Adjuvant trials for pancreatic cancer: where are we going and what is needed?

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The prognosis for pancreatic cancer remains poor and curative treatment currently involves multimodality therapy including resection. Effective systemic therapy regimens with or without radiation are needed; however, an optimal treatment paradigm is not clearly defined. Adjuvant therapy clinical trials are evaluating the potential benefit of targeted agents and the addition of radiation to systemic chemotherapy. Neoadjuvant treatments are also under investigation for resectable and borderline/potentially resectable tumors. Additional study goals include identification of patients at risk for pancreatic cancer and improvements in prediction and prognostication, which may lead to personalized treatment strategies. This article reviews data for neoadjuvant and adjuvant treatment for localized pancreatic adenocarcinoma and provides insight into the future evolution of treatment for patients with this deadly disease.

Keywords: adjuvant therapy • early stage pancreatic cancer • multimodality therapy • neoadjuvant therapy • personalized medicine • targeted therapy

Pancreatic cancer constitutes 6% of all cancers in the USA and is the fourth most common cause of cancer death. Approximately 43,100 new cancer patients are diagnosed per year resulting in more than 36,800 deaths [1]. The incidence of pancreatic adenocarcinoma is approximately 12 per 100,000 in the USA with a lifetime risk of one in 71. The prevalence of pancreatic cancer has increased by 52% over the last decade [1], as a reflection of and increase of the population at risk.

Although most patients present with distant metastases, approximately 15–20% will be diagnosed with disease amenable to curative surgical resection. Despite potentially curative resection for pancreatic adenocarcinoma, the 5-year survival rate for early-stage patients is <20% [2,3]. Patterns of failure demonstrate both a significant component of local-regional relapse (50–85%) and distant failure, primarily liver and metastatic intra-abdominal failure [2,4]. Adjuvant treatments are used in an attempt to prevent recurrence and improve survival. In an attempt to improve outcome for these patients, multimodality therapy has been a topic of active investigation. This article reviews data regarding adjuvant therapy for early-stage pancreatic cancer.

Adjuvant therapy

The first trial published in the USA demonstrating the benefit of adjuvant therapy in addition to surgery for patients with early-stage pancreatic cancer was published in 1985 [5]. The Gastrointestinal Tumor Study Group (GITSG) randomized 49 patients with histologically confirmed adenocarcinoma of the pancreas who underwent curative resection with negative surgical margins from 1974 to 1982, to observation or adjuvant radiation (two courses of 20 Gy, separated by a 2-week interval for a total dose of 40 Gy) with 5-fluorouracil (5-FU; 500 mg/m² intravenous [iv.]

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bolus delivered on day 1-3 of each course of radiation then continued weekly for 2 years or until disease progression) (Figure 1). Patients were stratified by surgical procedure, tumor location, stage and histological differentiation. The majority of tumors (95%) were located in the head of the pancreas (periampullary carcinomas excluded) and 28% were node-positive. The median survival was 20 months for the 21 patients who received adjuvant therapy versus 11 months for the 22 patients in the observation group in the final analysis consisting of 43 patients. Although these results did meet statistical significance (p = 0.035), the study is criticized for the small sample size, inferior radiation regimen and slow accrual. Furthermore, the trial was not designed to examine the relative benefit of chemotherapy or radiation therapy and it remains unclear from where the most benefit is derived [5].

Subsequent randomized trials evaluating the potential benefit from adjuvant treatment strategies were also limited by flawed methodology. A total of 14 years following the Gastrointestinal Tumor Study Group publication, the Gastro-Intestinal Tract Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer (EORTC) demonstrated a nonsignificant trend toward improved median survival (25 vs 19 months; p = 0.21) for patients receiving adjuvant chemoradiation (two courses of 20 Gy with 5-FU/leukovorin; 25 mg/kg on days 1-5 of each course of radiation only) compared with observation following curative resection. This trial included 218 patients in the randomization, 108 patients in the observation group, 110 patients in the treatment group; 11 patients were ineligible (five in the observation group and six in the treatment group); 114 patients (55%) had pancreatic cancer (54 in the observation group and 60 in the treatment group). In the treatment arm, 21 patients (20%) received no treatment owing to postoperative complications or patient refusal. The trial was confounded by inclusion of patients with periampullary tumors, which made up approximately 50%. When these patients were excluded from analysis, a nonsignificant trend toward improved median survival remained for 114 patients with pancreatic adenocarcinoma receiving adjuvant therapy (17 vs 13 months; p = 0.099) [6].

In an attempt to clarify the relative benefits of chemotherapy and radiation therapy in the adjuvant setting, the first European Study Group of Pancreatic Cancer (ESPAC)-1 was undertaken and subsequently published by Neoptolemos. The study was designed to compare chemoradiation (two courses of 20 Gy with 5-FU; 500 mg/m² iv. bolus delivered on day 1–3 of each course of radiation, then continued weekly for 2 years or until disease progression), to 6 months of adjuvant chemotherapy without radiation (5-FU; 425 mg/m² with leukovorin every 28 days for six cycles), to chemoradiation followed by 6 months of chemotherapy, and to observation (Figure 2). In all, 541 patients were randomized: 285 by 2 × 2 factorial design (70 chemoradiotherapy, 74 chemotherapy, 72 both, 69 observations). In addition, 68 patients were randomly assigned chemoradiotherapy or no chemoradiotherapy and 188 chemotherapy or no chemotherapy. The authors reported a statistically significant increase in 2-year survival for those patients receiving adjuvant chemotherapy (40 vs 30% for the observation group; hazard ratio = 0.71; p = 0.009) with median survival of 20 versus 15 months. The patients who received chemoradiation were reported to have worse outcomes (2-year survival 29 vs 40% for the observation group; hazard ratio for death 1.28; p = 0.05) with median survival of 16 versus 18 months. In addition, 5-year survival rates were reported for the four arms: chemotherapy 21% versus observation 8% (p = 0.009) and chemoradiation 10% versus observation 20% (p = 0.05) [7,8].

This study was also criticized for design and methodology flaws. Positive surgical margins were allowed in this study and margin status was stratified at randomization. The statistical design was conceived to demonstrate a 20% improvement in 2-year survival rate for 280 patients with negative margins, but was not reported for margin-negative patients, but for the entire group, yet no p values were reported. In addition, the trial did not reach the accrual goal of 280 patients with negative margins and the analysis was performed on 220 patients. Although perimpullary and nonadenocarcinomas were allowed on study to participate in only one of the two randomizations, the results were excluded from final analysis [7,8].

Although this trial established a benefit to adjuvant chemotherapy, the trial was not powered to compare results from the four arms in the 2×2 randomization. Nonetheless, the authors suggested that the chemoradiation strategy used in this protocol was detrimental as it delayed delivery of systemic doses of chemotherapy. There has also been criticism that the split-course radiation introduced a treatment break that potentially allowed for tumor repopulation, and does not accurately reflect modern radiation techniques. In addition, there was no quality assurance for the radiation treatments and patients received doses other than specified by the study.

Additional evidence demonstrating the benefit of adjuvant chemotherapy was reported with additional data from the ESPAC-1 plus trial and ESPAC-3 (v1) trial [9]. In the ESPAC-1 plus trial, 192 patients with the same eligibility criteria as ESPAC-1 were randomized to either 5-FU or observation alone using the same treatment regimens as ESPAC-1, but could receive 'background' chemoradiation at the physicians'

discretion. This group of patients was included as part of the ESPAC-1 trial with the intention of supplying additional evidence, therefore was not powered for analysis as a separate cohort. Final analysis of this study continued to demonstrate statistically improved survival (p < 0.001) for the patients who received chemotherapy, and the patients who received chemoradiation who continued to demonstrate a nonsignificant decrease in survival (p = 0.078). Although this study was not powered for analysis, it provided additional data to support the original observation that patients undergoing surgical resection benefit from the addition of adjuvant 5-FU-based chemotherapy.

The ESPAC-3 trial was designed as a 3-arm study comparing adjuvant 5-FU to adjuvant gemcitabine to observation (Figure 3); however, the observation arm was dropped (ESPAC-3 [v2]) after preliminary results were published following accrual of the first 122 patients, demonstrating an increase in 2-year survival (49 vs 37% for the observation arm; HR = 0.7, p = 0.003 [9]. Results from ESPAC-3 have now been reported for 1088 patients with pancreatic adenocarcinoma treated with curative resection who received either 5-FU/leukovorin (425 mg/m² iv. bolus given 1-5 days every 28 days) or gemcitabine (1000 mg/m² iv. weekly for three of every 4 weeks) for 6 months. A total of 551 patients were randomized to receive 5-FU/ leukovorin, and 537 were randomized to receive gemcitabine, with ineligible patients reported, two in each group, included in the analysis on an intention-to-treat basis - 486 patients (88%) received 5-FU/leukovorin (55% completed all six cycles) and 478 (89%) received gemcitabine (60% completed all six cycles). A total of 65 patients (12%) in the 5-FU/leukovorin group and 59 (11%) in the gemcitabine group did not start treatment. Gemcitabine did not result in improved survival compared with 5-FU in this study (median survival 23.6 vs 23 months, p = 0.7; HR = 0.94), similar to results observed in ESPAC-1. This study did not included radiation therapy and did not address whether radiation plays a role in the adjuvant setting [10].

There have been two additional randomized Phase III multicenter trials reported, evaluating adjuvant therapy regimens following surgical resection for pancreatic adenocarcinoma. The Radiation Therapy Oncology Group (RTOG) intergroup trial 97–04 randomized 451 patients with pancreatic adenocarcinoma who had undergone curative resection (75% T3/T4; 66% node-positive; 33% positive margins) to either 5-FU (continuous infusion of 250 mg/m²/day; n = 230) or gemcitabine (30 min infusion of 1000 mg/m² weekly; n = 221), both for 3 weeks prior to chemoradiation therapy and 12 weeks following chemoradiation (Figure 4). Chemoradiation with a continuous



Figure 1. Gastrointestinal Tumor Study Group (GITSG) treatment randomization.

infusion of 5-FU (250 mg/m²/day) was the same for all patients (50.4 Gy; 1.8 Gy/day, 5 days/week). Patients were stratified for tumor size and surgical margins and a subgroup analysis for pancreatic head tumors was performed. Survival for all patients and for those with pancreatic head tumors were the primary end points of the study. Although there was no statistically significant difference in disease-free, or overall survival between the two arms, there was a trend suggesting benefit to the addition of gemcitabine over adjuvant 5-FU-based chemoradiation. Subset analysis of patients with pancreatic head tumors (n = 388) demonstrated a median survival (20.5 vs 16.9 months) and a 3-year



Figure 2. European Study Group of Pancreatic Cancer (ESPAC)-1 treatment randomization.

[†]Chemotherapy: 5-fluorouracil plus leukovorin × six cycles [†]Chemoradiotherapy: total 4000 Gy (20 Gy/fraction) [split] + bolus 5-fluorouracil.

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Figure 3. European Study Group of Pancreatic Cancer (ESPAC)-3 treatment randomization.

survival (31% vs 22%) in favor of the gemcitabine arm for those patients with pancreatic head tumors (HR: 0.82; p = 0.09) [11]. Although this study did not reach statistical significance, patients treated on the 5-FU arm who experienced relapse were subsequently treated with gemcitabine, which may have reduced the observed benefit for this therapy. This study did not address the relative contribution of radiation therapy, however.

The Charite Onkologie-001 trial compared adjuvant gemcitabine (1000 mg/m² iv. weekly for three of every 4 weeks for six cycles) with observation. To detect a 6 months difference in disease-free survival, 368 patients were randomized. There was a statistically



Figure 4. Radiation Therapy Oncology Group (RTOG) 97–04 treatment randomization.

significant difference in disease-free survival between the arms regardless of tumor size, nodal involvement or margin status (gemcitabine 13.4 months vs observation 6.9 months; p = 0.001) (Figure 5) [12]. In the initial analysis, there was no apparent survival benefit; however, subsequent analysis demonstrated improved median and estimated 5-year survivals for the 179 patients receiving gemcitabine over the 175 patients who were observed (median survival 22.8 vs 20.2 months; p = 0.005 and estimated 5-year survival 21 vs 9%) [13]. It must be recognized, however, that there is likely more benefit to gemcitabine than demonstrated in this study, due to crossover in the observation arm, as these patients received gemcitabine at the time of relapse similar to the RTOG study. Once again, the issue of whether adjuvant chemoradiation offers a benefit was not addressed in this study.

Currently, the use of adjuvant radiation for patients with resected pancreatic cancer represents one of the central debates in gastrointestinal oncology. A collaborative study between Johns Hopkins Hospital and Mayo Clinic was reported that evaluated the potential benefit of adjuvant chemoradiation using modern treatment regimens and techniques [14]. The study consisted of 1045 patients with resected pancreas cancer, 530 (50.7%) of which received adjuvant 5-FU and radiation. Cox proportional hazards models were used with covariates age, sex, institution, margin status, node status, differentiation, surgery type and T-stage. Median survival was 22.5 for those patients receiving adjuvant therapy versus 16.3 months for the observation group (p < 0.001). Improved survival among all patients remained on univariate (RR = 0.71) and multivariate (RR = 0.62) analyses regardless of age, tumor size, margin status, nodal involvement or tumor differentiation and in all sub-groups (multivariate RR = 0.54-0.74; p < 0.05) [14]. Although this study demonstrated a statistically significant survival benefit to adjuvant chemoradiation, and not a detriment as reported by ESPAC-1, it did not provide the level of evidence achieved by a randomized prospective trial.

The EORTC has recently reported results from a randomized Phase II trial (40013) in which 90 patients who had undergone surgical resection were randomly assigned to receive either four cycles of gemcitabine (n = 45) or two cycles of gemcitabine followed by weekly gemcitabine with concurrent radiation (50.4 Gy) (n = 45). The primary objective was to demonstrate greater than 60% treatment completion and acceptable grade four toxicity. Secondary end points were late toxicity, disease-free survival and overall survival. In this study, gemcitabinebased chemoradiation was well tolerated, but the overall median and disease-free survival was similar for both arms. There was, however, a significant improvement in local control in the radiation arm [15].

Most recently, the intergroup randomized Phase II study, ECOG 2204, was reported at the 2010 American Society of Clinical Oncology. In this study, patients with resected pancreatic cancer were randomized to receive more aggressive systemic therapy. Patients received either cetuximab (400 mg/m² day 1, then 250 mg/m² weekly) or bevacizumab (5 mg/kg every 2 weeks until end of XRT, then 10 mg/kg every 2 weeks) in combination with gemcitabine given before and after capecitabine $(625 \text{ mg/m}^2 \text{ b.i.d. on days during } 5\frac{1}{2} \text{ weeks of radiation}$ (50.4 Gy). Cetuximab and bevacizumab were also given throughout chemoradiation. Even though both arms were fairly well tolerated, over 10% of patients recurred during adjuvant therapy. 2-year disease-free survival was 16% for the cetuximab-containing arm and 22% for bevacizumab, while 2-year overall survival was 35% for cetuximab and 37% for bevacizumab, with no compelling evidence to develop either arm further and no additional evidence to clarify the role of radiation in the adjuvant setting [16].

Regarding the benefit for chemoradiation, RTOG 97-04 did not address it, the EORTC trial did not demonstrate it and ESPAC-01 suggested that chemoradiation was detrimental to survival; however, this study has been criticized for design and methodology. Since the argument remains that local control is of limited benefit when systemic disease limits survival, further attempts to clarify whether or not adjuvant chemoradiation offers additional benefit over chemotherapy alone are being undertaken in large cooperative group trials. RTOG 0848, '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' (NCT01013649 [201]) is currently open for accrual and randomizes patients who have undergone surgical resection for adenocarcinoma of the head of the pancreas to gemcitabine alone or gemcitabine plus erlotinib, an oral EGF receptor tyrosine kinase inhibitor that has demonstrated a small, but statistically significant, survival benefit in patients with metastatic pancreatic cancer. Patients who do not progress after receiving 5 months of systemic therapy will then be randomized to either one additional month of the assigned systemic treatment or 1 month of the assigned systemic treatment followed by chemoradiation with concurrent protracted venous infusion 5-FU or capecitabine. It is anticipated that the results of this study will further clarify the benefit of the addition of radiation to systemic therapy in the adjuvant setting.

Other nonradiation-containing adjuvant treatment regimens currently under investigation include the multicenter Phase II American College of



Figure 5. Charite Onkologie-001 treatment randomization.

Surgeons Z5041 study 'Gemcitabine and Erlotinib Before and After Surgery in Treating Patients With Pancreatic Cancer That Can Be Removed by Surgery' (NCT00733746 [202]), in which patients receive perioperative chemotherapy consisting of pre- and postresection gemcitabine (days 1, 8, 15, 29, 36 and 43) and erlotinib (once daily on days 1–43), with 2-year overall survival as the primary end point.

Neoadjuvant therapy

Preoperative therapy for the treatment of resectable pancreatic cancer has several theoretical advantages and is currently a topic of investigation. The potential advantages of neoadjuvant treatment include the ability to provide systemic treatment earlier in the course of treatment, which may influence survival for patients whose tumors respond to therapy, and the ability to avoid surgery in those patients who have rapidly progressive disease or occult metastases that do not respond to treatment. It may also identify patients who do not tolerate systemic therapies and the associated morbidities prior to undergoing a major surgery, selecting patients who would benefit the most from resection. The use of neoadjuvant treatments may also result in a decrease in surgical complications. For example, it has been demonstrated that pancreatic anastomotic leaks are less frequent when preoperative radiation is delivered [17]. In addition, downstaging of tumor in response to treatment delivered prior to resection may result in improved margin negative resection rates and lower recurrence rates, especially for those tumors deemed 'borderline resectable' at the time of diagnosis. The effects of chemotherapy and radiation are expected to be enhanced in better perfused and oxygenated tissue prior to surgical manipulation. Preoperative therapies are generally better tolerated than adjuvant regimens. Specifically, it has been demonstrated that approximately 20-30% of patients undergoing pancreaticoduodenectomy for pancreatic cancer fail to receive planned adjuvant therapy due to refusal after a major surgery or poor tolerance [6]. In addition, there are often delays in initiation of adjuvant therapy in those patients who can tolerate treatment due to prolonged recovery time. Delivery of neoadjuvant therapy early in the course of treatment would be desirable for patients with pancreatic cancer since there is both a high-systemic and local-failure rate, often observed early in the postoperative period.

To date, there are no randomized clinical trials comparing neoadjuvant therapy to adjuvant therapy in pancreatic adenocarcinoma to provide clinical evidence to support these theoretical advantages. In the absence of randomized data, it remains unclear whether neoadjuvant therapy offers an advantage or survival benefit over the adjuvant approach. There are, however, several single- and multi-institutional studies suggesting that the neoadjuvant approach may be an effective treatment strategy. Both chemotherapy and chemoradiation regimens have been employed in the neoadjuvant setting.

Evans *et al.* published the first preoperative chemoradiation trial in the early 1990s for 28 patients receiving standard fractionation radiation (50 Gy over 5 weeks) concurrently with 5-FU chemotherapy [18] and a subsequent study used a rapid fractionation regimen (30 Gy over 2 weeks with 5-FU) in 35 patients [19]. Both regimens were well tolerated and approximately 60% of patients did not develop distant metastases and underwent surgical resection resulting in a median survival of 2 years, similar to results of adjuvant trials.

Multiple trials utilizing various preoperative treatment strategies for resectable pancreatic adenocarcinomas have been published and are outlined in Table 1. In summary, multiple chemoradiation regimens using different chemotherapeutic agents have been utilized, however, no single regimen demonstrated improvement in outcome for this group of patients. Both 5-FU and gemcitabine have been used in combination with radiation in the neoadjuvant setting. Talamonti et al. first reported results using systemic doses of gemcitabine in combination with radiation (36 Gy) from a cohort of 20 patients with potentially resectable pancreatic cancer. 85% of patients underwent resection resulting in a 94% negative margin rate [20]. This trial suggested that gemcitabine-based chemoradiation may be superior to 5-FU-based regimens and has led to further investigation. Subsequently, Evans et al. reported their Phase II results using gemcitabine-based chemoradiation (30 Gy) in 86 patients with stage I or II adenocarcinoma of the head of the pancreas. In this study, 73 patients ultimately went to surgery, the resection rate was 74% and negative margins were achieved in 89%. The median survival for 64 patients undergoing pancreaticoduodenectomy was 34 months, and the 5-year survival was 36% compared with 0% for 22 patients who did not undergo surgery [21]. Although these results were impressive, it must be recognized that these are highly selected patients from a single institution and further investigation is warranted prior to drawing conclusions.

Another study from the same institution explored the role of systemic chemotherapy in addition to chemoradiation in the preoperative setting. Neoadjuvant cisplatin and gemcitabine were delivered for 4 weeks prior to gemcitabine-based chemoradiation (30 Gy) and surgery. The study enrolled 90 patients; 79 patients (88%) completed chemo-chemoradiation; 62 (78%) of 79 patients were taken to surgery and 52 (66%) of 79 underwent PD,

Table 1. Neoadjuvant trials for resectable pancreatic cancer.								
Study (year)	Patients (n)	Chemotherapy	Radiation (Gy)	Resection rate (%)	Positive margin rate (%)	Median survival (months)	Median survival (months) resected patients	Ref.
Evans (2008)	86	Gemcitabine	30	74	11	23	34	[21]
Palmer (2007)	24 26	Gemcitabine, gemcitabine/cisplatin	None	38, 70	25, 25	9, 16	28	[23]
Varadhachary (2008)	90	Gemcitabine, cisplatin	30	58	4	17	31	[22]
Talamonti (2006)	20	Gemcitabine	36	85	6	NR	26	[20]
LeScodan (2009)	41	Cisplatin, 5-FU	50	63	NR	12	13	[59]
Moutardier (2004)	61	Cisplatin, 5-FU	45-60	66	7.5	13	27	[60]
White (2004)	96	5-FU \pm cisplatin/MMC	50.4	55	25	NR	39	[61]
Pisters (2002)	37	Paclitaxel	30 + IORT	54	32	12	19	[62]
Pisters (1998)	35	5-FU	30 + IORT	57	10	NR	25	[19]
5-EU: 5-fluorouracil: IORT: II	ntraoperative	radiation therapy: MMC: Mitor	nvcin C: NR: Not	reported				

Table 2. Neoadjuvant trials for borderline resectable pancreatic cancer.								
Study (year)	Patients (n)	Chemotherapy	Radiation (Gy)	Resection rate (%)	Response rate (%)	Median survival (months)	Median survival (months) resected patients	Ref.
Stokes (2011)	40	Capecitabine	50	46	90			[63]
Landry (2010)	21	Gemcitabine vs gemcitabine, 5-FU, cisplatin	50.4	30 20	NR	NR	NR	[64]
Small (2008)	41	Gemcitabine	36	33	5	76% at 1 year	NR	[65]
Golcher (2008)	103	Mixed	55.8	20	NR	10	54	[66]
Allendorf (2008)	78	Capecitabine, docetaxel, gemcitabine	50.4	76	NR	17	18	[67]
Massucco (2006)	28	Gemcitabine	45	39	22	15	21	[68]
Pipas (2005)	24	Gemcitabine, docetaxel	50.4	86	50	14	NR	[69]
Joensuu (2004)	28	Gemcitabine	50.4	61	NR	28	30	[70]
White (2004)	88	5-FU ± cisplatin/MMC	50.4	18	NR	NR	20	[61]
Ammori (2003)	67	Gemcitabine, cisplatin	50.4	33	NR	NR	18	[71]
Snady (2000)	68	5-FU, streptozocin, cisplatin	54	29	32	24	32	[72]
Kamthan (1997)	35	5-FU, streptozocin, cisplatin	54	14	43	15	31	[73]
5-FU: 5-fluorouracil; MMC: Mitomycin C; NR: Not reported.								

resulting in a margin-negative rate of 96%. The median overall survival was higher for the patients who were able to undergo surgery (31 months) compared with those who completed therapy but did not undergo resection (17.4 months). These results were compared with results for patients undergoing gemcitabine-based chemoradiation and the authors concluded that there was no apparent benefit to the addition of cisplatin [22]. Conversely, Palmer et al. demonstrated an improved resection rate, and median overall survival when cisplatin was added to gemcitabine preoperatively in a nonradiation-containing regimen for patients with resectable tumors in a randomized trial [23]. In this trial, 50 patients were randomized to receive either gemcitabine alone (n = 24) versus gemcitabine with cisplatin (n = 26). The resection rate was improved from 38 to 70% for patients receiving combined therapy. Although the resection rate was the same (25%), the median overall survival improved for the combination chemotherapy cohort (9 vs 16 months) [23].

American College of Surgeons Z5041 (NCT 00733746 [203]) is a Phase II trial that is currently enrolling patients to receive neoadjuvant gemcitabine and erlotinib followed by surgery and further systemic treatment using the same regimen for patients with initially resectable tumors. In addition, the Interdisciplinary Working Group of Gastrointestinal Tumors in Germany, Switzerland and Austria is enrolling patients in a prospective randomized Phase II trial

(NCT00335543 [204]), which may help determine whether there is a benefit to the addition of chemoradiation in the neoadjuvant setting. In this trial, patients will receive either upfront resection followed by adjuvant chemotherapy or neoadjuvant chemoradiation (gemcitabine, cisplatin, 50.4 Gy) followed by surgery, followed by adjuvant chemotherapy.

Similar neoadjuvant treatment approaches have been applied to patients with borderline resectable pancreatic cancer in attempt to downstage patients and improve R0 resection rates. Table 2 summarizes studies that have investigated the use of neoadjuvant therapy for borderline pancreatic cancer. Unfortunately, it is difficult to draw conclusions from these data as there is no consistent definition of borderline resectable tumors or preoperative staging among these studies. In addition, patients with borderline resectable tumors have often been included in studies for both resectable and locally advanced disease, leading to a wide range of resectability (1-76%) and response (3-90%) rates. A recent meta-analysis reviewed data from 4394 patients who received neoadjuvant therapy followed by re-staging and surgical exploration/resection for pancreatic cancer [24]. A total of 111 studies including 56 Phase I-II trials were divided further into initially resectable and borderline resectable/unresectable tumors. Neoadjuvant chemotherapy was given in 96.4% and neoadjuvant radiotherapy was delivered in 93.7% (24-63 Gy).

Complete/partial response rates were similar for both groups, estimated at 3.6/30.6% for the initially resectable patients and 4.8/30.2% for borderline/potentially resectable patients. Progressive disease was also similar for both groups at 20.9 and 20.8%. More patients underwent successful surgery in the initially resectable group (73.6%) compared with those deemed borderline/potentially resectable (33.2%). Combination chemotherapies resulted in higher estimated response and resection probabilities for the latter group of patients. Estimated median survival following resection was also similar for both groups of patients (23.3 vs 20.5 months) [24]. These studies suggest that neoadjuvant therapy may allow some patients with locally advanced disease to be downstaged enough to render the tumor resectable and improving the probability of cure, although the number is small and the optimal treatment regimen is unclear. In summary, survival data for neoadjuvant therapy is limited for borderline resectable disease, however, with effective staging and patient selection, approximately one out of three patients may be able to undergo surgery.

Efforts to improve patient selection include agreement on a consistent definition of surgical resectability. Currently, borderline resectable disease is defined by the NCCN as severe unilateral or bilateral superior mesenteric vein or portal impingement, less than 180 degrees of tumor abutment of the superior mesenteric artery or celiac axis, abutment or encasement of the hepatic artery (if reconstructable) and/or superior mesenteric vein occlusion. Others define borderline resectability by the ability to reconstruct the involved vessels [25]. Standardization of the definitions of resectable and borderline resectable pancreatic cancer by more precisely defining vascular involvement has been attempted by the American Hepatopancreaticobiliary Association [26] and will be important for consistency, comparison and interpretation of data from future trials.

Future perspective Targeted therapies

Pancreatic adenocarcinoma is resistant to many types of systemic and targeted therapies with only a few drugs offering limited benefit. Aggressive combination cytotoxic regimens have been relatively unsuccessful. However, recently the interim analysis results of a randomized Phase III trial (PRODIGE 4/ACCORD 11) demonstrated a survival advantage of the combination of 5-FU, leukovorin, irinotecan and oxaliplatin (FOLFIRINOX) over gemcitabine as first-line treatment for metastatic pancreatic adenocarcinoma [27] but at the cost of significant toxicity [28].

Another strategy to target tumor cells is to exploit tumor biology and develop targeted agents. The molecular basis of pancreatic adenocarcinoma is an area of considerable research interest. Pancreatic adenocarcinoma cells are derived from normal pancreatic ductal cells through a process that involves genetic mutations, including tumor suppressor genes and oncogenes and molecular alterations. These aberrations ultimately result in nuclear and morphological cellular changes associated with pancreatic adenocarcinoma cells.

Targeted agents delivered in combination with chemotherapy are generally better tolerated. The most notable targeted agent used in pancreatic cancer to date, erlotinib, is an oral EGF receptor tyrosine kinase inhibitor that results in an improvement in median overall survival in patients with advanced pancreatic cancer when delivered with gemcitabine [29]. Erlotinib is currently being evaluated in the adjuvant setting. Development and testing of other novel agents in advanced pancreatic cancer may provide further evidence as to whether they can become clinically useful for those patients with potentially curative disease. Table 3 summarizes the most common molecular alterations known in pancreatic cancer currently being explored as potential therapeutic molecular targets.

Several downstream pathways are also being investigated as potential molecular targets. Recently, several promising novel therapeutic approaches that are still early in clinical development have been recently reported with promising results. Some recently reported strategies with early, but encouraging results are described below.

K-ras is a small GTPase bound to the cell membrane that regulates multiple oncogenic pathways, and is mutated into a constantly active form in most pancreatic adenocarcinomas [30]. The MAPK or MEK pathway is downstream of K-ras and, therefore, is an appealing target. Although the utility of MEK inhibition has been evaluated in pancreatic and other cancers with limited success [31], there are promising newer agents under investigation. GSK1120212 is a novel MEK inhibitor with a broader therapeutic window than previous MEK inhibitors, which has recently been evaluated in combination with gemcitabine in a Phase Ib trial [32]. Although the trial was designed to evaluate the safety of this regimen, therapeutic potential is encouraging as one patient achieved a partial response and another three patients experienced stabilization of their disease sustained over several months.

It has also been shown that anticoagulation potentially exhibits antiangiogenic properties in preclinical pancreatic cancer models providing an alternative strategy of targeting tumor vasculature different than VEGF inhibition, which has been demonstrated to have limited therapeutic benefit in pancreatic cancer [16,33]. PCI-27483 is a small molecule that selectively inhibits coagulation factor VIIa serine protease. Tissue factor localizes VIIa to the cell membrane and it has been suggested that the tissue

Table 3. Molecular targets in par	ncreatic cancer.				
Mutation	Prevalence (%)	Significance	Targeted agents	Clinical benefit	Ref.
Kras oncogene mutation	74–100	Negative prognostic factor	Farnesyl transferase inhibitors	No benefit	[74]
Her-2/neu oncogene amplification/overexpression	16–65	No prognostic significance	Trastuzumab, Iapatinib	No benefit	[75,76,88-93]
Notch-1/sonic hedgehog pathway oncogene overexpression Associated with NF-κB pathway	50–90	Not established	RNA interference and inhibition; cyclopamine	Unknown	[94–100]
Akt oncogene amplification/overexpression	10–72	Akt-2 inhibition renders PC cells more sensitive to chemotherapy-induced apoptosis	RNA interference	Unknown	[132–134]
Cox-2 oncogene overexpression	40–50	Poor prognostic factor	Celecoxib, apricoxib	Not yet determined; mixed results	[77-80]
EGF receptor overexpression	25–65	Not established	Cetuximab, erlotinib, gefitinib	Erlotinib, beneficial; cetuximab + gefinitib, no benefit	[29,81-83]
VEGF receptor overexpression	90	Poor prognostic factor	Bevacizumab, vandetanib, vatalanib, aflibercept	No benefit	[16,33]
Matrix metalloprotease overexpression	Unknown	Poor prognosis	Marimastat, tanomastat	No benefit	[84-86]
MTOR protein kinase constituitive activation	Unknown	Not established	Temsirolimus, everolimus	Everolimus, no benefit Temsirolimus not yet determined	[87]
<i>p16/INK4</i> tumor suppressor gene	27–96	Inconsistent data	None		[101–105]
Muc-1/Muc-4 glycoprotein overexpression	Unknown	Poor prognostic factor	Muc-1 radiolabelled antibody, antisense Muc-4 RNA	Not yet determined	[106,107]
<i>p53</i> tumor suppressor gene	43–76	Inconsistent data	None		[108-117]
DPC-4/SMAD-4 tumor suppressor gene	50	Inconsistent data	None		[118-125]
BRCA2 tumor suppressor gene	6–17	Associated with familial pancreatic cancer; unknown prognostic significance	None		[126–131]
NF-κB transcription factor constituative activation	Unknown	Associated with resistance to gemcitabine and poor prognosis	Curcurmin, genistein, synthetic compounds	Not yet determined	[94,95, 135–139]

factor:VIIa complex promotes proangiogenic signals in tumors [34]. PCI-27483 has been evaluated in combination with gemcitabine in patients with advanced pancreatic cancer in a Phase I trial. Results were encouraging as of the five evaluable patients, four demonstrated stable disease for at least 4 months [35].

Several gene-therapy strategies are currently under investigation. Recently, an adenovirus mediated herpes simplex virus thymidine synthase gene delivery followed by antiherpetic drug has been tested in pancreatic adenocarcinoma with both promising and safe results. Bloomston et al. reported the results of a Phase I study in which the herpes simplex virus thymidine synthase gene was delivered to patients with locally advanced pancreatic cancer via endoscopic ultrasound or computed tomography-guided injection. Patients were then treated with valacyclovir for 14 days following the adenoviral delivery, followed by 5-FU-based chemoradiation. Although there were a number of grade three and four toxicities observed, two of 12 patients achieved a partial response and the median survival was reported at 12.2 months [36].

One immunotherapy approach currently under clinical investigation utilizes a lethally irradiated allogenic GM-CSF-secreting tumor vaccine following surgery for patients with resected adenocarcinoma of the pancreas. Each immunotherapy treatment was distributed equally among three lymph-node regions. The first treatment was delivered 8-10 weeks after surgical resection, followed by 5-FU-based chemoradiation, and 2-4 additional monthly immunotherapy treatments. One last immunotherapy treatment was delivered 6 months later. Results of a Phase II study in 60 patients demomonstrated that the treatment was well-tolerated and the median disease-free and overall survivals were at 17.3 and 24.8 months, respectively [37]. These results have not demonstrated sustained benefit over time compared with historical controls, however.

In summary, there are multiple promising agents currently under development or in the early phases of clinical investigation that may add therapeutic benefit in the adjuvant or neoadjuvant setting for patients with potentially curative pancreatic cancer, however, the efficacy of these treatment strategies have yet to be proven in the clinical setting.

The possibility of personalized medicine for pancreatic cancer patients

Despite advances in local therapy and aggressive surgery, distant metastases remain a challenge and better systemic treatment regimens, including some targeted therapies are being investigated in attempt to improve survival. At present, there are no proven methods to determine which patients will benefit from aggressive treatment or certain types of therapies. Future steps toward improved selection for personalized treatment strategies using validated prognosticators may improve outcome for patients with adequate performance status to tolerate aggressive regimens.

The use of prognostic and predictive markers associated with pancreatic adenocarcinoma has been a recent topic of investigation that may identify molecular subtypes of pancreatic cancers and provide insight into selection of patients likely to benefit from certain therapies, including surgery. Identification of patients at risk for development of pancreatic cancer may also provide an opportunity for aggressive screening and earlier detection of cancer that is still amenable to surgical resection and improved probability of cure.

Certain risk factors have been associated with the development of pancreatic cancer, including genetic predisposition. Approximately 10% of patients with pancreatic adenocarcinoma have one first-degree relative with pancreatic cancer [38-41]. In addition, known hereditary syndromes found in family clusters have been identified in approximately 3% of cases. Study of family clusters has also identified cancer gene mutations associated with increased incidence of pancreatic cancer, specifically hereditary pancreatitis [42], hereditary colorectal cancer [43], hereditary breast/ovarian cancer [44], familial atypical multiple mole melanoma syndrome [45], Peutz Jeghers Syndrome [46], Fanconi's anemia [47] and cystic fibrosis [48,49]. Genetic testing is currently available for hereditary nonpolyposis colorectal cancer, BRCA2 (associated with hereditary breast and ovarian cancer) and CDKN2A-p16 (associated with familial atypical multiple mole melanoma syndrome) [45], and an opportunity for screening exists in patients with Fanconi's anemia and cystic fibrosis who are usually identified with these genetic abnormalities early in life. Familial clusters of pancreatic cancer are also under investigation and a mutational analysis of tumors has identified a germline mutation (BRCA2 pathway gene, PALB2) associated with familial pancreatic cancer, which may also prove useful in earlier diagnosis in some patients [50]. The Pancreatic Cancer Genetic Epidemiology Consortium [51] is currently collecting prospective data on familial pancreatic kindreds using a whole genome scan and linkage analysis. To date, this program has screened approximately 30,000 cases and has identified approximately 2400 cases with a family history, and further identified three known mutations as well as at least three other potential areas in the genome carrying familial pancreatic genes [52,53]. Although there are data established to identify patients with increased susceptibility for pancreatic cancer, some of which may undergo genetic testing, it remains unclear how to manage individuals based on these findings. As more data

are collected, it is hopeful that uniform consensus on management recommendations may be developed in the near future.

Even if populations at risk for developing pancreatic cancer can be identified and screening for early detection is implemented, histologic diagnosis can be challenging, as tumors are often heterogeneous. Molecular markers may be useful in assisting with diagnosis when cytology is nondiagnostic. One such method of enhancing diagnosis has been explored using miRNAs. miRNAs are small noncoding RNA molecules that control the activity of approximately 30% of protein-coding genes. Deregulation of miRNA has been implicated in pancreatic cancer progression and development. Specific miRNAs upregulated in pancreatic cancer include miR-196a, miR-190, miR-186, miR-221, miR-222, miR-200b, miR-15b and miR-95 [54].

Recently a study was conducted to define global miRNA expression patterns from ductal and ampullary pancreatic adenocarcinoma, and compare with normal pancreas and chronic pancreatitis. This study identified 83 miRNAs that were differentially expressed between adenocarcinoma and normal pancreas and 32 miRNAs differentially expressed between adenocarcinoma and chronic pancreatitis. Of these, a signature of five miRNAs (miR-614, miR-492, miR-622, miR-135b and miR-196) were identified that were able to better discriminate pancreatic and ampullary adenocarcinomas from normal pancreas and chronic pancreatitis [55]. A LASSO classifier was implemented as a mathematical model incorporating previously published data identifying three miRNA signature profiles [56] to further differentiate miRNA profiles associated with cancer. The LASSO classifier using 19 miRNAs was found to separate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis with 98% accuracy [55]. Prospective studies are still needed to determine if this panel of miRNAs is clinically useful for early diagnosis, especially in high-risk populations, possibly rendering more patients candidates for curative resection. It remains unclear whether screening of an entire population for a relatively uncommon cancer using these techniques will be cost effective. Even if only high-risk patients undergo screening, this subset represent only a

Executive summary

- The prognosis for pancreatic cancer remains poor prognosis and prolonged survival is achieved only by resection with adequate margin status. Effective systemic therapy regimens with or without radiation therapy are clearly needed, although the optimal treatment paradigm is not clearly defined.
- Eagerly awaited results from the Radiation Therapy Oncology Group 0848 may help clarify whether or not radiation in addition to chemotherapy is beneficial in the adjuvant setting.
- The Radiation Therapy Oncology Group 0848 and American College of Surgeons Z5041 may also determine whether erlotinib provides additional benefit when used as adjuvant therapy as it does in the metastatic or locally advanced disease setting.
- ECOG 2204 has failed to provide evidence that the addition of targeted agents (bevicizumab and cetuximab) to gemcitabine offers an advantage following surgery. As additional targeted agents are being developed and tested for efficacy in patients with metastatic disease, it remains hopeful that these agents will also prove beneficial in the neoadjuvant or adjuvant setting.
- There is a strong rationale for a neoadjuvant approach, since a substantial percentage of patients present with nonmetastatic, locally advanced disease not amenable to initial R0 surgical resection. Emerging data suggests that neoadjuvant chemoradiation is feasible and results in improved margin-negative status, which is associated with good survival for those that ultimately are eligible for resection. We await the results from the Interdisciplinary Working Group of Gastrointestinal Tumors trial, which may help determine whether there is any benefit from neoadjuvant chemoradiation in addition to adjuvant chemotherapy for patients with resectable disease. Combination cytotoxic and targeted systemic treatment strategies are also being evaluated for use in the preoperative setting.
- Since not all patients with early-stage pancreatic cancer will benefit from aggressive treatment, the development of predictive and prognostic tools are being evaluated to identify populations likely to respond. Also, screening populations at increased risk for pancreatic cancer may help to diagnose cases early enough to undergo curative therapy. It is possible that the development of effective patient selection tools may lead to personalized treatment strategies that will predict which patients are likely to benefit from certain therapies, improve outcome for subsets of patients and allow other patients to avoid treatment that will not be of benefit.
- Epidemiologic and genetic research has established that there are individuals at risk for developing pancreatic cancer. Genetic susceptibility appears to be heterogeneous and currently limited genetic testing is available. Risk stratification is possible, but screening for pancreatic cancer remains a controversial subject for future research.
- Earlier histologic diagnoses may be facilitated by recently identified miRNA expression signatures. Although earlier detection may render a higher proportion of patients amenable to curative resection, prospective studies are needed to evaluate the clinical utility of this technique for early diagnosis.
- Nomograms using clinicopathologic and molecular biomarker variables are being proposed to improve patient selection for aggressive therapies, but potential clinical application is yet to be validated.

small percentage of the pancreatic cancer population, as the majority of cases are not associated with known genetic mutations.

Even if pancreatic cancer screening becomes feasible and cost effective, it must be recognized that not all cases may benefit from the aggressive treatment and early intervention may not lead to a survival benefit for all patients. Approximately 80% of patients who undergo curative resection will die of pancreatic cancer, many within 6 months of surgery. For this reason, it would be attractive to identify subsets of patients who would be likely to respond to particular therapies that may help direct treatments leading to the best possible treatment strategy for an individual patient. Identification of predictive and prognostic biomarkers is being evaluated to that end. Recently, a prognostic nomogram for resectable pancreatic cancer was proposed in which biologically relevant molecules were evaluated as prognostic indicators in patients with resected pancreatic adenocarcinomas. Aberrant S100A4 calcium-binding protein expression was correlated with survival in 372 patients undergoing curative resection [57]. High S100A2 [58] and S100A4 [57] expression from operative specimens were found to be an independent poor prognostic factors. Aberrant expression of these proteins and tumor size, were stratified into three distinct prognostic groups and integrated into a proposed nomogram for the selection of patients who were predicted to benefit from aggressive surgery. Since measurements of S100A4 and S100A2 were obtained from operative specimens, the authors demonstrated that samples analyzed with quantitative RT-PCR on tissue obtained from endoscopic ultrasound-guided FNA prior to surgery correlated well with amounts of S100A4 and S100A2 found in resected specimens [57]. Although the development and application of such nomograms in routine clinical practice has the potential to improve patient selection for aggressive therapies and, ultimately, improve outcome for selected subsets of patients, the potential clinical application is yet to be validated.

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