



Sofia Cáceres. *Para Echar Raíces (Growing Roots)*. Acrylic on canvas, 30" × 42".

*Patients can benefit from the advances made in the assessment and treatment of borderline resectable pancreatic cancer.*

## **Borderline Resectable Pancreatic Cancer: On the Edge of Survival**

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**Background:** *Patients with borderline resectable pancreatic cancer are at high risk of having positive surgical margins due to involvement of the tumor with adjacent vasculature. This article reviews the management of this subset of pancreatic cancer patients.*

**Methods:** *The authors review the current definitions of borderline resectable pancreatic cancer and how it is diagnosed and staged. The history, current approaches, and future directions in neoadjuvant therapy for borderline resectable pancreatic cancer are also reviewed with emphasis on various chemotherapy regimens that have been used. The application of intensity-modulated radiation therapy and image-guided radiation therapy that accounts for respiratory motion to targeting the gross tumor volume in the pancreas are discussed, and the promise of integrating targeted therapies in neoadjuvant treatment programs is highlighted.*

**Results:** *The use of neoadjuvant treatment programs that employ gemcitabine-based chemotherapy regimens followed by chemoradiation increases the likelihood of subsequent margin-negative resection in borderline resectable pancreatic cancer.*

**Conclusions:** *There has been progress in the imaging, staging, surgical technique, and the use of chemotherapy and chemoradiotherapy in the management of borderline resectable pancreatic cancer. Patients can benefit from multidisciplinary management at high-volume pancreatic cancer treatment centers.*

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**Abbreviations used in this paper:** PV = portal vein, SMV = superior mesenteric vein, 5-FU = 5-fluorouracil, ECOG = Eastern Cooperative Oncology Group, MTD = maximally tolerated dose, EGFR = epidermal growth factor receptor, PET = positron-emission tomography.

### **Introduction**

The 5-year survival rate for patients with histologically confirmed metastatic ductal adenocarcinoma of the pancreas approaches 0%, with a median overall survival of 5 to 6 months.<sup>1-3</sup> Long-term survival after a diagnosis of pancreatic cancer is attained only in patients who are diagnosed prior to the development of distant metastasis and are able to undergo complete surgical resection with negative margins. This subset constitutes about 15% to 20% of all newly diagnosed pancreatic cancer patients.<sup>4</sup> Nevertheless, only about 20% of

this subset (3% to 4% of all patients) will survive beyond 5 years. The median overall survival of patients who undergo complete resection with negative margins ranges between 12 and 26 months.<sup>5</sup> Therefore, until more effective systemic therapy is discovered, complete surgical resection is the superior treatment modality for patients with resectable disease. Approximately one-third of patients presenting with locally advanced pancreatic cancer will be marginally or “borderline” resectable. The application of existing multimodality therapies, despite their limited efficacy, can have the greatest impact on the borderline pancreatic cancer patient by downstaging them to resectability. In principle, a modest tumor response to neoadjuvant therapy may translate into a potential doubling of survival and preservation of the opportunity for cure by facilitating successful resection with negative margins.

## The Evolving Assessment and Definition of Borderline Resectable Pancreatic Cancer

In the past, the determination of whether a pancreatic cancer was resectable, unresectable, or borderline resectable was made at surgical exploration. The development of modern imaging techniques with improved resolution has allowed for the preoperative staging of patients. Institutions vary in the use of these techniques and the criteria that are used to stratify patients. There is no definite national consensus on which approach is best. The common theme is to use some combination of complementary imaging modalities to define the size, geometry, and extent of vascular involvement of disease. The Moffitt Cancer Center Multidisciplinary Pancreatic Cancer Clinic employs a uniform preoperative assessment algorithm that consists of a multi-detector, thin-section pancreatic protocol computed

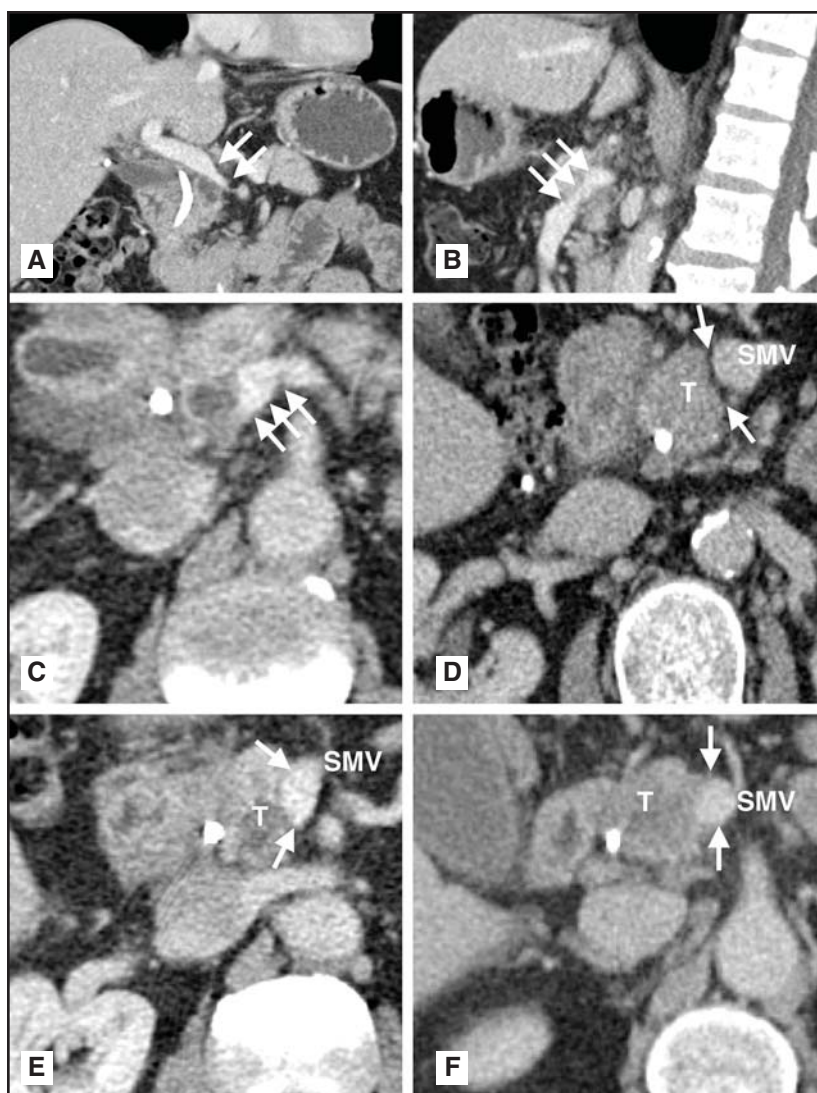


Fig 1. — Multidetector high-resolution CT scans in staging pancreatic cancer. Coronal (A) and sagittal (B) reconstructed images of a patient with an unresectable pancreatic tumor that encases and constricts the PV (arrows). (C) Teardrop deformation of the PV/SMV that abuts a pancreatic tumor for 180°. Varying degrees of SMV abutment (D-F) with tumor (T). (D) No SMV abutment. (E) < 180° SMV abutment. (F) 180° SMV abutment.

tomography (CT) scan, an endoscopic ultrasound, a positron-emission tomography (PET) scan, and a determination of serum CA19-9. Multidetector CT scan is approximately 80% accurate in predicting resectability and almost 90% accurate in assessing vascular invasion (Fig 1).<sup>6</sup> Endoscopic ultrasound serves a complementary role. It is 75% to 95% accurate in assessing T stage and 74% to 87% accurate in assessing N stage.<sup>7-9</sup> It is particularly useful in identifying smaller pancreatic tumors that are < 2 cm and can confirm the presence of vascular invasion or venous thrombosis. At our institution we obtain a PET scan to identify potential sites of distant metastasis that may not be detected by a conventional CT scan of the thorax, abdomen, and pelvis. While this is not yet standard, we have noted instances where patients were spared a pancreaticoduodenectomy after “occult” metastases were unmasked on PET scan (Fig 2A). PET scan as a modality for the diagnosis, staging, and monitoring of treatment of pancreatic and other cancers is currently being assessed nationally in a Medicare outcomes study. Our center is a participant in the National Oncologic PET Registry, which has given our institute an opportunity to evaluate this imaging modality in pancreatic cancer. In a series of 82 patients with potentially resectable pancreatic cancer who were staged with PET/CT and CT scan, the sensitivity and specificity of PET scan were 89% and 88%, respectively. The sensitivity for detecting metastasis

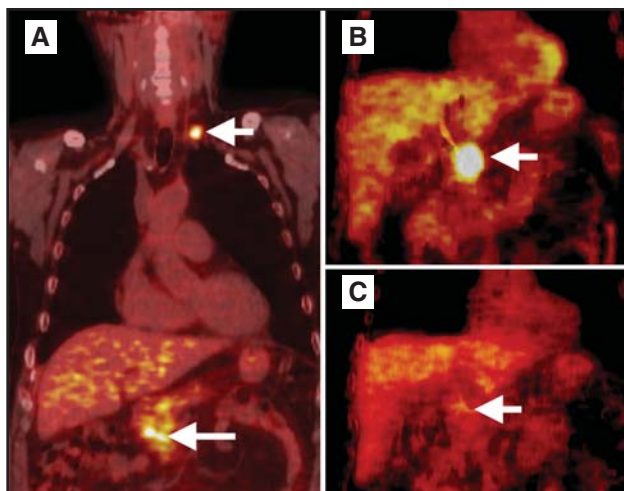
was 61% for PET/CT scan, 59% for CT scan, and 87% for the combination of the two. Clinical management was altered by the PET findings in 11% of cases.<sup>10,11</sup> For patients who are judged to be borderline and recommended to undergo neoadjuvant therapy, having a baseline PET scan and CA19-9 allows for assessment of tumor metabolic response during therapy (Figs 2B-C).

There is general agreement that patients with a patent portal vein (PV), a superior mesenteric vein (SMV), and a fat plane between the tumor and the superior mesenteric and celiac arteries without distant metastasis are potentially resectable.<sup>3</sup> At the Moffitt Multidisciplinary Pancreatic Cancer Clinic, these patients are scheduled for immediate surgical resection. Patients who have encasement of the superior mesenteric artery (SMA), celiac artery, aorta, or inferior vena cava (IVC) are classified as unresectable. PV or SMV encasement by greater than 180° over an extended segment is also classified as unresectable. This is based on the observation that the extent of vessel circumference that is in contact with the tumor correlates with the probability of vessel invasion (Table 1).<sup>12,13</sup> With ≤ 180° abutment, the likelihood of vessel invasion is overall about 40%. With > 180° abutment, the likelihood of invasion is 80%. When encasement by > 270° is present, vessel invasion is present in almost 100% of cases. Borderline patients are those who have circumferential tumor abutment with the SMV, PV, or SMA over ≤ 180°. Short segment (approximately 1.5 cm) encasement of the PV or SMV that is amenable to partial vein resection and reconstruction is classified as borderline. Involvement of both the PV/SMV and SMA that would require resection

**Table 1. — CT Imaging Signs and Probability of Invasion for Pancreatic Cancer**

CT Imaging Sign	Probability of Invasion (%)
No tumor abutment with vessel	0–3
> 90° tumor abutment with PV	30–60
> 180° tumor abutment with PV	80–100
> 5 mm length of PV contact	80
> 90° tumor abutment with SMV	80
> 180° tumor abutment with SMV	80
> 5 mm length of SMV contact	80
PV/SMV constriction or thrombus	100
Teardrop deformation of SMV	98

and reconstruction of both arterial and venous systems is classified as unresectable. Finally, encasement of the gastroduodenal artery up to the origin of the hepatic artery is considered borderline. In these instances, the likelihood of a resection with positive margins (R1 or R2) is increased. Neoadjuvant therapy is intended to optimize the likelihood of obtaining an R0 resection. An additional criterion is the presence of a teardrop-shaped deformity of the SMV, which is normally symmetrically round or oval on CT scan.<sup>14</sup> This triangular-shaped protrusion from the vessel is a strong indication of vessel invasion. Its presence, along with other CT scan signs, has a sensitivity of 91%, a specificity of 98% and an accuracy of 95% in predicting unresectability of pancreatic cancer. Finally, the presence of dense periarterial soft tissue portends a low likelihood for resectability, whereas fine periarterial stranding does not.<sup>6</sup>



**Fig 2. — Use of PET scans in staging and monitoring treatment response in pancreatic cancer.** (A) This 50-year-old man had a potentially resectable pancreatic cancer based on CT scan criteria. The PET scan confirmed the presence of the hypermetabolic pancreatic mass but also identified a hypermetabolic left supraclavicular lymph node. This lymph node was biopsied, metastatic pancreatic cancer was confirmed, and surgery was avoided. (B) Pretreatment PET scan of a 61-year-old man with a borderline unresectable pancreatic mass. (C) PET scan of the patient after neoadjuvant therapy with GTX for 3 cycles and 5-FU–based chemoradiation to 50.4 Gy. This patient underwent subsequent R0 resection.

### Neoadjuvant Therapy for Borderline Resectable Pancreatic Cancer: Past, Present, and Future

There are a number of theoretical and practical benefits to neoadjuvant therapy for borderline patients. First, the chief objective is to induce a partial tumor response and therefore increase the likelihood of complete resection with negative margins. Second, exposure of the tumor to chemotherapeutic agents prior to resection allows for the sensitivity of the tumor to those agents to be assessed. If the tumor responds, then the same therapy can be employed if the patient has a recurrence. Third, intensive multiagent multimodality treatment programs may be better tolerated by patients prior to surgery compared to following pancreaticoduodenectomy. Patients who experience major complications after surgery may require prolonged recovery times during which chemotherapy and radiation might not be given. Fourth, adequate perfusion should allow for the delivery of radiosensitizing oxygen and chemotherapy within the tumor tissue. This should increase the effectiveness of radiation. Surgery may

potentially disrupt blood flow to the operative bed and might limit the effectiveness of postoperative radiation. Finally, the fact that most successfully resected patients nevertheless recur is de facto evidence that micrometastases are present at an early stage of the disease. Neoadjuvant therapy potentially allows for the early control of occult micrometastasis.

## Chemoradiotherapy in the Pre-Gemcitabine Era

One of the earliest attempts to develop a neoadjuvant treatment program for patients with borderline resectable pancreatic cancer utilized radiation only.<sup>15</sup> Seventeen patients with borderline unresectable pancreatic cancers were treated preoperatively with radiation at doses of 40 to 46 Gy over 4 to 5 weeks. The observed response rate was 29%, and 6 patients (35%) became resectable. Only 2 patients (12%) had negative margins but they survived for more than 5 years.

In 1981, the Gastrointestinal Tumor Study Group subsequently demonstrated the superiority of 5-fluorouracil (5-FU)-based chemoradiation over radiation alone in the setting of locally advanced unresectable disease, reporting a 5.7 month median survival in the radiation alone arm of 60 Gy vs 10 months in the arms receiving bolus 5-FU and 40 Gy vs 60 Gy.<sup>16</sup> The radiation volumes treated were large, including the entire pancreas and the elective regional nodes at risk.

In the 27 years that have followed since this early report, an increase in the dose to the pancreatic primary for unresectable disease has been associated with improved local control rates but without a benefit in survival. With conventional external-beam approaches, doses are limited in the abdomen secondary to the adjacent normal tissues including the liver, kidneys, stomach, small bowel, and spinal cord. Approaches have thus evolved to incorporate a boost dose of radiation so that the volume of normal tissue irradiated to a high dose could be reduced. Early attempts included the use of intraoperative radiation therapy (IORT) or brachytherapy. Roldan et al<sup>17</sup> reported a series of unresectable patients treated with the combination of external-beam radiation and IORT vs external-beam radiation alone. Local control was 82% with combination therapy vs 48% with external-beam radiation alone at 1 year and 66% vs 20% at 2 years ( $P < .0005$ ). This did not translate into any improvement in median or overall survival. Similarly, Raben et al<sup>18</sup> reported no improvement in median survival with the Memorial Sloan-Kettering experience of implanting <sup>103</sup>Pd brachytherapy at the time of staging laparotomy in the treatment of primary unresectable disease. However, they did note increased toxicity.

To evaluate the multimodality approach in potentially resectable patients, investigators from M. D. Anderson Cancer Center explored a concurrent chemoradiation

approach. Evans et al<sup>19</sup> reported on the treatment of 28 patients with potentially resectable tumors who received a dose of 50.4 Gy of radiation with concurrent 5-FU at 300 mg/m<sup>2</sup> per day. Five patients (18%) progressed to metastatic disease during therapy and were not taken to surgery. Of the 23 patients (82%) who underwent laparotomy, 6 (26%) were found to be unresectable or had occult metastasis. Of the remaining 17 who underwent pancreaticoduodenectomy, 3 had positive margins. Therefore, the goal of complete resection with negative margins was achieved in 14 (50%) of the 28 patients, and they had a median survival that was greater than 19 months. A similar program that delivered 45 Gy of radiation concurrently with 5-FU at 225 mg/m<sup>2</sup> per day to 16 patients who were surgically staged achieved only 2 (12%) resections with negative margins.<sup>20</sup> It is likely that differences in patient selection accounts for part of the difference in outcome between these similar treatment programs. Also, intraoperative radiation therapy was employed in the M. D. Anderson series. Additional data from Memorial Sloan-Kettering Cancer Center has also looked at the pathologic features of patients undergoing preoperative combined modality therapy (CMT) vs no preoperative therapy. Results showed that patients who received preoperative CMT had smaller tumors at surgery (mean 2.3 cm vs 3.1 cm,  $P < .01$ ) were less likely to have T3 tumors (54% vs 80%,  $P < .01$ ), were less likely to have positive lymph nodes (29% vs 58%,  $P < .01$ ), and had fewer positive nodes (mean 0.4 vs 1.9,  $P < .01$ ).

Since escalation of radiation dose in locally advanced pancreatic cancer has not been shown to be more effective in prolonging survival, others have focused on improving efficacy by using multiagent chemotherapy regimens along with conventional radiation.<sup>16</sup> Investigators at Fox Chase Cancer Center performed pilot studies employing 50.4 Gy of radiation with a combination of 5-FU 1,000 mg/m<sup>2</sup> per day continuous infusion on days 2 to 5 and days 29 to 32 and mitomycin-C 10 mg/m<sup>2</sup>. In a series of 34 patients who received this neoadjuvant therapy, 25 were taken to surgery.<sup>21</sup> Eleven underwent pancreatectomy, and 10 of these patients had negative margins, thus yielding a promising resection rate of 40%. For this group of patients, a 45-month median survival was observed. The preliminary data from this series served as the impetus for a Eastern Cooperative Oncology Group (ECOG) trial of this procedure. ECOG PD-289 was a phase II study that was the first neoadjuvant multimodality trial for potentially resectable pancreatic cancer that was performed by a cooperative group.<sup>22</sup> A total of 53 eligible patients were treated. Of these, 12 (23%) progressed or died prior to surgery. Of the 41 patients taken to surgery, 24 (45%) underwent resection. The others were found to be unresectable. Of those who were resected, 21 were examined for mar-

gin status, and 7 had positive margins. Therefore, the goal of resection with negative margins was achieved in a maximum of 17 of the original 53 patients (32%). The overall resection rate (45%) was comparable to the Fox Chase experience, but the median survival for the resected patients was lower (16 months vs 20 months).

The Pancreaticobiliary Treatment Group of New York employed a three-drug regimen of 5-FU continuous infusion 1,000 mg/m<sup>2</sup> per day over 108 hours, with cisplatin 100 mg/m<sup>2</sup> every 28 days and streptozotocin 300 mg/m<sup>2</sup> on days 1 through 3 every 28 days.<sup>23</sup> Radiotherapy was given to a dose of 54 Gy. The neoadjuvant program was given to 68 patients who were unresectable based on CT imaging, endoscopic ultrasound, laparoscopy, or laparotomy. It was associated with a 27% incidence of grade 3 and 4 toxicity. Of the 68 patients, 22 (32%) either progressed during neoadjuvant therapy or did not have an objective radiologic response. Of the remaining 46 patients, 22 were deemed eligible for resection. Six patients (9%) out of 68 had a pathologic complete response. Apparently, 1 of 20 resected patients had a positive margin. Therefore, resection with negative margins was achieved for 19 of the original 68 patients (28%). The median survival of this group was approximately 32 months.

The available data emphasize the importance of optimal patient selection for trimodality therapy in order to enhance the potential conversion to an R0 resection. Results have consistently shown that conversion of an unresectable cancer to a resectable one is less likely than conversion of a borderline lesion. Massucco et al<sup>24</sup> reported on 28 patients who were treated with a neoadjuvant chemoradiation approach with the result that only 1 unresectable tumor was converted successfully vs 7 out of 18 that were borderline resectable. They further reported that only R0 resections in both groups gave the chance of disease-free survival longer than 24 months. In a series from Duke University Medical Center incorporating a median dose of 45 Gy along with 5-FU-based chemotherapy, White et al<sup>25</sup> reported that 28 patients (53%) who were potentially resectable and 11 patients (19%) who were deemed locally advanced were able to be converted after chemoradiation. They achieved negative surgical margins in 72% and found negative lymph nodes in 70% of resected patients. Additional data revealed no increase in morbidity or mortality following pancreaticoduodenectomy with neoadjuvant combined-modality therapy.<sup>26</sup> In fact, investigators found a marked reduction in the incidence of pancreatic leak.

### **Neoadjuvant Chemoradiotherapy in the Gemcitabine Era**

Gemcitabine was approved by the US Food and Drug Administration (FDA) in 1998 and became the standard of care for patients with advanced pancreatic cancer.

This was based on the results of seminal studies performed by Burris et al<sup>27</sup> that demonstrated improvements in median survival (5.6 vs 4.4 months) and clinical benefit response (24% vs 5%) when gemcitabine was compared to bolus 5-FU.<sup>27</sup> Response rates to single-agent gemcitabine are typically between 5% and 15% in patients with locally advanced unresectable and metastatic pancreatic cancer. Given its superiority in metastatic pancreatic cancer, it is not surprising that the efficacy of gemcitabine would then be explored in the neoadjuvant setting. The rationale for this strategy was strengthened when preclinical studies using human pancreatic and colon cancer cell lines demonstrated that gemcitabine was a potent radiosensitizer.<sup>28,29</sup>

In the late 1990s, efforts to integrate gemcitabine into chemoradiotherapy programs for locally advanced pancreatic cancer commenced with phase I dose escalation trials that were aimed at identifying the maximally tolerated dose (MTD) of gemcitabine when given with 50.4 Gy of radiation delivered in 1.8 Gy fractions.<sup>30</sup> Weekly doses of gemcitabine were escalated from 200 mg/m<sup>2</sup> to 700 mg/m<sup>2</sup>. Dose-limiting gastrointestinal and hematologic toxicities occurred at 700 mg/m<sup>2</sup>. Responses were seen at doses greater than 500 mg/m<sup>2</sup>. However, doses greater than 400 mg/m<sup>2</sup> were also associated with late duodenal strictures.

A retrospective series of 53 patients with unresectable pancreatic cancer treated with gemcitabine 250 to 300 mg/m<sup>2</sup> per week for 7 weeks with concurrent hypofractionated radiation (30 to 33 Gy in 10 fractions) was compared to 61 patients treated with concurrent continuous infusion 5-FU and radiation.<sup>31</sup> The radiotherapy volume was large and included not only the primary tumor but also the regional lymphatics in the porta hepatis, celiac axis, and superior mesenteric vessels. Here again, the group receiving gemcitabine as a radiosensitizer experienced greater toxicities (23% vs 2%) such as mucosal ulceration, hemorrhage, and hospital admission for supportive care for 5 or more days. Two of these patients developed late duodenal complications, which were ulceration and bowel obstruction. Downstaging to resectability was accomplished for 5 (9%) of 53 patients who received gemcitabine and 1 (2%) of 61 patients who received 5-FU. There was no significant difference in median survival (11 vs 9 months). Since it appears to be necessary to de-escalate the dose of gemcitabine to below 400 mg/m<sup>2</sup> to reduce toxicity, this approach administers what is likely a suboptimal dose of gemcitabine for systemic control of disease in order to maintain conventional radiation doses.

Investigators at the University of Michigan Comprehensive Cancer Center have pursued an alternate approach to developing a gemcitabine-based chemoradiotherapy.<sup>32</sup> The standard dose of gemcitabine used for systemic therapy (1,000 mg/m<sup>2</sup>) was maintained,

and the dose of conformal radiation was escalated from 24 Gy to 42 Gy in 15 fractions of 1.6 to 2.8 Gy. The radiation was directed to the primary tumor volume but without elective prophylactic nodal coverage. Thirty-four patients with unresectable pancreatic cancer were treated. At the 42 Gy dose, 2 of 6 patients experienced dose-limiting toxicity. One patient had grade 4 vomiting and the other had duodenal ulceration. There were 2 complete responses and 8 partial responses. There was no evidence of increased nodal failure in these patients who were treated without prophylactic elective nodal coverage as only 3 of 67 experienced nodal progression. In order to reduce the toxicity of the regimen, the recommended phase II dose of radiation going forward is 36 Gy. Phase II studies evaluating the efficacy of gemcitabine-based chemoradiation are underway. Most of these are being performed in locally advanced unresectable patients rather than the select subset of potentially resectable borderline patients.

Another strategy to maintain the systemic efficacy of gemcitabine-based chemoradiotherapy programs is to use combination chemotherapy regimens with drugs that have synergy with gemcitabine. In the treatment of patients with stage IV pancreatic cancer, platinum compounds have displayed *in vitro*, *in vivo*, and clinical synergy when combined with gemcitabine. Based on this observation, investigators at the University Hospital Grosshadern in Munich evaluated the combination of gemcitabine and cisplatin in 47 patients with locally advanced unresectable pancreatic cancer.<sup>33</sup> The patients were treated with gemcitabine 300 mg/m<sup>2</sup> and cisplatin 30 mg/m<sup>2</sup> on days 1, 8, 22, and 29. This was given concurrently with 45 to 50 Gy in 1.8 to 2.0 Gy fractions, with the radiation volume consisting of the tumor and regional nodes. Restaging with CT scans found that 27 (60%) of 45 patients responded sufficiently to meet criteria for potential resectability. Of the 25 patients taken to surgery, 13 had R0 resections, 7 had R1 resections, and surgery was aborted at exploration in 5 patients due to unresectable disease or metastasis. Therefore, the goal of downstaging to resectability with negative margins was accomplished in 13 (29%) of 45 patients. The median survival of the 13 patients who had R0 resections was 24.2 months compared with 8.5 months for those who had R1 resections. Patients who were not downstaged had a median survival of 7.4 months. The main toxicities observed were neutropenia (68%) and thrombocytopenia (61%). Eleven patients developed cholangitis.

Gemcitabine has also been evaluated in combination with paclitaxel. The Brown University Oncology Group performed a phase I trial to identify the MTD of gemcitabine when given with paclitaxel 40 mg/m<sup>2</sup> weekly for 6 weeks.<sup>34</sup> The dose of gemcitabine was escalated from 75 mg/m<sup>2</sup> to 150 mg/m<sup>2</sup>. Radiation was given concurrently to a large field encompassing the

primary tumor and the regional peripancreatic, celiac, and porta hepatis nodes to a dose of 45 Gy in 25 fractions followed by a 3-fraction boost to the primary plus a 1- to 1.5-cm margin, so that the total dose received was 50.4 Gy. The MTD of gemcitabine was 75 mg/m<sup>2</sup>. Toxicities included grade 3 and 4 diarrhea, anorexia, dehydration, and pneumonitis. Of 10 patients treated at the MTD, 4 had radiographic responses and 5 had stable disease. Two of the responders and 1 of those with stable disease were able to undergo resection with negative margins. Therefore, downstaging to resectability with negative margins was accomplished in 3 (30%) of 10 patients, and median survival was 11.5 months. This program is being evaluated in a Radiation Therapy Oncology Group phase II trial, RTOG-PA-0200, that has enrolled 174 patients.

The incorporation of gemcitabine in neoadjuvant concurrent chemoradiotherapy regimens is feasible. However, either the gemcitabine dose or the radiation dose/volume must be decreased to reduce the incidence of severe acute and late gastrointestinal toxicity. There appears to be a trend toward higher response rates with gemcitabine-based chemoradiation that must be confirmed in multicenter trials. The optimal dose and schedule of gemcitabine alone or combined with additional chemotherapy agents and concurrent radiation remain to be established.

The optimal radiation field volume, dose, and technique must also be determined. Conventional fields have been large, including not only the grossly enlarged primary tumor and nodes but also the elective nodal regions. The University of Michigan investigators<sup>32</sup> have reported no significant risk of nodal failure by targeting

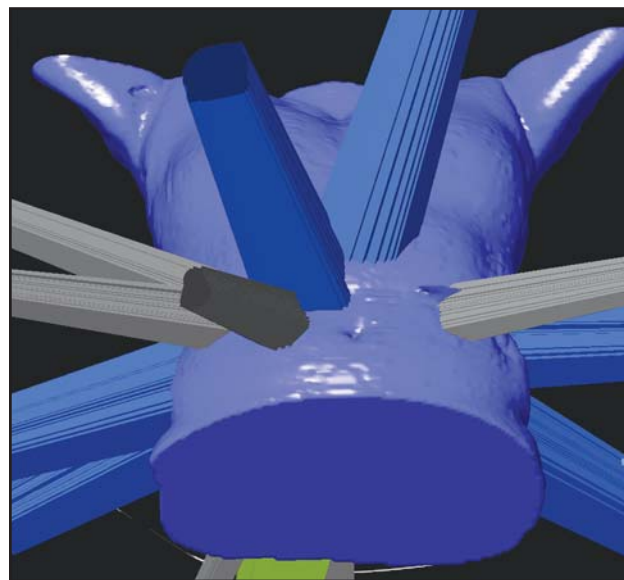


Fig 3. — Representation of the external beams of radiation used to irradiate a patient with disease involving the pancreatic head. Note that the patient is immobilized in the supine position with her arms over her head. This allows multiple beam angles to conform the high-dose volume to the patient's disease.

known disease only. With the advent of PET scanning for pancreatic cancer patients, radiation oncologists will be able to incorporate biologic data into delineation of the target volume as well. Surgical data have reinforced the concept for omitting elective nodal irradiation since a series from Johns Hopkins has shown that an extended retroperitoneal lymphadenectomy resulted in increased complications but no increased benefit.<sup>35,36</sup> By designing smaller radiation volumes with less mucosa in the path of the beams, more aggressive combined regimens may be feasible. The Radiation Therapy Oncology Group has begun excluding uninvolved lymphatics from the treatment volumes on its recent protocols, such as RTOG-0411.

Conventional techniques with 3 or 4 radiation fields and 3-dimensional techniques are being deferred in favor of intensity-modulated radiation therapy (IMRT). With IMRT, radiation oncologists are able to deliver the same or higher doses to the target while sparing more normal tissue (Fig 3). Brown et al<sup>37</sup> reported data from the National Institutes of Health touting the superior ability of IMRT to escalate the dose to 64.8 Gy while simultaneously achieving acceptable normal tissue constraints. The best technique in their study was the use of an integrated IMRT boost. In practice, using this technique means that instead of the traditional radiation convention of using larger fields to 45 Gy in 25 fractions and then proceeding with a boost to a smaller volume over 3 additional fractions, all target volumes are identified and treated up front. The known disease is identified as the gross target volume (GTV) for treatment planning purposes and is designated to receive the highest dose. The areas of microscopic disease constitute a clinical target volume (CTV), which receives a lower total

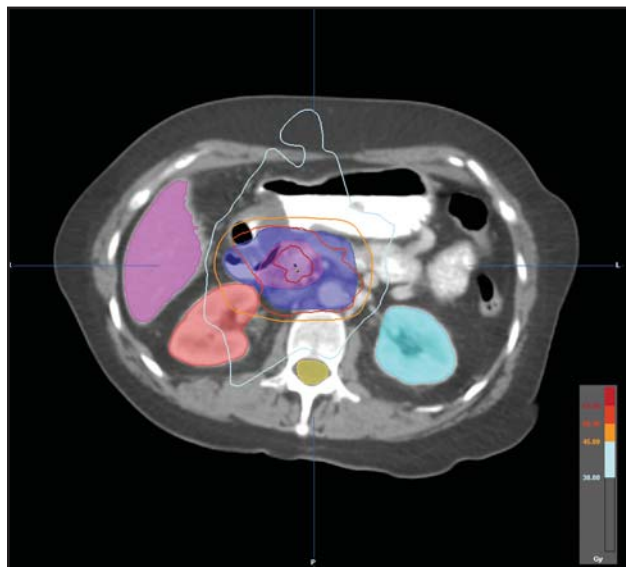


Fig 4. — Axial image displaying the 45-Gy isodose line (in orange) to the clinical target volume and the 50.4-Gy isodose line (in red) to the gross target volume. Note that the dose falls off rapidly from the surrounding normal tissue.

dose (Fig 4). This technique, also referred to as dose painting, would allow treatment in 25 days to the CTV at 1.8 Gy per day to 45 Gy while simultaneously treating the GTV at 2.0 Gy per day to 50 Gy (Fig 5).

With the evolution of smaller fields and potentially higher doses being delivered to the gross tumor, treatment strategies are now incorporating some of the many recent advances in management of respiratory motion, image-guided radiation therapy (IGRT), and stereotactic body radiation therapy (SBRT). We now have the ability to image patients at the time of setup (simulation) with time-correlated image acquisition scans (4-D CT). These scans are able to image the tumor in the upper abdomen as it moves with respiration. Bryan et al<sup>38</sup> found that the average superior-to-inferior excursion of the pancreas on ultrasound was 1.8 cm in the supine position from a study that evaluated 36 normal volunteers. Bussels et al<sup>39</sup> reported a mean craniocaudal movement of 2.3 cm, a 1.2-cm left-to-right movement, and a 6-mm anterior-to-posterior movement when they evaluated pancreatic motion on dynamic MRI. Still other investigators have found that the maximum superior-to-inferior range of the pancreas with respiration can be as much as 3.4 cm.<sup>40</sup> Since we now have the ability to see how much the tumor moves in a pancreatic cancer patient, we need to be able to account for this in treatment planning.

A variety of approaches integrate patient-specific respiratory motion into radiation delivery. At our institution, each patient with pancreatic cancer undergoes a 4-D scan to determine respiratory motion of both the pancreas and the adjacent kidneys. If there is signifi-

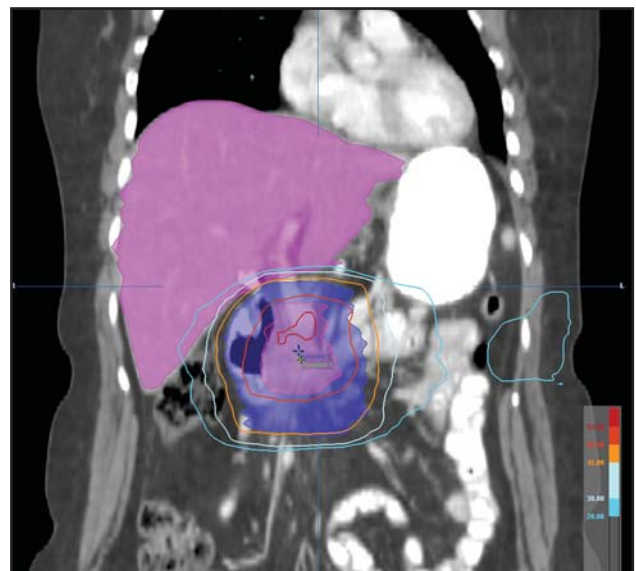


Fig 5. — Coronal image displaying the treatment plan delivering 45 Gy in 25 fractions to the clinical target volume followed by a 5.4-Gy boost to the gross target volume. Note that the surrounding bowel is in the low-dose region. The C-loop of the duodenum is within the clinical target volume. This case was planned using 4-D CT to individualize the margin needed to account for respiratory motion. Treatment was delivered on the Novalis unit with daily image guidance using the spine to verify the treatment position.

cant motion, the target volumes from the maximum inspiration and expiration scans are delineated and fused together to create what is called an internal target volume. An additional planning volume margin is then created around the internal target volume. This way, the pancreatic target, no matter where it is at any given time, will receive the prescribed dose. Other institutions are developing gated technology whereby the radiation delivery machine turns “on” only when the tumor is in a certain phase of the breathing cycle.<sup>41,42</sup> There are also a variety of patient breath hold techniques, including those that train patients to hold their breath by themselves or with the aid of an active breathing control device that occludes airflow during exhalation while the beam is on.<sup>43,44</sup>

Other techniques to account for motion incorporate the implantation of fiducial markers directly into the pancreas (either by CT or at surgical exploration) and the ability to track the markers during treatment. This approach takes advantage of newer IGRT capabilities so that the markers can be imaged on a daily basis to ensure that the intended target receives the intended dose of radiation. It is in this setting that SBRT or extracranial stereotactic radiosurgery (SRS) is being explored. This concept originated with intracranial SRS where a single fraction was delivered with high precision to a fixed target. With the advent of extracranial delivery systems, sites can now be treated in the lung, liver, and pancreas. SRS refers to single-fraction treatment and SBRT refers to delivery in multiple fractions.

Koong et al<sup>45</sup> have shown that 100% local control is possible with a single fraction of extracranial radiosurgery. In their phase I trial, they evaluated locally advanced tumors less than 7.5 cm in greatest dimension and did not include elective sites. Gold fiducial markers were implanted directly into the tumor by CT, laparoscopy, or open laparotomy. The stereotactic treatment was then delivered with the CyberKnife (Accuray Inc, Sunnyvale, California), with escalating doses from an initial 15 Gy, then 20 Gy, and finally 25 Gy. With complete local control at the 25-Gy dose, the trial was stopped. The rate of distant progression was high, and thus the median overall survival was only 11 months.

Koong et al<sup>46</sup> have sought to improve these results by adding a course of conventionally fractionated treatment to the SRS boost. In this phase II trial, they designed an IMRT field targeting the tumor and regional nodes (peripancreatic, celiac, superior mesenteric, porta hepatic, and retroperitoneal) to 45 Gy in 25 fractions. Patients received current 5-FU-based chemotherapy during irradiation. One month after the combined modality therapy, a 25-Gy SRS boost was delivered with the CyberKnife. A 94% local control rate was reported, with distant progression as the first site in all cases. Median overall survival was

33 weeks. The trial reported more gastrointestinal toxicity with RTOG grade 3 events acutely and with the development of symptomatic duodenal ulcers 4 to 6 months following treatment.

Therefore, to design an optimal chemoradiation program, the goal would be to define the gross disease as precisely as possible, determine its motion with respiration, limit the volume of adjacent normal tissue to allow more potent radiosensitizing agents to be given concurrently, and validate on a daily basis that the volume intended to be irradiated is actually receiving the dose. In the next few years, additional data should be available to guide further selection and integration of these treatment techniques.

### Induction Chemotherapy Followed by Chemoradiation

As noted in many of the studies discussed previously, between 10% and 30% of patients will experience disease progression during chemoradiation. The presence of metastatic sites of disease frequently becomes manifest in locations outside of the radiation field. Again, this is a reminder that micrometastatic disease is usually already present at initial diagnosis despite the localized appearance on imaging studies. Understanding this reality, investigators at the M. D. Anderson Cancer Center hypothesized that a period of induction chemotherapy might allow for the selection of those locally advanced patients who might truly benefit from subsequent chemoradiation. Patients who develop metastasis during induction chemotherapy can go on to other chemotherapy or clinical trials. Nonprogressing patients could be treated for 2 to 3 months and then given chemoradiation. Krishnan et al<sup>47</sup> conducted a retrospective analysis of 323 patients with locally advanced pancreatic cancer who received either upfront chemoradiation (n = 247) or induction chemotherapy with a gemcitabine-based regimen (mostly gemcitabine and cisplatin, n = 76) for a median of 2.5 months. Median overall survival was superior in the induction chemotherapy group compared to the upfront chemoradiation group (11.0 vs 8.5 months,  $P < .001$ ). There was no difference between the two groups in the proportion of patients who progressed locally vs at distant sites. This suggests that the brief course of gemcitabine and cisplatin was not effective in clearing micrometastatic sites.

A similar strategy was employed by Columbia University using the GTX regimen consisting of gemcitabine, docetaxel (Taxotere), and capecitabine (Xeloda) as induction chemotherapy for 3 cycles over 9 weeks followed by gemcitabine-based chemoradiation.<sup>48</sup> GTX was developed based on the demonstration of preclinical in vitro synergy of the combination. In the metastatic setting, the regimen reportedly has a response rate that approaches 30% to 40% (Fig 6).<sup>49</sup> In a series of 14

patients with locally advanced pancreatic cancer, only 1 (7%) progressed during induction with GTX. Eight patients (57%) were downstaged to resectability, and all had negative margins.

In 2003, a prospective, randomized cooperative trial (ECOG 1200) attempted to compare upfront gemcitabine-based chemoradiation followed by surgery to induction chemotherapy (with gemcitabine, cisplatin, and 5-FU) followed by 5-FU chemoradiation and then surgery. ECOG 1200 sought to identify potentially resectable patients and then compare the margin positive rates after neoadjuvant therapy with the two approaches. Unfortunately, the study was ended early due to poor accrual.<sup>50</sup>

As the benefits of neoadjuvant multiagent chemotherapy for borderline pancreatic cancer have been realized, the question of whether all resectable patients should receive this has arisen. In a prospective phase II study at the Swiss Hepato-Pancreato-Biliary Center, 28 patients with resectable pancreatic cancer were treated with gemcitabine and cisplatin given every 2 weeks over an 8-week period, followed by restaging and then surgical resection.<sup>51</sup> Of the 28 patients enrolled, 26 (93%) were still resectable at restaging. Peritoneal carcinomatosis was discovered in the other 2 patients. The R0 resection rate was 80% and the overall survival of resected patients was 19.1 months. Therefore, as seen with borderline patients, neoadjuvant chemotherapy for resectable pancreatic cancer patients does not

impair the ability to do a subsequent resection, and there appears to be a favorable impact on disease-free and overall survival.<sup>51</sup>

### Integration of Targeted Therapies: The Future of Neoadjuvant Regimens

The era of targeted therapy for pancreatic cancer arrived in 2005 with the FDA approval of erlotinib for advanced pancreatic cancer. Erlotinib is an orally bioavailable small-molecule inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TK). The combination of gemcitabine and erlotinib was compared to gemcitabine alone in 569 patients with stage III or IV pancreatic cancer in a multicenter, randomized, placebo-controlled phase III clinical trial (PA3) conducted by the National Cancer Institute of Canada Clinical Trials Group.<sup>52</sup> PA3 demonstrated that the combination of gemcitabine and erlotinib improved the 1-year survival rate from 17% to 24% (hazard ratio 0.81). Erlotinib was approved at a dose of 100 mg daily.

Similar to gemcitabine, erlotinib is now being evaluated in early-phase toxicity and feasibility trials in the locally advanced and neoadjuvant setting. The rationale for this approach is based in part on the ability of EGFR inhibitors to act as radiosensitizers. For example, concurrent radiation and chemotherapy including cetuximab, an anti-EGFR antibody, has improved survival and locoregional control in a phase III trial in 424 patients with squamous cell carcinomas of the head and neck.<sup>53</sup>

Also, survival and regrowth of cancer cells after radiation is in part dependent on EGFR signaling.<sup>54</sup> In locally advanced pancreatic cancer, at least two phase I clinical trials are examining the safety and feasibility of integrating erlotinib into concurrent chemoradiotherapy regimens. Investigators at Memorial Sloan-Kettering Cancer Center have evaluated gemcitabine 40 mg/m<sup>2</sup> twice per week and erlotinib at either 100 mg or 125 mg given concurrently with 50.4 Gy of radiation in 28 fractions.<sup>55</sup> Eligible patients had laparoscopically staged locally advanced pancreatic cancer. After concurrent chemoradiotherapy, they received maintenance gemcitabine and erlotinib for 4 cycles. After 9 patients were treated, the MTD of erlotinib was 100 mg. Dose-limiting toxicities at the 125-mg dose were prolonged myelosuppression and grade 3 transaminitis. Of the ini-

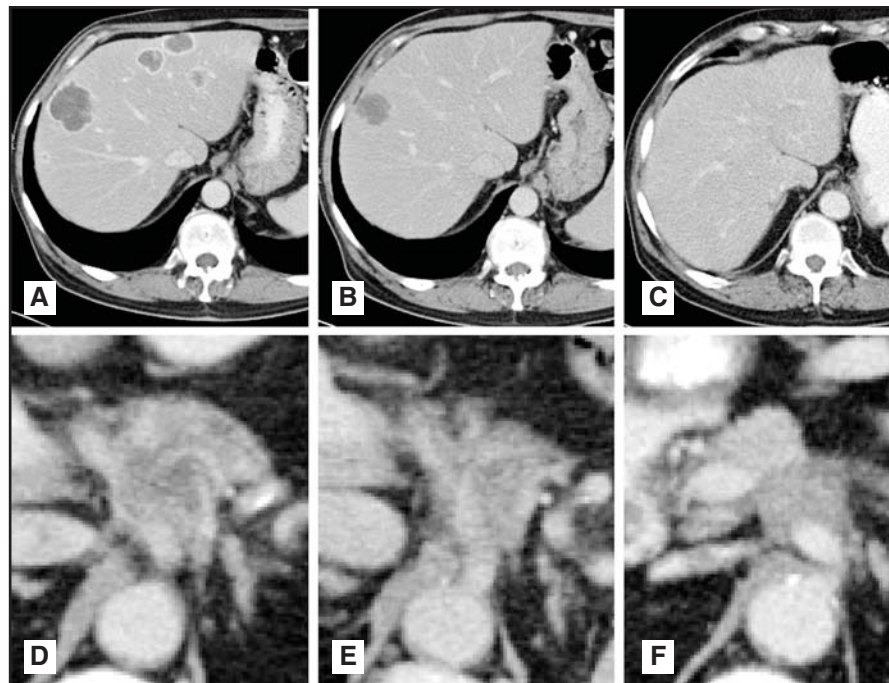


Fig 6. — Metastatic pancreatic cancer treated with GTX chemotherapy. This 64-year-old man with stage IV pancreatic cancer was treated with a combination of gemcitabine, docetaxel (Taxotere), and capecitabine (Xeloda) for 0 months (A and D), 6 months (B and E) and 9 months (C and F). The patient had a complete response of multiple lesions in the liver (A-C) and > 50% response of the primary tumor (D-F). Such chemotherapy regimens may be used as induction chemotherapy for borderline unresectable pancreatic cancer patients.

tial 9 patients enrolled, restaging CT scans revealed that 7 (80%) had stable disease and 1 (11%) had progression of disease. One patient appeared to have been downstaged and underwent a margin positive resection.

Investigators at the Brown University Oncology Group have built on their prior experience with a regimen of gemcitabine 75 mg/m<sup>2</sup> and paclitaxel 40 mg/m<sup>2</sup> weekly for 6 weeks with concurrent radiation to 50.4 Gy as described above. They have now added erlotinib to this regimen in a phase I clinical trial at escalating doses between 50 and 100 mg per day.<sup>56</sup> The concurrent treatment is then followed with maintenance erlotinib 150 mg per day. The MTD of erlotinib in this combination was 50 mg per day. At doses of 75 mg or greater, the dose-limiting toxicities included grade 3 rash, diarrhea, dehydration, and thrombocytopenia. One patient developed a small bowel stricture 2 months after radiation that required endoscopic dilation. Of the 19 patients enrolled, 17 were treated. Thirteen of these had locally advanced pancreatic cancer and 10 were surgically staged. Partial radiographic responses were seen in 6 (46%) of 13 patients. It is interesting to note that most responses were not evident until 4 to 6 months after chemoradiation was completed. Median survival was 14 months, which appears to be a further improvement on the 11.5 months seen with gemcitabine and paclitaxel alone in the prior phase I study. It should also be noted that 12 of the 17 treated patients died of metastatic disease.

Thus far, the feasibility studies incorporating erlotinib into concurrent chemoradiotherapy studies are consistent in requiring doses of 100 mg or less due to toxicity. Neither of these studies focus specifically on the subset of locally advanced pancreatic cancer patients who are borderline resectable. Since both studies incorporate the novel concept of maintenance erlotinib, the question will arise as to whether any improvements in survival are due to improved response rates during the chemoradiation or possible extension of the period of disease stabilization after chemoradiation by the maintenance erlotinib. It is the former that is likely to be of greatest relevance to the borderline resectable patient.

Cetuximab combined with gemcitabine and concurrent radiation is also being evaluated in a prospective randomized phase II trial at the University of Heidelberg.<sup>57</sup> Similar to the erlotinib studies described, the PARC study will give additional therapy with gemcitabine after chemoradiation with or without cetuximab in patients with locally advanced pancreatic cancer.

Bevacizumab is an anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody that is the first FDA-approved antiangiogenesis therapy. It has become part of standard care in colon, rectal, and lung cancers.<sup>58</sup> Since tumor hypoxia contributes to radioresistance, combining an anti-VEGF agent with

radiation may at first appear to be counterproductive. However, the effects of bevacizumab on tumors are complex. The blood vessels that sustain a tumor are abnormal in structure and density. While these vessels lead to increased tumor perfusion, this also increases tumor interstitial pressure. It has been suggested that the net effect of bevacizumab is to “normalize” the tumor microvasculature.<sup>59</sup> While this decreases microvascular density and tumor perfusion, it also decreases interstitial pressure and increases tumor oxygenation.<sup>60</sup> In principle, the improved oxygenation and greater accumulation of cytotoxic agents in the tumor may allow for synergy of VEGF inhibition with chemotherapy and radiation. The feasibility of this approach has been studied in a phase I trial at M. D. Anderson Cancer Center.<sup>61</sup> Bevacizumab was administered at doses between 2.5 and 10 mg/kg starting 2 weeks prior to chemoradiation and continuing every 2 weeks throughout radiation and then until disease progression. Capecitabine was used as a radiosensitizer at either 650 mg/m<sup>2</sup> b.i.d. or 825 mg/m<sup>2</sup> b.i.d. with 50.4 Gy of radiation. Four patients with duodenal invasion developed bleeding duodenal ulcers that were grade 3 or greater. These were mostly within the confines of the radiation field. One of these patients had bleeding that was not controlled with embolization, and this led to a grade 5 event. The trial was completed after amendment of the protocol to exclude patients with duodenal involvement. Other toxicities were as expected (eg, hypertension, transient hematologic, and hand-foot syndrome). Of 46 evaluable patients, 9 (20%) had partial radiographic responses. Most responses occurred at the 825-mg/m<sup>2</sup> dose of capecitabine and doses of bevacizumab at 5 mg/kg or greater. Four (8.5%) of the 47 patients responded sufficiently to undergo surgical resection with negative margins. There were no bevacizumab-related perioperative complications.

## Gene Therapy for Locally Advanced Pancreatic Cancer

An innovative strategy that combines direct intratumoral therapy with biologic gene therapy is currently being explored. This approach employs TNFerade, a second-generation adenoviral vector that is engineered to express human tumor necrosis alpha (TNF- $\alpha$ ). TNF- $\alpha$  is a cytokine with potent proapoptotic effects in cancer cells. Its clinical utility has been limited by systemic toxicity. Therefore, efforts have been made to develop means of local production of TNF- $\alpha$  in tumors. The TNF- $\alpha$  gene in TNFerade is linked to a promoter element from the early growth response gene, Egr-1. This promoter element is activated and induced in response to radiation. Therefore, when tumors are injected with TNFerade and an activating dose of local radiation is delivered to the tumor, TNF- $\alpha$  is produced within the tumor a con-

centrations that can induce apoptosis and cellular necrosis. The safety, toxicity, and preliminary efficacy was evaluated in a phase I study in 36 patients with various tumor types.<sup>62</sup> The most frequent toxicities were fever, injection site pain, and chills. No dose-limiting toxicities occurred. Seventy percent of the treated patients had an objective radiologic response of the treated lesion, including 5 patients who had complete responses. Five patients with pancreatic cancer were treated and 3 had responses. Based on these findings, a large randomized, controlled multicenter phase II/III trial of TNFerade, designated PACT, was initiated in patients with locally advanced pancreatic cancer. This trial will enroll 330 patients. The results of an interim analysis of the first 51 patients has been reported.<sup>63</sup> Currently, the 1-year survival rate is 70.5% for the TNFerade arm compared with 28% for the control arm. If the efficacy of this strategy is confirmed, it may also be integrated into the management of borderline pancreatic cancer patients.

## Conclusions

There has been improvement in the noninvasive assessment and neoadjuvant treatment of borderline resectable pancreatic cancer. The complementary use of high-resolution, multidetector pancreatic protocol CT scans and endoscopic ultrasound has allowed for improved selection of patients who are likely to benefit

from neoadjuvant therapy. PET scan is currently being evaluated as a means to identify metastasis and assess metabolic response to therapy. It also has the potential of confirming smaller volumes for radiation therapy targeting. Over the past 30 years, neoadjuvant therapy has evolved from conventional radiation therapy alone to combined modality therapy with multiagent chemotherapy regimens employing potent radiosensitizers along with optimized radiotherapy (Table 2). Novel radiation imaging techniques and planning capabilities are providing the framework for limiting normal tissue toxicities without compromising dose. Improvements in local control have the potential to be maximized and integrated with the best sensitizing agents to achieve R0 resection in this borderline patient population. The weight of available evidence suggests that the rate of successful resections and survival can be improved. The notion that locally advanced pancreatic cancer cannot be downstaged is false. The optimal regimen for neoadjuvant therapy remains to be defined. Prospective controlled trials are needed in patients who meet carefully defined modern imaging criteria to compare the various approaches that are under development. Pancreatic cancer should be a high-priority disease for testing the many targeted agents now being developed. As new molecular targets are discovered, validated, and moved to clinical translation, the opportunities for more effective

Table 2. — Selected Clinical Trials Relevant to Borderline Unresectable Pancreatic Cancer

Trial	Radiation Treatment	Chemotherapy Treatment	% Resectability With Negative Margins
Pilepich 1980 <sup>15</sup>	40–46 Gy	None	12 (2/17)
Evans 1992 <sup>19</sup>	50.4 Gy	Concurrent 5-FU 300 mg/m <sup>2</sup> /day	50 (14/28)
Jessup 1993 <sup>20</sup>	45 Gy	Concurrent 5-FU 225 mg/m <sup>2</sup> /day	12 (2/16)
Hoffman 1995 <sup>21</sup>	50.4 Gy	Concurrent 5-FU 1000 mg/m <sup>2</sup> /day Mitomycin-C 10 mg/m <sup>2</sup> /day	29 (10/34)
Hoffman 1998 <sup>22</sup>	50.4 Gy	Concurrent 5-FU 1000 mg/m <sup>2</sup> /day Mitomycin-C 10 mg/m <sup>2</sup> /day	32 (17/53)
Snady 2000 <sup>23</sup>	54 Gy	Concurrent 5-FU 1000 mg/m <sup>2</sup> /day Cisplatin 100 mg/m <sup>2</sup> /day Streptozotocin 300 mg/m <sup>2</sup>	28 (19/68)
Crane 2002 <sup>31</sup>	30–33 Gy	Concurrent gemcitabine 250–300 mg/m <sup>2</sup> /wk for 7 wks	9 (5/53)
Wilkowski 2004 <sup>33</sup>	45–50 Gy	Concurrent gemcitabine 300 mg/m <sup>2</sup> Cisplatin 30 mg/m <sup>2</sup>	29 (13/45)
Safran 2002 <sup>34</sup>	50.4 Gy	Concurrent gemcitabine 75 mg/m <sup>2</sup> Paclitaxel 40 mg/m <sup>2</sup>	30 (3/10)
Fogelman 2007 <sup>48</sup>	45 Gy	Induction chemotherapy: Gemcitabine 750 mg/m <sup>2</sup> Docetaxel 30 mg/m <sup>2</sup> Capecitabine 750 mg/m <sup>2</sup> then: Concurrent Gemcitabine 250 mg/m <sup>2</sup>	57 (8/14)
Crane 2006 <sup>61</sup>	50.4 Gy	Concurrent capecitabine 825 mg/m <sup>2</sup> Bevacizumab 2.5–10 mg/kg	8 (4/47)

tive therapy of borderline patients can only increase. After all, these patients are already on the edge of achieving longer survival.

## Disclosures

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