemcitabine alone or combined modality treatment. For those with R2 resections, combined modality treatment is indicated. The relative contribution of chemoradiation versus chemotherapy in the adjuvant setting is unanswered pending results of ongoing studies, such as the EORTC 40013 study looking at gemcitabine versus gemcitabine plus radiotherapy in patients with resected tumors.

In locally advanced pancreatic cancer, common practice in the United States is for patients to receive infusional 5-FU in combination with EBRT. Patients who achieve resectability have a significantly prolonged survival, and therefore strategies leading to improved responses and increased resectability rates are being developed. Drugs such as gemcitabine, paclitaxel, and, more recently, cetuximab, bevacizumab, and other growth factors and cell signal inhibitors are being used to maximize sensitization to the effects of radiotherapy with the hope of improving outcome.

In the metastatic setting, the outlook is extremely grim. Gemcitabine given over 30 minutes is still considered the standard of care and no studies to date have shown a survival advantage with combination chemotherapy when compared to gemcitabine alone—despite an improved tumor control rate with combinations. The first study in metastatic pancreatic cancer to show an improved survival over the standard of care was the phase III NCIC study looking at erlotinib added to gemcitabine. Despite a very modest survival benefit, the results emphasize the potential role of targeted therapies in translating improved activity into improved survival. Several other targeted agents are being looked at in combination with gemcitabine or gemcitabine combinations in pancreatic cancer including the two large phase III studies looking at the role of either cetuximab (SWOG) or bevacizumab (CALGB) added to gemcitabine in the treatment of advanced pancreatic cancer.

In conclusion, a variety of new systemic approaches are under development, and many of the best chemothera-

peutic and targeted therapeutic strategies are being applied to clinical investigation. The possibilities for therapeutic progress in pancreatic cancer have never been greater.

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