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The Role of Chemoradiation for Patients with Resectable or Potentially Resectable Pancreatic Cancer

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Abstract

Conflicting data and substantial controversy exist regarding optimal adjuvant treatment for those patients with resectable or potentially resectable adenocarcinoma of the pancreas. Despite improvements in short-term surgical outcomes, the use of newer chemotherapeutic agents, development of targeted agents, and more precise delivery of radiation, the 5-year survival rates for early stage patients remains less than 25%. This article critically reviews the existing data for various adjuvant treatment approaches for patients with surgically resectable pancreatic cancer. Our review confirms that despite several randomized clinical trials, the optimal adjuvant treatment approach for these patients remains unclear.

Summary—Despite improvements in short-term surgical outcomes, use of newer chemotherapeutic agents, development of targeted agents, and more precise delivery of radiation, the 5-year survival rates for early stage patients remains less than 25%. Despite several randomized clinical trials in these patients, the optimal treatment approach remains unclear. We review data the data regarding adjuvant therapy for patients with early stage pancreas cancer and discuss potential tumor factors that can be used to select patients for optimal adjuvant therapy. The probability of long-term survival is higher in patients who undergo margin-negative resections but local and distant failures are common, indicating the need for adjuvant therapies. Improved systemic treatment is desperately needed and the role of adjuvant radiation remains unclear. Neoadjuvant chemoradiation is being studied as an alternative to postoperative therapy. Potential molecular targets have been identified and the benefit of the addition of biologic agents to adjuvant treatments is being explored.

Keywords

Pancreatic Adenocarcinoma; Radiotherapy; Combined Modality Therapy; Biological Markers; Molecular Targets; Neoadjuvant

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Background

Cancers of the pancreas are the 10th most common cancer in men and women in the United States, but the 4th leading cause of cancer deaths [1]. In 2010 over 44,000 new patients were diagnosed with pancreas cancer and over 37,500 patients died of the disease[1]. The incidence of pancreas cancer has increased about 1% per year since 1998 with a current age adjusted incidence rate of 12 per 100,000 men and women per year [2].

Overall survival for patients with pancreas cancer is closely linked to stage at presentation (Table 1). Patients with pancreas cancer commonly present with distant metastatic disease. Five-year survival for these patients is approximately 2%. About 30% will present with locally advanced, unresectable disease and a five-year survival of around 7-10%. Potentially curative resection is possible in the remaining 20% of patients who present with localized disease.

Unfortunately, despite improvements in short-term surgical outcomes, the use of newer chemotherapeutic agents and combinations, and more precise delivery of radiation, pancreas cancer remains a menacing disease with 5-year survival rates for early stage patients of less than 25% [1-3]. Over the last 30 years, the overall 5-year survival rate has increased only marginally; from 3% between 1975-77 to 6% between 1999-2006 [1]. Attempts to improve outcomes with more extensive lymph node dissections have failed to show any benefit, but consistently show a higher complication rate with more extensive surgery [4-6]. Five-year survival rates following surgical resection remain around 10% with around 75% of recurrences occurring in the abdominal cavity (peritoneum and liver) and local failure, either alone or with simultaneous distant failure, which occurs in 50-80% of cases [3,7-14]. The relative value of adjuvant radiation and chemotherapy is the issue of some debate. It is clear that distant (outside a reasonable radiation field) failure remains a major problem for most patients. However, as will be discussed below, in a subset of patients localized failures represent the bulk of disease. Even in those patients who experience a distant failure, local progression can be a major source of both morbidity and mortality. Identifying the patients in whom local disease will become symptomatic, likely holds a key to improving quality of life in patients with pancreas cancer. In this article, we review the mixed data regarding adjuvant therapy for patients with early stage pancreas cancer and discuss potential tumor factors that can be used to select patients for optimal adjuvant therapy.

Early Data

In 1985 the Gastrointestinal Tumor Study Group (GITSG) published the first US trial demonstrating the benefit of adjuvant therapy in addition to surgery for patients with early-stage pancreas cancer [15,16]. In this small trial, 43 patients with documented adenocarcinoma of the pancreas who underwent curative resection with negative surgical margins were randomized to 1) observation or 2) adjuvant radiation with 5-fluorouracil (5-FU). Radiation was delivered in a split course of 20 Gy, a two-week break, and an additional 20 Gy. 5-FU was delivered as a rapid intravenous (IV) bolus of 500 mg/m² on day 1-3 of each radiation course. In contrast to current practice, following completion of radiation, 5-FU was continued weekly for 2 years or until disease progression. Nearly all tumors (95%) were located in the head of the pancreas and about one-quarter of tumors were node-positive. Median survival improved from 11 months for the 22 patients in the observation group to 20 months for the 21 patients who received adjuvant therapy. To confirm these results, an additional 30 patients were treated with adjuvant therapy and demonstrated similar outcomes (median survival 18 months). A number of criticisms of this trial have been raised over the years ranging from the small sample size, inferior radiation regimen,

slow accrual (1974-1982), and inability to separate the relative benefit of chemotherapy or radiation.

Fourteen years later, the European Organization for Research and Treatment of Cancer (EORTC) published this results of a similar trial (#40891) randomizing patients to 1) adjuvant chemoradiation vs. 2) observation. Radiation was again given as two courses of 20 Gy and chemotherapy consisted of 5-FU/leukovorin. During the first course of radiation, chemotherapy was given 25 mg/kg/24 hours during radiation and during the second course chemotherapy dose was adjusted based on toxicity. A significantly larger trial with 108 patients in the observation group and 110 in the treatment group, this trial was confounded by the inclusion of nearly 50% of patients with periampullary tumors, and a 20% rate of patients in the treatment arm receiving no treatment due to postoperative complications or individual refusal. On an intention to treat basis, this trial demonstrated a non-significant trend toward improved median survival (25 vs. 19 months; $p=0.21$) for patients receiving adjuvant chemoradiation vs. observation [17]. When patients with periampullary tumors were excluded from the analysis, a trend toward improved median survival remained favoring adjuvant therapy (17 vs. 13 months, $p=0.099$). Long-term follow-up documented that local failure as a component of failure in 50% of patients, but failed to demonstrate a benefit to chemoradiation [18]

There are several potential explanations for the discrepancies seen between these trials. Perhaps most importantly, different approaches to adjuvant chemotherapy were taken with patients in the GITSG trial receiving up to 2 years of additional 5-FU and patients in the EORTC trial receiving no additional therapy. In addition, 20% of subjects in the EORTC trial did not receive any adjuvant therapy and 44% did not receive chemotherapy per protocol. While both studies are small, the GITSG study in particular is limited by its small cohort size.

Separating chemotherapy from radiation

The subsequent European Study Group of Pancreatic Cancer (ESPAC)-1 trial was undertaken to try to clarify the relative benefits of chemotherapy and radiation therapy. Designed as a 2×2 trial, the trial compared 1) observation, 2) chemotherapy, 3) chemoradiation, and 4) chemoradiation and chemotherapy. Again, radiation was given as two 20 Gy courses. Concurrent chemotherapy was 5-FU (500 mg/m²) delivered on day 1-3 of each course of radiation. Chemotherapy was bolus 5-FU and leukovorin given for 5 consecutive days (425 mg/m²/day) every 28 days for a total of 6 cycles. In addition to the 285 patients randomized by 2×2 factorial design, an addition 254 patients were randomized to chemoradiation vs. no chemoradiation or chemotherapy vs. observation. A statistically significant increase in 2-year survival was seen for patients receiving adjuvant chemotherapy (30% vs. 40%, $p=0.009$) with a five-month improvement in median survival from 15 to 20 months [19,20]. Patients who received chemoradiation had worse outcomes compared to those who did not receive chemoradiation (two-year survival of 29% vs. 41%, and median survival of 16 vs. 18 months, respectively; $p=0.05$).

This trial too, was criticized for design and methodological flaws. Patients with margin positive disease were allowed, and although this was stratified for at randomization, the statistical design was designed to demonstrate a 20% improvement in 2-year survival for 280 patients with negative margins. Unfortunately, the trial did not reach the accrual goal of 280 patients with negative margins and the analysis was performed only a smaller subset.

The results from this trial have been interpreted to suggest that the chemoradiation strategy used in this protocol was detrimental due the delay of adequate systemic therapy. It has been hypothesized that delivery of radiation prior to any systemic chemotherapy results in

adverse delays in adequate tumor-killing chemotherapy. This hypothesis has been used to alter the sequencing of therapy in subsequent studies.

In addition, the GITSG, EORTC, and ESPAC-1 studies utilized what is now known to be an inferior radiation treatment schedule; as it is now believed that the treatment break in split course schedules allows for tumor repopulation and subsequently worse outcomes. These studies also failed to include quality assurance for the radiation treatments, a factor we now know to be associated with treatment deviations and worse outcomes in numerous disease sites including pancreas cancer [21]. Finally, the radiation delivered in these trials utilized significantly larger fields and target volumes than are currently used.

Adjuvant chemotherapy

A number of additional trials have been conducted to confirm the role of adjuvant chemotherapy. The ESPAC-1 Plus trial utilized the same eligibility criteria as ESPAC-1 and randomized 192 patients to either 5-FU or observation alone. However, patients could receive chemoradiation at the discretion of the treating physician. Final analysis of this study demonstrated improved survival for the patients who received chemotherapy [22].

The ESPAC-3 trial was designed as a 3-arm study comparing adjuvant 5-FU to adjuvant gemcitabine to observation. An interim analysis after accrual of the first 122 patients led to discontinuation of the observation arm who had a significantly worse 2-year survival [22]. In all, ESPAC-3 enrolled 1,088 patients who received 6 months of either 5-FU/leukovorin (425 mg/m² given days 1-5 every 4 weeks) or gemcitabine (1,000 mg/m² weekly for 3 of every 4 weeks). All told, over 10% of patients never began chemotherapy (12% 5-FU/leukovorin and 11% gemcitabine) and just over half completed all six months of therapy (55% and 60%, respectively). Analyzed on an intention-to-treat basis this study showed similar results for each arm (median survival 23.6 vs. 23 months, $p=0.7$) [23].

In an attempt to address the question of whether earlier delivery of chemotherapy would improve the therapeutic ratio for adjuvant chemoradiation, the Radiation Therapy Oncology Group (RTOG) trial 97-04 randomized 451 patients after curative resection to either 5-FU (continuous infusion of 250 mg/m² per day) or gemcitabine (1,000 mg/m² weekly) for 3 weeks prior to beginning chemoradiation therapy with the same continuous infusion 5-FU used for all patients. Following completion of chemoradiation, patients received 12 additional weeks of their initial chemotherapy. Radiation was delivered once daily for 5 week to a total dose of 50.4 Gy. While no statistically significant difference between arms was noted in disease-free survival or overall survival, there was a trend suggesting a benefit to gemcitabine [24]. One potential confounding factor contributing to the lack of benefit seen in this trial is that following relapse, patients treated on the 5-FU arm were treated with gemcitabine.

The Charite Onkologie-001 trial compared adjuvant gemcitabine (1,000 mg/m² IV weekly for 3 out of 4 weeks) with observation. This trial demonstrated a statistically significant improvement in disease-free survival favoring the gemcitabine arm (13.4 months vs. 6.9 months for observation; $p=0.0001$) [25]. While the initial analysis did not demonstrate an overall survival benefit, a subsequent analysis showed a doubling in 5-year survival (19.5% vs. 9%; $p=0.005$) [26]. Again, there was significant crossover in the observation arm with most patients receiving gemcitabine at the time of progression.

Based on these studies and the data showing the efficacy of gemcitabine in recurrent/metastatic pancreas cancer, there is now general acceptance that adjuvant gemcitabine is indicated following curative resection of pancreas cancer, no definitive conclusions

regarding the role or timing of adjuvant chemoradiation has been reached. Several groups have used lower category evidence to attempt to clarify current best practices.

Additional Data

In attempt to address this issue in patients treated with modern radiation treatment planning techniques, a collaborative analysis by Johns Hopkins Hospital and the Mayo Clinic was undertaken to evaluate the role of adjuvant chemoradiation. The study included over 1,000 patients with resected pancreas cancer treated with adjuvant 5-FU and radiation. Using multiple covariates and Cox proportional hazard models the authors showed a significant improvement in median survival (22.5 months vs. 16.3 months; $p < 0.001$) for those receiving adjuvant chemoradiation [27].

The EORTC reported results from a randomized Phase II trial (40013) which randomized 90 patients following surgical resection to receive either four cycles gemcitabine or two cycles of gemcitabine followed by chemoradiation (weekly gemcitabine and 50.4 Gy). While the primary objective was to demonstrate at least a 60% treatment completion rate and acceptable toxicity, secondary survival endpoints were also included. While gemcitabine-based chemoradiation was well tolerated, overall and disease free survival was similar for both arms. However, a significant improvement in first local recurrence was seen in the radiation arm (24% vs. 11%) [28].

At the 2010 American Society of Clinical Oncology Annual Meeting the results of ECOG 2204 were reported. This phase II study incorporated adjuvant chemoradiation with targeted agents. Patients with resected pancreas cancer were randomized to receive 1) cetuximab (400 mg/m² day 1, then 250 mg/m² weekly) or 2) bevacizumab (5 mg/kg q 2 weeks until end of RT, then 10 mg/kg q 2 weeks). Both targeted agents were given in combination with gemcitabine and were given throughout chemoradiation with capecitabine (625 mg/m² b.i.d. Monday – Friday throughout radiation to 50.4 Gy). While both arms were well tolerated, two-year overall survival was 35% for cetuximab and 37% for bevacizumab [29].

At this time, the benefit to adjuvant chemoradiation remains unclear. Certainly, systemic disease represents the major risk for failure following resection of pancreas cancer, however some patients clearly benefit from locally directed therapy. The RTOG has a study open that may help address the issue of radiation timing. RTOG 0848 (NCT01013649) randomizes patients following surgical resection for pancreatic head adenocarcinoma to five months of 1) gemcitabine alone, or 2) gemcitabine plus erlotinib (an oral epidermal growth factor receptor tyrosine kinase inhibitor). Patients without evidence of progression are then randomized to 1) one month of additional chemotherapy, or 2) one month of additional chemotherapy followed by chemoradiation with concurrent 5-FU or capecitabine.

Neoadjuvant Therapy

Multiple institutions use neoadjuvant chemotherapy and radiation for patients with pancreas cancer with the hope of improving outcomes for those who are able to go on to surgery. It is thought that delivery of systemic therapy earlier in the course of care by using a preoperative approach may improve outcomes [30-32]. In addition, this approach may identify those patients with rapidly progressive disease who likely would not benefit from aggressive surgical management. Some have also suggested that neoadjuvant therapy can result in improved margin negative resection rates and lower recurrence rates for tumors deemed borderline resectable at the time of diagnosis [33]. However, prospective randomized trials have not been completed and retrospective studies comparing pre- with post-operative chemoradiation have not demonstrated a survival benefit.

Multiple neoadjuvant chemotherapy and radiation regimens have been used for patients with resectable pancreas cancer. Many incorporate either 5-FU or gemcitabine with radiation (Table 2). And at least one group has suggested that adding cisplatin to the regimen improves the resection rate. The Interdisciplinary Working Group of Gastrointestinal Tumors is enrolling patients in a prospective randomized phase II trial (NCT00335543) that is asking the question of whether there is a benefit to neoadjuvant chemoradiation. Patients will be randomized to surgery followed by adjuvant chemotherapy vs. neoadjuvant chemoradiation with gemcitabine, cisplatin, and 50.4 Gy radiation followed by surgery and adjuvant chemotherapy.

For patients with borderline resectable pancreas cancers, similar neoadjuvant approaches have been used in attempts to downstage patients and improve R0 resection rates. While multiple institutions have reported their outcomes with this approach (Table 3), as there has been no consistent definition of borderline resectable tumors or even preoperative staging it is quite difficult to draw conclusions from these studies. A recent meta-analysis reviewed data from over four thousand patients who had received neoadjuvant therapy [33]. Chemotherapy was given in 96% and radiotherapy (24-63 Gy) in 94% and patients were divided into initially resectable vs. borderline/potentially resectable patients. Complete responses were seen in 3.6% and 4.8% and partial responses were seen in 30.6% and 30.2% of patients, respectively. Similar rates of progressive disease were also seen for both groups (21% for each). Not surprisingly, more patients in the initially resectable group underwent surgery (74% vs 33%) although median survival following resection was similar in both groups (23 months for initially resectable vs. 21 months for borderline/potentially resectable).

We await the results of ongoing adjuvant/neoadjuvant phase II/III trials designed to investigate the optimal treatment strategy for resectable/potentially resectable adenocarcinoma of the pancreas (Table 4.)

Targeted Therapies

Over the last ten years, cancer therapeutics have begun to target mutations or alterations from normal cellular biology in an attempt to widen the therapeutic ratio (Table 5). Since the identification of K-ras mutations in the majority of pancreas cancers [34,35], the molecular basis of pancreatic adenocarcinoma has remained an area of significant research interest. The most notable targeted agent used in pancreatic cancer, erlotinib, is an oral inhibitor of the tyrosine kinase function of the Epidermal Growth Factor Receptor (EGFR). In a large trial of 569 patients with unresectable, locally advanced, or metastatic pancreatic cancer patients were randomized to 1) standard gemcitabine plus erlotinib or 2) standard gemcitabine plus placebo. A miniscule, but statistically significant, improvement in median survival was seen in patients treated on the gemcitabine plus erlotinib arm (median 6.24 months v 5.91 months, $p=0.038$) [36]. Erlotinib is currently being investigated in the adjuvant setting as an adjunct to chemoradiation or chemotherapy alone. However, extrapolating from other disease sites with a high rate of K-ras mutations (reviewed in [37]), and from preclinical in vitro and in vivo studies [38], it is quite possible that the presence of mutations in K-ras will render these strategies unsuccessful.

In pancreas cancer as in most other disease sites, “targeted” agents are most commonly being tested in combination with standard chemotherapy for patients with advanced or recurrent cancers. Unfortunately, early stage clinical studies investigating these agents in combination with radiation often don't occur until after acceptance of an agent as a systemic therapy. Without the continued investment in preclinical and early stage clinical trials it is possible that we will underestimate the potential benefit of targeted agents, that may only be

evident when used in combination regimens. A number of potential radiosensitizers show little single agent activity. For example, several groups have investigated the utility of targeting pathways downstream of EGFR to radiosensitize pancreas cancer. On their own, these agents have little activity; however, using both in vitro and animal models [38,39] enough activity has been seen to move to early stage clinical trials that have shown some promise [40].

Gene therapy provides another avenue by which to personalize therapy. Bloomston and colleagues reported a phase I study in which the herpes simplex virus (HSV) thymidine synthase gene was delivered via image guidance to patients with locally advanced pancreatic cancer [41]. Patients received valacyclovir for 14 days following virus delivery and then received 5-FU based chemoradiation. Two of 12 patients achieved a partial response and the median survival was 12.2 months.

Stimulating a patient's immune system to aid in tumor detection and control is also under clinical investigation. Using irradiated allogeneic granulocyte-macrophage colony stimulating factor (GM-CSF) secreting tumor vaccine following surgery for patients with resected pancreas cancer, it may represent the best chance for us to concretely identify a subset of patients primarily at risk for local failure who may benefit from more aggressive local therapy. Each immunotherapy treatment was distributed among 3 lymph node regions with the first delivered 8 to 10 weeks after surgery. 5-FU based chemoradiation was then followed by 2 to 4 additional monthly immunotherapy treatments with a final treatment delivered 6 months later. In a recently published phase II study of 60 patients, the treatment was well tolerated and the median overall survival was 24.8 months [42].

Personalized therapy

Despite tremendous efforts directed at improving therapy of systemic pancreas cancer, distant failure following surgery remains a significant problem. The approach being used in many centers of 2-4 cycles of systemic therapy followed by chemoradiation is reasonable, but would certainly benefit from an improved ability to select those patients who will develop a local recurrence. Several groups have suggested that the lymph node ratio (positive/total nodes identified) provides greater prognostic power than the absolute number of lymph nodes involved [43-45]. However, this is more predictive of overall survival and disease free survival than local control. Additional molecular factors have been identified as correlating with survival including the calcium-binding proteins Bax [46,47], Bcl2 [46-48], survivin [49,50], e-cadherin [51,52], COX-2 [53,54], and S100A4 and S100A2 [51,55]. While initially identified in operative specimens, some of these biomarkers including S100A4 and S100A2, have subsequently been validated in ultrasound-guided endoscopic biopsy specimens so that they could be used as preoperative predictive factors [55].

Perhaps the most promising biomarker identified to date is the tumor suppressor SMAD-4(DPC-4), a common mediator of TGF-B signals with important functions in a number of biological processes [56]. In a rapid-autopsy series of 76 patients with pancreas cancer at the Johns Hopkins University, 30% of patients were documented to have died with locally destructive pancreatic cancer and 70% with widespread metastatic disease [8]. Patients with intact SMAD4(DPC4) on immunohistochemistry were more likely to die with locally destructive pancreatic cancer while those with loss of SMAD4(DPC4) were more likely to die with metastatic disease. In a separate cohort of patients treated on a phase II trial, 73% of patients with intact SMAD4(DPC4) had a local-dominant pattern of progression while 70% of patients with SMAD4(DPC4) loss demonstrated a distant-dominant pattern of progression [57].

At this time, SMAD4(DPC4) expression remains under investigation. Additional confirmatory studies are needed to validate its utility as a marker of local recurrence. However, if this biomarker can be validated, either alone, or in combination with additional markers, it may represent the best chance for us to for concretely identify the phantom menace of local failure in what is a largely systemic disease.

Expert Commentary

The prognosis for patients with pancreatic cancer remains poor and current data regarding optimal adjuvant therapy for patients with resectable or potentially resectable adenocarcinoma of the pancreas is conflicting. Analysis of published data is difficult as many of the studies are limited by design flaws as outlined in our review. However, it has been demonstrated that long-term survival is seen most commonly in patients who can undergo margin-negative resections. Neoadjuvant chemoradiation approaches may hold promise in sub-selecting patients who may achieve complete resection, and improve outcome for this small group of patients. Despite tremendous efforts directed at improving therapy of systemic pancreas cancer, distant failure following surgery remains a significant problem for the majority.

The approach being used in many centers of 2-4 cycles of systemic therapy followed by chemoradiation is reasonable, which may improve ability to select those patients with disease resistant to systemic therapy who will develop distant metastases despite local control, as well as those patients who will develop a local recurrence. Desperately needed improvements in systemic therapy will increase the value of obtaining local control, but currently it remains difficult to identify patients who will benefit from locally directed postoperative therapy. Patient performance status continues to play an important role in selection of treatment regimens. With continued advances in supportive care, discovery of additional effective therapies and improved understanding the biology of pancreatic adenocarcinoma, physicians may become able to more confidently stratify patients for various adjuvant therapies.

Five-year Review

Despite recent advances in understanding the biology underlying the development and progression of pancreatic adenocarcinoma, there has been little progress in development of therapeutic regimens that offer an improvement in outcome for patients with this terrible diagnosis.

Preclinical and clinical investigations continue to explore novel approaches that may help to better select patients and therapies which may offer a clinical benefit. Over the next 5 years we expect the following to influence recommendations for treatment of patients with pancreatic cancer.

- Over the next five years RTOG 0848 will provide additional prospective randomized data to help clarify whether adjuvant radiation adds benefit to patients undergoing pancreaticoduodenectomy.
- Subset analyses of RTOG 0848 may provide additional data which may help stratify patients who may benefit from adjuvant radiation, leading to more personalized treatment regimens.
- There will be continued investigation of the potential clinical benefit for new systemic agents.

- Improvements in systemic therapy improvements in systemic therapy will increase the value of obtaining local control and the role of adjuvant radiation will be further clarified.
- Additional data evaluating neoadjuvant treatment regimens may improve patient selection for patients undergoing pancreaticoduodenectomy who may achieve complete resection, and improve outcome for this small group of patients.
- Systemic agents currently being tested in the adjuvant setting will be evaluated in the neoadjuvant setting
- Correlative science studies may help us better understand the biology of pancreatic cancer on a molecular level.
- Improved understanding of the biology of pancreatic adenocarcinoma will lead to further development and testing of targeted agents, and perhaps, personalized treatments.
- Combination therapies including targeted agents will be investigated in the clinical setting.
- Molecular markers will begin to be used routinely as prognosticators and may guide personalized therapeutic decisions.
- Improvements in supportive care will help patients better tolerate treatment regimens.

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Key Issues

- Overall survival for patients with resectable or potentially resectable adenocarcinoma of the pancreas remains poor despite improvements in short-term surgical outcomes, the use of newer chemotherapeutic and targeted agents, and more precise delivery of radiation.
- Conflicting data exist regarding optimal adjuvant therapy.
- Improved systemic treatment is desperately needed as distant metastases remain common.
- Local failure is also common but there is substantial controversy over whether adjuvant radiation provides benefit in patients undergoing pancreaticoduodenectomy and systemic therapy.
- Neoadjuvant chemotherapy +/- radiation is being studied as an alternative to postoperative therapy but the potential benefit over an adjuvant approach is yet to be proven.
- Recent improvements in understanding the biology of pancreatic adenocarcinoma have led to identification of molecular prognosticators but we have yet to define how best to use them.
- Recent improvements in understanding the biology of pancreatic adenocarcinoma have also led to the development of new targeted agents, which are currently being tested in preclinical and clinical models, but have yet to prove benefit in the clinical setting.
- The exact timing and current data regarding optimal adjuvant therapy for patients with resectable or potentially resectable adenocarcinoma is yet to be defined and continues to be evaluated both in the preclinical and clinical setting.
- With current limited data, a reasonable adjuvant treatment approach is to deliver 2-4 cycles of systemic therapy followed by chemoradiation, which may improve ability to select those patients with disease resistant to systemic therapy who will develop distant metastases despite local control, as well as those patients who will develop a local recurrence.

Table 1

Five year relative survival for pancreas cancer. [1]

All stages	Localized	Regional	Distant
6%	23%	9%	2%

Table 2

Studies of neoadjuvant therapy for resectable pancreas cancer.

Study (year)	Patients (n)	Chemotherapy	Radiation (Gy)	Resection rate (%)	R1 or R2 resection	Median survival overall/resected (months)	Reference
Evans et al. (1992)	28	5-FU	50.4	61	NR	NR/NR	[30]
Evans et al. (2008)	86	Gemcitabine	30	74	11	23/34	[31]
Palmer et al. (2007)	24	Gemcitabine	None	38	25	9/28	[58]
	26	Gemcitabine/cisplatin	None	70	25	16/28	[58]
Varadhachary et al. (2008)	90	Gemcitabine, cisplatin	30	58	4	17/31	[32]
Talamonti et al. (2006)	20	Gemcitabine	36	85	6	NR/26	[59]
Le Scodan et al. (2009)	41	Cisplatin/5-FU	50	63	NR	12/13	[60]
Moutardier et al. (2004)	61	Cisplatin/5-FU	45-60	66	8	13/27	[61]
White et al. (2004)	96	5-FU +/- cisplatin/MMC	50.4	55	25	NR/39	[62]
Pisters et al. (1998)	35	5-FU	30 + IORT	57	10	NR/25	[63]

5-FU: 5-fluorouracil; IORT: Intraoperative radiation therapy; MMC: Mitomycin C; NR: Not reported

Table 3
Studies of neoadjuvant therapy for borderline resectable pancreas cancer

Study (year)	Patients (n=)	Chemotherapy	Radiation	Resection Rate	Response Rate	Median Survival overall/resected (months)	Ref.
Stokes et al. (2011)	40	Capecitabine	50 Gy	46%	90%		[64]
Landry et al. (2010)	21	Gemcitabine vs.	50.4 Gy	30%	NR	NR/NR	[65]
		Gemcitabine, 5FU, Cisplatin	-----	20%			
Small et al. (2008)	41	Gemcitabine	36 Gy	33%	5%	1 yr 76%/NR	[66]
Golcher et al. (2008)	103	Various chemotherapeutic agents	55.8 Gy	20%	NR	10/54	[67]
Allendorf et al. (2008)	78	Capecitabine Docetaxel Gemcitabine	50.4 Gy	76%	NR	17/18	[68]
Massucco et al. (2006)	28	Gemcitabine	45 Gy	39%	22%	15/21	[69]
Pipas et al. (2005)	24	Gemcitabine Docetaxel	50.4 Gy	86%	50%	14/NR	[70]
Joensuu et al. (2004)	28	Gemcitabine	50.4 Gy	61%	NR	28/30	[71]
White et al. (2003)	88	5FU +/- Cisplatin/MMC	50.4 Gy	18%	NR	NR/20	[62]
Ammori et al. (2003)	67	Gemcitabine Cisplatin	50.4 Gy	33%	NR	NR/18	[72]
Snady et al. (2000)	68	5FU Streptozocin Cisplatin	54 Gy	29%	32%	24/32	[73]
Kamthan et al. (1997)	35	5FU Streptozocin Cisplatin	54 Gy	14%	43%	15/31	[74]

5-FU: 5-fluorouracil; MMC: Mitomycin C; NR: Not reported

Table 4
Selected ongoing and recently completed adjuvant/neoadjuvant trials for resectable adenocarcinoma of the pancreas

Study	Sponsor	Identifier	Phase	N	Primary Endpoint	Status
Gemcitabine Hydrochloride With or Without Erlotinib Hydrochloride Followed By the Same Chemotherapy Regimen With or Without Radiation Therapy and Capecitabine or Fluorouracil in Treating Patients With Pancreatic Cancer That Has Been Removed By Surgery	RTOG 0848	NCT01013649	III	952	Survival	ongoing
Gemcitabine and Erlotinib Before and After Surgery in Treating Patients With Pancreatic Cancer That Can Be Removed by Surgery	ACOSOG Z05041	NCT00733746	II	90	2 year OS	ongoing
Adjuvant Therapy in R0-resected Pancreatic Cancer Patients with Gemcitabine plus Erlotinib vs. Gemcitabine over 24 Weeks - a Prospective, Randomized Phase III Study	CONKO-005	DRKS000000247	III	436	Relapse-free survival	ongoing
Additive therapy for R1 resected pancreatic carcinoma with gemcitabine plus sorafenib vs. gemcitabine plus placebo over 12 months- a double blind placebo-controlled phase IIb study	CONKO-006	DRKS000000242	IIb	162	Relapse-free survival	ongoing
Combination versus single agent chemotherapy (Gemcitabine and Capecitabine vs. Gemcitabine alone) in resectable pancreatic cancer	ESPAC-4	UKCRN 4307	III	1080	Survival	ongoing
Randomized phase III trial of adjuvant chemotherapy with gemcitabine versus S-1 in patients with resected pancreatic cancer: Japan Adjuvant Study Group of Pancreatic Cancer	JASPAC-01	UMIN000000655	III	360	Survival	completed

Table 5

Molecular alterations in pancreatic cancer as therapeutic targets.

Mutation	Prevalence (%)	Drug	Clinical benefit?	Ref.
EGFR overexpression	25-65%	Cetuximab, erlotinib, gefitinib	Erlotinib: beneficial; cetuximab and gefitinib: No	[36,75,76]
K-ras	74-100%	Farnesyl transferase inhibitors	No	[77]
Her-2/neu amplification/overexpression	16-65%	Trastuzumab, lapatinib	No	[78-81]
VEGF receptor overexpression	90%	Bevacizumab, vandetanib, vatalanib, aflibercept	No	[29,82]
Matrix metalloprotease overexpression	Unknown	Marimastat, tanomastat	No	[83-85]
Cox-2 overexpression	40-50%	Celecoxib, apricoxib	Mix results	[86-88]
MTOR activation	Unknown	Temsirolimus, everolimus	Erevelimus: No; temsirolimus: unknown	[89]
Muc-1/Muc-4 glycoprotein overexpression	Unknown	Muc-1 radiolabeled antibody, antisense Muc-4 RNA	Unknown	[90]
NF- κ B	Unknown	Curcumin, genistein, synthetic compounds	Unknown	[91-95]
Notch-1/Sonic hedgehog pathway oncogene overexpression	50-90%	Cyclopamine, RNA interference	Unknown	[91,92,96,97]
Akt oncogene amplification/overexpression	10-72%	RNA interference, nelfinavir	Unknown	[38,40,98-100]