Pancreatic adenocarcinoma, even when resectable, remains highly lethal. Although surgical outcomes have improved considerably, median overall survival after surgery and adjuvant therapy such as single-agent gemcitabine remains less than 2 years. We discuss preclinical and clinical data supporting the contention that even early-stage pancreatic cancer is a systemic disease. Autopsy series reveal that 70% to 85% of patients die of systemic recurrence, rather than local disease, after pancreatic cancer resection. Preclinical studies using genomics and mouse models reveal evidence of metastatic spread even before histopathologic evidence of a pancreatic tumor. Analogous to breast cancer, we propose that the Halstedian approach of treating pancreatic cancer as a local, surgical problem should be replaced by Fisher's alternative hypothesis of cancer as a systemic disease. Newer multiagent chemotherapy regimens have shown meaningful response rates and improvement in overall survival in the metastatic setting and, for the first time, offer investigators an opportunity to use effective systemic therapy. We emphasize that a surgery-first approach is not resonant with our current understanding of pancreatic adenocarcinoma biology and that an upfront systemic approach for even resectable pancreatic cancer warrants testing in clinical trials.


The trend toward improvement in cancer outcomes due to a combination of improved detection, targeted therapeutics, and better supportive care has yet to reach the world of pancreatic cancer. In the United States, although pancreatic cancer is the tenth most common malignancy, it is the fourth most common cause of cancer-related death (1). Even more alarmingly, at least one report suggests that pancreatic cancer will become the second leading cause of cancer-related death in this country by the end of the current decade (2). This is because of both rising incidence (1,2) and continued poor clinical outcomes. Mortality rates have improved for several malignancies, but for pancreatic cancer, 5-year overall survival remains at 6%, barely improving from 2% in the 1970s (1).

In the metastatic setting, encouraging results from recent clinical trials have finally provided some glimmers of hope. In a recently reported randomized controlled trial in the first-line treatment of metastatic pancreatic cancer, the combination of gemcitabine and nab-paclitaxel achieved a median overall survival of 8.5 months, compared with 6.7 months with gemcitabine alone (hazard ratio [HR] = 0.72; P < .001) (3). This report follows results from the trial of the so-called FOLFIRINOX regimen—a combination of 5-fluorouracil, irinotecan, and oxaliplatin—that also showed substantial improvement in outcomes in metastatic pancreatic cancer with a median overall survival of 11.1 months compared with 6.8 months with gemcitabine alone (HR = 0.57; P < .001) (4). In addition to improvement in median survival, what was unusual for the pancreatic cancer setting was the response rate: 31.6% of patients randomized to FOLFIRINOX had objective responses compared with 9.4% with gemcitabine alone. This is an important improvement over previous trials of combination chemotherapy regimens that typically reported objective response rates in the range of 5% to 20% (5-8).

Currently, the standard of care for early-stage disease is surgery followed by adjuvant therapy. Although surgical resection is widely considered curative, observed outcomes do not support that presumption. An analysis of more than 300,000 patients from the National Cancer Data Base demonstrated that median overall survival after surgical resection was only 13 months (9). In a recent single-institution analysis of resected pancreatic adenocarcinoma from 1983 to 2009, 30-day mortality after resection of pancreatic adenocarcinoma declined from 5% in the 1980s to 1.3% in the 2000s, but median overall survival for 1-year survivors improved only minimally from 23.2 months to 24.5 months over the same time period (10). Other large surgical series, as well as surgery-alone arms of randomized adjuvant therapy trials, have also shown that median overall survival after surgery remains less than 2 years (11-13). Even with adjuvant therapy such as single-agent gemcitabine, median overall survival is less than 2 years (13).

Why do patients do so poorly after curative surgical resection? Because 30-day mortality after pancreatic adenocarcinoma resection is now less than 2% (11,12), poor overall outcomes are more likely attributable to the emergence of metastatic disease early in the course of the malignancy. A cohort study evaluated recurrence patterns after margin-positive resection of pancreatic cancer in 285 patients and demonstrated that 76% of patients with recurrence had distant disease (14). Similarly, autopsy series of patients with pancreatic adenocarcinoma who previously underwent resection showed that 85% to 90% died of recurrent disease, with 70% to 85% of all patients dying of systemic recurrence, rather than local disease.
This underscores the systemic nature of pancreatic cancer, even when the clinical presentation is that of a local disease. Indirect evidence also emerges from the fact that adjuvant radiation, an additional local treatment, does not appear to meaningfully improve survival outcomes in this disease (17,18). Results from randomized trials comparing chemotherapy with chemotherapy plus radiation generally indicate no meaningful improvement in survival with radiation (19,20). Furthermore, in studies of preoperative or neoadjuvant therapy, 15% to 32% of patients experience progressive systemic disease (21,22). Together, these clinical data support the concept that pancreatic cancer is a systemic disease even in early-stage settings.

Preclinical data lend further evidence to this concept. Recent laboratory studies focusing on detailed genomic analyses of primary and metastatic pancreatic tumors have shown that there is a high degree of genomic instability and heterogeneity in pancreatic adenocarcinoma (23,24). Notably, a study in a mouse model showed that pancreatic epithelial cells invaded the bloodstream and were detected in distant sites even before detailed histologic analyses could find a primary pancreatic tumor (25). This behavior is associated with very early epithelial-to-mesenchymal transition, which is facilitated by inflammation mediated by several molecules, such as MUC1, Notch-1, and TGF-β, ultimately leading to early systemic dissemination (26–28).

Because pancreatic cancer is a systemic disease, should it not be treated with systemic therapy at the first detection of clinical disease? Conceptually, this discussion is analogous to the controversies surrounding optimal treatment of breast cancer in the 20th century. William Halsted strongly believed that cancer spread in contiguous fashion, dismissing clinical evidence of distant metastases that he encountered during his surgeries thus: “The dissemination probably takes place by way of the lymphatics—not by the blood-vessels—and the disease holds together without important interruptions.” Furthermore, “cancer of the breast in spreading centrifugally preserves in the main continuity with the original growth” (29). Therefore the extended radical mastectomy, a remarkable procedure, remained the sine qua non of breast cancer treatment for more than 50 years. Similarly, Allen Oldfather Whipple’s procedure remains the backbone of pancreatic cancer treatment more than 75 years since its first description (30). In breast cancer, a paradigm shift in approach was led by Bernard Fisher and others (31). These investigators approached breast cancer as a systemic disease, based on laboratory investigations that revealed circulating tumor cells in patients undergoing cancer surgery, as well as bench work on mechanisms of metastasis (31,32). Together, these studies demonstrated clearly that regional lymph nodes played a role in initial tumor immunity, failing which malignant cells were disseminated by lymphovascular routes to distant organs. This process happened unpredictably, depending on host–tumor interactions, making anatomical barriers irrelevant (33). Fisher coined an “alternative hypothesis” of cancer wherein lymph nodes are an indicator of host–tumor relationships rather than a way station on the orderly journey of tumor cells (34). Over the next several years, Fisher and colleagues showed that bringing together just enough local treatment to eradicate all disease at the primary site and aggressive systemic therapy to eliminate micrometastatic disease afforded the best clinical outcomes (31,32,34,35). The finding most pertinent to pancreatic cancer today is that “[v]ariations in local-regional treatments are unlikely to substantially affect survival” (34). Questions have regularly been asked of the alternative hypothesis, citing data whereby local therapies have been associated with improved survival outcomes (36,37). That is an important point to be noted: we cannot forgo surgery, which remains the backbone of solid tumor treatment, but we should approach the disease as a systemic problem (38). As Fisher stated, “[A]bandonment of Halstedian principles of cancer surgery does not imply that sloppy surgery can be condoned” (39). Moreover, “[o]perable breast cancer is a systemic disease,” and while “every effort must be made to control locoregional disease to prevent further tumor cell dissemination, … tumor and host factors that are in play before the diagnosis and treatment of cancer are of primary importance with regard to determining survival” (38). In other words, cancer is a systemic disease from the outset, and should be treated as such.

How do we apply these lessons to pancreatic cancer? We propose that early institution of aggressive systemic therapy before surgical resection is a rational approach that acknowledges the systemic nature of pancreatic cancer. Historically, preoperative approaches have been studied in several early-phase trials in resectable/borderline resectable pancreatic adenocarcinoma [reviewed in (21,22,40)]. The results are difficult to extrapolate clinically, given nonrandomized designs, heterogeneous study populations, and small sample sizes. Generally, the use of preoperative therapy in resectable pancreatic adenocarcinoma allowed for a resection rate of 55% to 85%, and a median overall survival in the range of 24 to 30 months (21,22,40). For borderline resectable disease at presentation, preoperative therapy allowed for resection in 15% to 33% of cases, with a median overall survival in the range of 18 to 20 months in those undergoing surgical resection (21,22,40). In each setting, if the patient was unable to undergo resection, overall survival was equivalent to that seen in metastatic disease. Therefore, it appears that preoperative therapy allows us to select out “bad biology”; a counter-argument is that by using largely ineffective preoperative therapies, we only select “good biology” by pure chance. Either way, this approach allows physicians to spare patients most at risk of clinical systemic disease an extensive operation—patients with resectable disease who are unable to get to surgery because of disease progression during preoperative therapy are those who develop systemic disease, and local resection is unlikely to affect that outcome. It must be noted that most of these previous studies of preoperative therapy used suboptimal single- or double-agent chemotherapy regimens at low doses, with or without radiation. Now, the recent successes with FOLFIRINOX and gemcitabine/nab-paclitaxel in the metastatic setting represent an important breakthrough and finally allow investigators new and more effective systemic therapy options. A recently presented phase II clinical trial of gemcitabine and nab-paclitaxel as preoperative therapy for 25 patients with resectable pancreatic cancer showed a partial objective response in 36% of all patients and a grade III/IV pathologic response in 29% of resected cases (41). This could be the first of new studies that use effective systemic regimens as front-line therapy even in resectable pancreatic adenocarcinoma, likely improving systemic disease control and survival outcomes in the long run. A few clinical trials using such an approach are currently underway (41,42).

It is time, therefore, to acknowledge that pancreatic cancer is a systemic disease from the earliest stages and that a surgery-first
approach is not resonant with our current understanding of pancreatic adenocarcinoma biology. We and others are working on bringing systemic therapy up front to study the effect of aggressive chemotherapy regimens and novel agents in well-designed clinical trials, comparing multi-agent regimens to single-agent approaches and preoperative therapy vs the current standard of surgery followed by adjuvant chemotherapy. Although we understand that there is no guarantee of success, the preponderance of preclinical, clinical, and genetic data makes it imperative that we acknowledge the “alternative hypothesis” in pancreatic cancer and set about testing it in well-designed clinical trials.

References


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