Treatment of Pancreatic Cancer: Current Limitations, Future Possibilities

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Drs. Blackstock, Cox, and Tepper have outlined some salient aspects of the management of pancreatic cancer. I agree with most of their comments, and will address some issues from my own perspective, colored largely by a symposium on cancer of the pancreas held in Newport, Rhode Island, in July 1994. This gathering of a large nucleus of investigators with a major interest in pancreatic cancer provided some additional insights that I will explore in my commentary and that largely complement the points made by Blackstock et al. Among other issues, my remarks will focus on: (1) the use of molecular markers for diagnosis and treatment, (2) preoperative chemoradiation, and (3) some surgical considerations that still generate controversy; ie, the extent of resection.

The survival rate from cancer of the pancreas is 5% overall [1], and even in patients with locally resectable pancreatic cancer, surgical resection has been reported to yield 5-year survival rates no better than 10% to 25% [2]. In the National Cancer Data Base report involving 17,970 patients with pancreatic cancer, the 5-year survival rate was 12% in patients with resectable pancreatic cancer, opposed to 4% in those with unresectable disease [2]. Although several groups have recorded higher survival rates (19% to 24%) [3,18-21], these are still exceptions and not the rule. The higher survival rates may reflect more selective staging and resectability criteria at some centers, among other factors.

In resected patients, factors associated with a significantly shorter median survival include tumor size more than 2 cm, blood vessel invasion, and lymph node metastasis [3]. The absence or presence of nodal metastasis is the single best predictor of survival. Patients without nodal metastases have a median survival of 56 months, as compared with 11 months for those with metastatic disease ($P$ less than .05) [3].

Molecular Pathology and Chromosomal Abnormalities

Recent studies of molecular pathology and chromosomal abnormalities in pancreatic cancer have provided additional information about the pathogenesis of this cancer beyond that afforded by classical pathology. Allison and colleagues [4] measured the DNA content of pancreatic cancers in patients who had undergone pancreaticoduodenectomy and determined that 60% of primary tumors were aneuploid. Ploidy was the single most important predictor of long-term survival (10.5 months for aneuploid tumors vs 25 months for diploid tumors) [4].

Direct chromosomal analysis has yielded additional clues to the specific genes involved in the pathogenesis of pancreatic cancer. Studies using a panel of molecular probes specific for each chromosome arm have provided techniques for precise allotype mapping, allowing one to survey gene pairs for allelic loss. Studies by Seymour et al [5] and Hahn et al [6] showed high frequencies of loss at 1p, 6p, 6q, 8p, 8q, 9p, 9p, 10p, 10q, 12p, 12q, 17p, 17q, 18q, 21q, and 22q. The loss of one allele of the tumor-suppressor gene results in the loss of gene function if the second copy is mutated. Thus, the tumor-suppressor gene p53, located on the short arm of chromosome 17 (17p), was lost in 95% of the cancers studied by Hahn et al [6]. The "deleted in colon cancer" tumor-suppressor gene (DCC) located on the long arm of chromosome 18 (18q) and a recently characterized multiple tumor suppressor 1 (MTS 1) gene, which resides on chromosome 9p, were lost in 88% and 76% of the cancers, respectively.
In addition to loss of tumor-suppressor genes, K-ras abnormalities and related oncogenes are commonly expressed in pancreatic cancer. K-ras, H-ras, and N-ras encode G proteins, which are involved in signal transduction [7]. Point mutations in codons 12, 13, and 61 of K-ras inactivate the protein product by interfering with its GTPase activity [7]. Approximately 80% of pancreatic cancers contain activating point mutations in codon 12 [8]. The mutated K-ras expressed in pancreatic cancer was more prevalent in tumors obtained from smokers than from nonsmokers (88% vs 68%), suggesting that carcinogens in cigarette smoke may be related to the K-ras mutations in these patients. The finding of K-ras mutations in hyperplastic "pancreatic duct lesions" appears to be analogous to the increased prevalence of K-ras mutations among intermediate adenomas in the model of colorectal tumor progression [9]. This finding suggests that these duct lesions may be precursors to pancreatic cancer.

### Screening for K-ras Mutations Has Potential

It may be possible to take advantage of these abnormalities in screening for early disease because K-ras mutations are virtually restricted to a single codon (codon 12). An assay based on identification of K-ras mutations, which appears to occur prior to the development of invasive cancer, should be able to detect pancreatic cancers and offer sensitive methods for screening.

Tada et al collected pancreatic juice endoscopically from patients with pancreatic cancer and from control patients with chronic pancreatitis or choleodocholithiasis [10]. K-ras mutations were detected in the pancreatic juice from all six cancer patients studied but from none of the controls. Of interest, K-ras mutations could also be detected in circulating cells in the peripheral blood of some patients with pancreatic cancer [10].

Caldas et al have extended these studies and screened for K-ras mutations in the stools of patients with clinical pancreatitis, cholangiocarcinoma, and pancreatic cancer [11]. They found K-ras mutations in stool specimens from nine patients, six of whom had pancreatic cancer. In five cases, mutations found in the pancreatic tumor itself were the same as those found in the stool. In the remaining four patients, the mutations identified were identical to those isolated from intraductal lesions present in the resected pancreatic specimen. These data suggest that mutations found in pancreatic cancers and intraductal pancreatic lesions may be detected in the stool [11]. These researchers are currently testing for K-ras in stool specimens from a large number of patients; this approach may have potential as a screening test for early pancreatic cancer.

As Blackstock et al discuss, K-ras may represent a target for therapeutic intervention using farnesyl transferase inhibitors (FTIs). These compounds inhibit attachment of the 15-carbon isoprenyl group, which is necessary for attachment of ras with the cell membrane and for ras-mediated transformation. By preventing the joining of the mutant K-ras with the cell membrane, FTIs may interrupt signals leading to cell proliferation in established pancreatic cancer.

### Relationship of p53 Mutations to Pathogenesis

Tumor-suppressor gene abnormalities also play an important role in the pathogenesis of pancreatic cancer. Mutations of p53 are found in over half of primary pancreatic cancers [12,13] and correlate well with allelic loss of 17p. Thus, p53 mutations may precede the development of invasive cancer. Several groups have found overexpression of p53 product, a marker for p53 mutations, in intraductal lesions in the pancreas [14,15]. The expression of mutated p53 and K-ras in the same tumors suggests some association between these two gene abnormalities. There also appears to be a correlation of mutated p53 with tumor grade and decreased survival in patients with pancreatic cancer [15].

### Potential Impact of New Diagnostic Technologies

It is obvious that the greatest impact on survival in pancreatic cancer will probably come from earlier diagnosis. New technology, such as fast spiral CT using dynamic intravenous contrast, has resulted in high-resolution images of small masses, which has improved the accuracy of vascular staging [16]. Endoscopic retrograde cholangiopancreatography (ERCP) with improved cytology, brushes, and biopsy forceps should enhance preoperative diagnosis of this malignancy. Endoscopic ultrasound also may help detect small lesions and determine the depth of invasion and vascular involvement. The potential for vastly improved MRI images with three-dimensional reconstruction (MRI with cholangiopancreatography) may permit earlier diagnosis and management of these patients. Unfortunately, screening for pancreatic cancer is not yet feasible. A Japanese screening study of 10,162 persons over 40 years of age with Ca 19-9 and elastase-1 or ultrasonography revealed only four cases (P = 0.042) of pancreatic cancer, including only one patient who was operated on for cure [17].

When pancreatic cancer is suspected, imaging with CT or the more sensitive spiral CT, plus CT-directed FNA cytology and ERCP with brushings should result in a definitive diagnosis. Although
CT-guided FNA is probably now the most common method of performing the biopsy, it is controversial because of the potential risk of peritoneal contamination [30]. Evans et al have examined the effect of preoperative CT-guided FNA on the cytologic washings obtained a median of 3 weeks later [30]. Among 60 consecutive patients who had peritoneal lavage for cytology, 49 (82%) had CT-guided FNA, and 11 did not. Peritoneal washings yielded four patients (6.6%) with positive cytology; 3 of 49 patients (6.1%) had undergone preoperative CT-FNA and 1 of 11 (9.1%) did not. All four patients developed metastatic disease about 5 months later, suggesting that this was simply due to advanced disease rather than being secondary to the FNA. The value of laparoscopy as a staging technique has long been championed by Warshaw et al [32], as well by Evans and the M.D. Anderson group [30]. Laparoscopy permits direct visualization of the liver, the serosal surface, and provides opportunity for peritoneal cytology. With care, one can examine the porta hepatis, the peripancreatic region, and in some cases examine and biopsy accessible peripancreatic nodes. Laparoscopy also permits placement of a tube jejunostomy and cholecystojejunostomy as needed, if preoperative therapy is planned.

**Extent of Resection Still Debated**

Currently, surgical resection is the only potentially curative treatment for pancreatic cancer. The actuarial 5-year survival rate at Johns Hopkins was 26% in 195 patients who underwent pancreaticoduodenectomy for carcinoma of the head of the pancreas [3,18]. This is similar to survival rates reported in other series, including those of Geer and Brennan [19] at Memorial Sloan-Kettering and Trede et al [20] in Germany.

Some of the factors that have been shown to influence survival include:

- Tumor size (median survival, 30 months for tumors less than 2 cm vs 11 months for those more than 2 cm) [18]
- Vessel invasion (median survival, 39 months in patients with vessel invasion vs 11 months in those without invasion)
- Lymph node involvement (median survival, 56 months if negative vs 12 months if positive).
- Blood loss also appears to have an impact on survival. In one study, median survival was 25 months if fewer than 3 units of blood were given, as compared with 10 months if 3 or more units were transfused [18].

Mortality from the Whipple procedure has improved markedly. In the Hopkins experience, mortality has changed from 20% over 2 decades ago to 2.5% in the last 326 patients. In the more recent series, no deaths occurred in 145 consecutive operative procedures [3,18,21]. The question of the extent of resection--ie, whether to perform a total or subtotal Whipple procedure or a more aggressive regional resection--is still a matter of debate. The Mayo Clinic found no survival difference between patients treated with partial vs total pancreatectomy [22]. In contrast, a review by Farley et al found that the long-term survival rate following total pancreatectomy in 11 series involving 643 patients was 8.5%, as compared with a rate of 11.5% in 1,491 patients treated with partial pancreatectomy [22]. Studies of more extended resections (ie, the regional pancreatectomy of Fortner [23] and a similar procedure by Sindelar [24]) have failed to confirm a true benefit from these more aggressive procedures [22]. However, Japanese authors, such as Ishikawa et al [25], Nakagawa [26], and Manabe et al [27], have claimed that regional pancreatectomy prolongs survival, and Kairaluoma et al [28] of Finland have asserted that extended pancreatic resection affords some benefit. On the other hand, other researchers, such as Satake and colleagues [29], have found that extended lymphadenectomy confers no survival advantage in patients with T1 cancers.

One further point about the extent of surgery (radical surgery vs pylorus-preserving pancreaticoduodenectomy) deserves comment. The Lahey group have demonstrated no difference in the tumor involvement of resection margins in patients undergoing pylorus-preserving surgery vs those undergoing proximal or total pancreatectomy [35]. Moreover, the incidence of marginal ulceration and bleeding gastritis after pylorus-preserving procedures was lower than with standard pancreaticoduodenectomy with hemigastrectomy or antrectomy and vagotomy. The 5-year survival rate was 6.1% in patients who underwent pylorus-preserving resection for pancreatic duct cancer and median survival was 18 months [35]. This is in contrast to the 19% to 26% recorded survival rate for the Whipple procedure or more extended resections [3,18,21,36]. Again, such differences may reflect patient stage and selection rather than something unique to the surgical procedure per se.

**Preoperative Chemoradiation and Intraoperative External-Beam Radiation**
Because of the high rate of potential nodal involvement (up to 50% risk of finding involved nodes within the resected specimen), the addition of therapy to augment surgical resection would be appear to be of value. Several authors have addressed the potential benefits of these approaches [30,31].

Evans et al at M.D. Anderson have explored the value of preoperative chemoradiation prior to pancreatic resection and intraoperative external-beam radiotherapy [30,33]. An updated study encompassed 51 patients who completed chemoradiation [30]. At the restaging of 13 patients, 3 (25%) were found to have metastatic disease and did not undergo surgery. A total of 38 patients underwent laparotomy, and resection was not performed in 8 patients because of metastases (3 patients) or locally unresectable disease (5 patients). Of 30 patients undergoing potentially curative pancreaticoduodenectomy, 26 received external-beam intraoperative radiotherapy (IORT) following tumor removal; there were no operative deaths from myocardial infarction.

Median survival for the entire group of 51 patients was 11.7 months (18.6 months for the 30 resected patients and 6.7 months for the unresected patients). At a median follow-up of 15 months, 22 patients had died (18 from their cancer), 1 was alive with disease, and 7 (23%) showed no evidence of disease. Of the patients who died of disease, 83% had metastases to the liver or lung as the first sign of failure [33]. The median tumor sizes prior to treatment were 3 cm and 3 cm (anteroposterior [AP] and lateral diameters, respectively) and the median tumor shrinkage following chemoradiation was .5 cm and .4 cm, respectively.

There were no measurable differences in tumor size between the patients who were able to undergo resection and those who were not (AP tumor diameter was 3 cm and lateral, 3 cm). In none of the patients was preoperative radiation associated with a complete response; however, a grade 2B (destruction of 51% to 90% of tumor cells) or grade 3 pathologic response (more than 90% tumor cell destruction) was seen in 40% of the resected patients. There were no positive margins at the resection line, although there was microscopic evidence of cancer in the retroperitoneal margin in approximately 15% to 20% of patients [30,33].

A similar approach has been used by Hoffmann and colleagues at the Fox Chase Cancer Center [31]. They treated 63 patients with preoperative radiation therapy and two 96-hour infusions of fluorouracil (1,000 mg/m²/d on days 2 to 5 and days 29 to 32) and a single bolus of mitomycin (Mutamycin; 10 mg on day 2). Patients who had no evidence of distant disease and were considered resectable underwent pancreatic resection (16 Whipple procedures, 7 total pancreatectomies, and 2 distal pancreatectomies).

Thirty-eight percent of the patients had grade 3 or 4 toxicity from chemoradiation, and one patient died during chemoradiation of biliary sepsis. Operative mortality in 25 patients with potentially curative resection was 4%; one of four patients who underwent palliative resection died. Median survival for those undergoing pancreatic resection was 22 months and the 5-year survival rate was 20%. Recurrence was noted in 20 patients and was primarily in the liver in 50% of the patients.

In this protocol, 37 patients made up the Fox Chase pilot study and 26 patients were part of a larger phase III trial run under the auspices of the Eastern Cooperative Oncology Group (ECOG). A recent report from the senior author updated the actual ECOG phase II study [34]. This included 53 eligible patients who were accrued to the ECOG trial examining the efficacy of preoperative therapy with radiation (180 cGy in 28 fractions) and two 96-hour infusions of fluorouracil (1,000 mg/m²/d on days 2 to 5 and days 29 to 32) and bolus mitomycin (10 mg on day 2).

There were two treatment-related deaths, and 18 patients (34%) experienced grade 4 toxicity. The incidence of toxicity was higher in those who did not undergo previous surgical staging than in those who did. Forty-one patients underwent surgery and 23 (56%) had resection. Four patients (17%) had positive surgical margins. Median survival was 16.6 months from the time of registration for the patients who underwent resection. The 2-year survival rate was 30% in the group as a whole and 33% in the 19 patients with N0 disease. Nine of the 41 resectable patients are alive at 30 to 33 months' follow-up.

These survival results were thought to be less favorable than those reported from a single institution (Fox Chase Cancer Center) using a similar preoperative regimen ($P = 0.085$). However, preoperative chemoradiation was considered to be a safe intervention in the cooperative study setting.

**Conclusion**

This article by Blackstock, Cox, and Tepper is an informative chapter in the continuing saga of research, diagnostic, and interventional developments being made to address a formidable disease process, which is only recently beginning to yield ground. I would anticipate (and hope) that a similar chapter 3 to 5 years hence would be more optimistic regarding outcome.
References:

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