Adjuvant therapy for pancreas cancer in an era of value based cancer care

Daniel H. Ahn[a], **Terence M. Williams**[a], **Daniel A. Goldstein**[b], **Bassel El-Rayes**[b], and **Tanios Bekaii-Saab**[a,*]

[a]The Ohio State University Wexner Medical Center, 310 W. 10th Ave, Columbus, OH, United States

[b]Winship Cancer Institute, Emory University, 1365-C Clifton Rd NE, Atlanta, GA, United States

Abstract

In resected pancreas cancer, adjuvant therapy improves outcomes and is considered the standard of care for patients who recover sufficiently post operatively. Chemotherapy or combined chemotherapy and radiation therapy (chemoradiation; CRT) are strategies used in the adjuvant setting. However, there is a lack of evidence to suggest whether the addition of RT to chemotherapy translates to an improvement in clinical outcomes. This is true even when accounting for the subset of patients with a higher risk for recurrence, such as those with R1 and lymph node positive disease. When considering the direct and indirect costs, impact on quality of life and questionable added clinical benefit, the true "net health benefit" from added RT to chemotherapy becomes more uncertain. Future directions, including the utilization of modern RT, integration of novel therapies, and intensifying chemotherapy regimens may improve outcomes in resected pancreas cancer.

Keywords

Pancreatic cancer; Adjuvant therapy; Chemotherapy; Chemoradiation; Net health benefit

Introduction

Pancreas cancer remains the fourth leading cause of cancer deaths in the United States with a dismal prognosis and a 5-year overall survival of <5% across all stages [1]. In 2014, there were approximately 46,420 new cases of pancreatic cancer with only 9% with localized disease [2]. Patients with localized disease that is deemed resectable will undergo a pancreaticoduodenectomy (Whipple procedure) or a distal pancreatectomy with the intent to achieve a complete (R0) resection [3,4]. Despite a curative intent, most patients will eventually succumb to recurrent disease [5]. Adjuvant therapy improves relapse free and

*Corresponding author at: A454, Starling Loving Hall, 320 West 10th Avenue, Columbus, OH 43221, United States. Tel.: +1 614 293 9863. Tanios.saab@osumc.edu (T. Bekaii-Saab).

overall survival following resection and the administration of adjuvant treatment is considered the standard of care for patients who recover sufficiently within 4–12 weeks post operatively [6]. While the role of chemotherapy (CT) has been established in randomized trials, there is no consensus on the role of combined chemotherapy and radiation (chemoradiation; CRT) due to inconsistent results from trials. Herein, we provide an overview on the role of adjuvant therapy in pancreatic cancer, a cost analysis based on the various modalities and an assessment of future directions integrating novel therapeutic strategies.

Adjuvant therapy following resection

The role of adjuvant chemotherapy in resected pancreatic cancer

Numerous studies investigating the use of adjuvant chemotherapy have shown a significant improvement in clinical outcomes in comparison to observation. CONKO-001, which investigated the use of adjuvant gemcitabine versus observation, showed a significant improvement in disease-free survival of 13.4 months in patients who received adjuvant chemotherapy vs. 6.9 months in the observation group [7]. This finding was consistent across all subgroups, including patients with node-positive disease and microscopically positive margin (R1) resections. Updated results from this trial revealed a significant overall survival benefit for adjuvant gemcitabine, with a median overall survival of 22.8 months in the gemcitabine group vs. 20.2 months (HR 0.76, $p = 0.01$) in the observation group [8]. Results from a smaller phase III Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer trial resulted in similar findings to CONKO-001 [9]. Another large study, ESPAC-3 compared the benefits of adjuvant gemcitabine, bolus 5-fluorouracil and leucovorin (5-FU/LV) or observation in resected pancreatic adenocarcinoma (Table 1) [10]. The observation arm was removed from the design following the results of ESPAC-1 [11], which demonstrated that chemotherapy (5-FU/LV) was superior to observation and CRT. There was a comparable overall therapeutic benefit for the 2 chemotherapy arms (23.0 vs 23.6 months in the 5-FU/LV and gemcitabine arms) with a more favorable toxicity profile associated with gemcitabine (Table 1). Based on these studies, there appears to be a clear clinical benefit for patients with resected pancreatic adenocarcinoma receiving adjuvant chemotherapy regardless of nodal and resection status.

The role of adjuvant chemoradiation therapy in resected pancreatic cancer

Earlier randomized clinical trials investigating the role of combined chemotherapy and radiation (CRT) have been largely under-powered with flawed designs and mixed results. Nonetheless, CRT had been recommended as a treatment option in the adjuvant setting. The historical precedent for adjuvant chemoradiotherapy stems from the results of the Gastrointestinal Tumor Study Group (GITSG) 9173 trial published in 1987, which demonstrated a 9-month survival benefit for adjuvant fluorouracil (5-FU) based chemoradiation over observation in resected pancreatic cancers (20 months in the chemoradiation group versus 11 months in the observation arm) [12]. The study was underpowered with 43 patients included in the analysis. An archaic 2D radiation technique was utilized, where patients received two 20 Gy courses (total 40 Gy) separated by 2 weeks, with large treatment radiation fields (covered residual pancreas, pancreatic bed, and at-risk

lymph node regions). Subsequent trials attempting to confirm the benefit of adjuvant chemoradiation were not able to reproduce similar findings (Table 1). In 1999, the EORTC study, which compared adjuvant chemoradiotherapy to observation in pancreas cancer, showed a non-statistically significant trend towards a survival benefit [13]. Similarly to GITSG, a split course of radiation (2×20 Gy separated by two weeks, total 40 Gy) was administered to patients, utilizing 3D radiation technique with tissue limits to the liver, kidneys and spine. A subset analysis did suggest a trend towards survival benefit in patients with pancreatic head tumors only, with a 2 year overall survival of 34% versus 26% in the observation group ($p = 0.099$) [13].

More recently, published in 2008, RTOG 9704, a phase III randomized controlled trial, investigated the role of adjuvant concurrent 5-fluorouracil (5-FU) and radiation, sandwiched between either 5-fluorouracil (5-FU) or gemcitabine. This was the first modern radiation therapy randomized phase III trial, where standardized guidelines were given in regards to radiation fields, dosing and targets. RT was conducted by 3D technique (no IMRT), administering 45 Gy with 1.8 Gy fractions to all targets, followed by a boost of 5.4 Gy (over 3 fractions) to the tumor bed, for a total of 50.4 Gy. The results of this study showed no major differences in patient outcomes between gemcitabine and 5-FU in the adjuvant setting, except in patients with tumors in the head of the pancreas where gemcitabine seemed to be of further benefit (20.5 versus 16.9 months). Despite the use of modern radiation techniques and quality control measures, the locoregional recurrence rate remained relatively high in both treatment arms (Table 1) [14]. Additionally, grade 3 or 4 toxicities were high in both treatment arms, which were 62 and 79 percent in the 5-FU and gemcitabine arm. The design of RTOG 9704 was to compare two different regimens in the adjuvant setting, but failed to address the potential added role for radiation therapy in resected pancreatic cancer. Therefore findings from this study did not address the role of adjuvant chemo-radiation therapy in this disease.

Chemotherapy (CT) versus chemo-radiation therapy (CRT): What should the standard be?

The role of adjuvant CT is well established in patients with resected pancreas cancer. However, there is a noticeable paucity of studies that help us understand the added role of radiation (as in CRT) to CT in resected pancreas cancer. One such study is ESPAC-1, a phase III randomized control trial that attempted to address the role of radiation therapy in resected pancreatic cancer by comparing the overall benefits of CRT vs. CT. The trial used a two-by-two factorial design in which patients were randomized to receive CRT or CT, observation, or both treatments. RT was administered with either 2D or 3D technique. ESPAC-1 showed a survival benefit for adjuvant CT in comparison to concurrent CRT, 20.1 versus 15.9 months, respectively (Table 1). Concurrent CRT proved to be detrimental with higher recurrence rates (12 month recurrent rate 46 versus 55 percent), shorter recurrence-free survival (10.7 versus 15.2 months) and increased toxicity (6 versus 4 percent) in comparison to CT [11]. The trial had many limitations including a high rate of non-adherence (lack of uniformity of treatments or absence of treatments in 30% of the patients), the allowance of background CRT or CT, an unconventional study design, and the use of suboptimal radiation therapy techniques and quality assurance [11]. Thus, while this study

confirmed the benefits of adjuvant CT, it did not demonstrate any benefit from CRT in the adjuvant setting.

In the absence of results from well-designed prospective clinical trials, we are limited to cross-study historical comparisons while acknowledging the limitations of such data. Table 1 summarizes results from prospective randomized trials with postoperative adjuvant strategies in pancreatic cancer. The data in the table consistently suggest that the addition of CRT in the adjuvant setting may not enhance the benefits observed with CT alone. Additionally, in a disease process where patients experience a significant burden of symptoms and likely spend an average of a quarter of their remaining lifetime on adjuvant therapy, toxicities (and cost) should become an important consideration. In RTOG 9704, 58% of patients experienced grade 3 or higher non-hematologic toxicities in the gemcitabine arm while only 3% did so in CONKO-001. While RTOG 9704 did not include a quality of life (QOL) analysis, results from CONKO-001 suggest no detriment in QOL and an increase in weight with the administration of single agent gemcitabine [7,14].

To date, randomized trials investigating the role of adjuvant CRT have not demonstrated any added benefit in comparison to CT or observation. In the setting of a disease such as pancreas cancer whose outcomes are predominantly driven by early metastatic dissemination, the role of additional loco-regional therapy (i.e. CRT) remains unclear. One strategy includes examining the role of CRT following a reasonable period of exposure to systemic therapy in patients who remain disease-free. This strategy is being addressed in an ongoing phase III randomized control trial examining the role of CRT in patients without evidence of recurrent disease following the completion of 5 cycles of systemic gemcitabine (RTOG 0848, Clinical Trials.gov NCT01013649). Patients without evidence of recurrence after completion of the planned 5 cycles will be randomized to receive one additional cycle of systemic gemcitabine or 1 cycle of chemotherapy followed by CRT (either capecitabine or 5-FU; 50.4 Gy in 28 fractions of 1.8 Gy). It is possible that further incorporating more aggressive systemic approaches may help to better establish the role of loco-regional therapies. Strategies examining the role of FOLFIRI-NOX or gemcitabine/nab-paclitaxel vs. gemcitabine are underway, which we will discuss in detail below.

Do certain defined subgroups of patients with resected pancreas cancer benefit from the addition of CRT?

Do patients with microscopic residual disease (R1) following resection benefit from the addition of adjuvant CRT?—One assumption being made about CRT was that patients with microscopic residual disease (R1) following resection would derive benefit from the addition of RT. The rationale for this hypothesis is that radiation therapy to the surgical bed might allow for "sterilizing" the area of residual microscopic disease and thus delaying or preventing localized recurrent disease. An in depth analysis into the results of RTOG 9704 demonstrates a loco-regional control rate that is no different than other studies, with CT alone such as CONKO-001 (Table 1). Based on the high R1 resection rates in RTOG 9704 (35%), proponents of CRT have suggested a potential benefit in this subset of patients. However, it is notable that approximately 25% of the patients included in this study had an unknown resection status, making an accurate description of the breakdown of

margin resection status difficult to interpret [14]. In contrast, in CONKO-001, 100% of patients had their resection margin status known [7]. Moreover, patients with a positive surgical margin in both CONKO-001 and RTOG 9704 seem to derive a similar benefit from therapy when compared to those with negative or unknown surgical margins. This suggests that the addition of CRT does not have a greater impact on local control when compared to the effects of full dose systemic therapy.

Do patients with lymph node positive disease benefit from adjuvant CRT?—In contrast to margin resection status, the presence of lymph node involvement appears to be a poor prognostic factor in both CONKO-001 and RTOG 9704 [7,14]. A recent retrospective analysis of resected pancreatic cancer patients confirmed that LN involvement was a significant factor associated with poor survival, while resection status is only a prognostic factor in tumors where there is absence of lymph node involvement [15]. Initial, limited datasets from retrospective analyses suggested that patients with LN involvement demonstrated a clinical benefit from adjuvant CRT as compared to no therapy [16–18].

Our group recently examined the role of potential as related to risk factors associated with survival in patients with recurrent pancreatic cancer following resection. Our study suggested that the absence of lymph node involvement was associated with a significant survival benefit when compared to those with lymph node involvement (25.6 vs. 10.6 months). Interestingly, lymph node involvement was associated with early recurrence (6 months) and patterns of disseminated disease at the time of recurrence [19]. This may help explain the lack of benefit from CRT in this group of patients, where recurrent pancreatic cancer typically manifests with diffuse, disseminated disease. Collectively, these findings suggest that improving strategies for systemic control should take priority in resected pancreatic cancer.

Adjuvant strategies in pancreas cancer: assessing the value of treatment options

Given the lack of evidence of benefit of adjuvant CRT in comparison to CT in resected pancreatic cancer, we conducted a cost analysis to compare the two treatment modalities. A recent ASCO initiative confirmed a shift in paradigm to determine a "net health benefit" (NHB) that takes into consideration the cost of treatment, indirect costs (related to toxicities, supportive care costs, quality of life) and clinical benefit [20]. The value of NHB in cross study comparisons is still unknown, however, our collaborating group has published multiple studies assessing the value of care for emerging and established therapies [21–27]. To estimate the unit price of each drug, we used the 2014 average sales price by the Centers for Medicare and Medicaid services (CMS) [28]. To calculate chemotherapy doses, we used a body surface area of 1.86 m^2 based on mean US values [29]. Administration costs, radiation costs, and physician visits were calculated using Current Procedure Terminology (CPT) codes according to the Medicare physician fee schedule for 2014 (Table 2) [30]. Using the CONKO-001 and RTOG 9704 studies, we calculated the cost (including cost of drugs, administration and clinic visits) of (1) six months of adjuvant gemcitabine, versus (2) RTOG 9704-type treatment: the cost of two months of adjuvant gemcitabine and two months of concurrent 5-FU and radiation followed by two months of gemcitabine (Table 2).

The cost of adjuvant chemotherapy was approximately $2,989.11 per patient for the total course of 6 cycles, in comparison to $18,078.79 per patient for concurrent CRT. Thus, the addition of CRT results in a net difference of $15,089.68 per patient. With 46,420 new cases of pancreas cancer per year in the U.S., including 9% being localized and potential candidates for adjuvant therapy, the annual cost for adding CRT is approximately $75.5 million annually in comparison to $12.5 million for CT alone, which amounts to a difference of approximately $63 million per year. These cost differences are likely to be higher since they do not take into account treatment-related complications, where grade 3 and 4 toxicities were approximately 4% in CONKO-001 in historical comparison to 79.5% in the gemcitabine arm of RTOG 9704 [7,14]. Additionally, and acknowledging the limitations of cross-study comparisons between clinical trials, adjuvant CT and CRT do show very similar survival benefits in the adjuvant setting in pancreas cancer (Table 1).

In summary, it is difficult to justify the routine utilization of CRT in the adjuvant setting in pancreas cancer given the lack of added historical benefit, the added direct costs, the likely added indirect costs (including risk of toxicities) and the possible impact on quality of life over CT alone [8,14]. The measure of determining true value in the decision-making process in selecting adjuvant therapies should be strongly considered and should also be integrated prospectively into the future development and approval processes of novel therapeutic modalities in pancreas cancer.

Future directions: strategies to improve outcome in adjuvant therapy in pancreas cancer

Despite advances in pancreas cancer treatment, patient outcomes in resected disease remain dismal. Thus, novel strategies and agents continue to be urgently needed in the adjuvant setting. Herein, we provide a brief overview of strategies that are being investigated in the adjuvant setting.

The evolving landscape of radiation therapy (RT)—Standard CRT in the adjuvant setting consists of five to six weeks concurrent CT (e.g. 5-FU) with standard 50.4 Gy over 28 fractions as delivered in RTOG 9704, or the ongoing successor trial RTOG 0848. Recognizing that prolonged courses of radiation do not sufficiently prevent loco-regional and disseminated recurrence, studies have attempted to shorten courses and intensify radiotherapy dosing with techniques including intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). SBRT delivers ablative doses of highly conformal radiation to the gross tumor volume, while minimizing radiation exposure and collateral damage to the normal, surrounding tissues, over 3–5 days. [31]. The high biologically effective doses and shorter overall treatment time with SBRT may provide advantages in local control, disease outcomes, quality of life, and cost-effectiveness, and may represent an increasingly common radiation treatment option in the future for centers with expertise and quality-safety programs in place for SBRT. Because of the shorter overall treatment time compared to standard fractionated therapy, patients receiving SBRT are able to resume systemic therapies sooner allowing for both loco-regional and systemic control. Several studies, in locally advanced pancreatic cancer have demonstrated the feasibility, safety, and efficacy of SBRT, with similar clinical outcomes and acceptable GI toxicities that are seen with conventional chemoradiation. [31–36]. Limitations of SBRT in the adjuvant

setting relates to the smaller fields that may limit coverage to less than the surgical bed. While SBRT has not been explored in the adjuvant setting, based on the safety and efficacy data seen with locally advanced pancreas cancer, the benefits of SBRT will hopefully translate to the treatment of resected pancreas cancer in the adjuvant setting. One of the challenges of SBRT in the adjuvant setting would be toxicity related to having normal tissues within the radiated field. Thus, if this approach is to be considered, prospective clinical trials need to establish the safety of this approach. Further studies are needed to confirm the potential clinical benefit of SBRT given all the above and its lower cost compared to traditional radiation techniques (Table 2).

Additional local therapies of interest include proton radiotherapy with its potential advantages in sparing normal tissue beyond the tumor target given the physical properties of protons in tissue, which allow for a steep dose fall-off. Proton radiation is increasingly being tested in gastrointestinal malignancies, including pancreatic cancer. There are multiple small trials testing proton therapy in the neoadjuvant, borderline resectable, locally advanced, and adjuvant settings for pancreatic cancer. Some trials have been reported already with favorable preliminary results, including low rates of GI toxicity [37–39]. The current cost of proton therapy however remains a significant concern.

Taken together IMRT, SBRT and proton therapy may represent a practice-changing and novel paradigm for radiotherapy in the management of pancreatic cancer if future randomized trials suggest a favorable cost-benefit ratio.

Incorporating intensified chemotherapy regimens

Given the observed benefits seen with disease control in the more advanced setting, the role of intensified chemotherapy regimens such as FOLFIRINOX and gemcitabine/nab-paclitaxel are being explored in the adjuvant setting (Table 3). Current ongoing phase III studies, PRODIGE24/ACCORD24 (NCT01526135) and APACT (NCT01964430) are investigating the role of adjuvant FOL-FIRINOX and gemcitabine/nab-paclitaxel respectively, in comparison to gemcitabine alone. Another phase III study, ESPAC-4 (ISRCTN96397434), investigating the role of adjuvant capecitabine plus gemcitabine in comparison to gemcitabine has completed accrual.

Moreover, these recent advances in systemic chemotherapy have allowed us to incorporate more aggressive treatment regimens into strategies to improve surgical outcomes in patients with advanced but localized disease. The incorporation of intensified chemotherapy regimens such FOLFIRINOX or gemcitabine/nab-paclitaxel allows for systemic control while improving the chances for R0 resection [40,41]. This strategy has been investigated in several small studies, including from our institution, where the majority of patients with borderline resectable or locally advanced pancreatic cancer who received neoadjuvant FOLFIRINOX with or without radiation were able to undergo successful resection of their disease [42–45].

Moving these more aggressive strategies into the neoadjuvant setting for the clearly resectable patients may allow to further enhancing the likelihood of R0 resection, to improve

the selection of patients who will benefit from surgery and to allow for a more rational incorporation of RT strategies.

Molecular targeted signal pathway inhibitors

Previous studies that have investigated molecularly targeted agents have resulted in disappointing results. The only molecular targeted agent in use in pancreatic cancer is erlotinib, which was approved in 2007 based on a phase III controlled trial showing a very modest benefit when combined to gemcitabine in the advanced setting [46]. Based on these findings, studies assessing whether the clinical benefit seen with erlotinib would translate in the adjuvant setting or in locally advanced pancreatic cancer. CONKO-005 investigated the role of erlotinib added to gemcitabine vs. gemcitabine alone in R0 resected pancreas cancer, where LAP07, assessed the role of erlotinib added to gemcitabine and CRT vs. gemcitabine and CRT in locally advanced pancreatic cancer [47] [48]. Unfortunately, the results for both studies failed to show an added benefit with the biologic agent. In CONKO-005, no significant difference in clinical efficacy was seen with the addition of erlotinib, with similar patient outcomes in median disease free survival (11.6 months in both arms) and median overall survival (24.6 versus 26.5 months) (Table 1). LAP07 demonstrated a detrimental effect with the addition of erlotinib, where patients who received the combination of erlotinib and gemcitabine had worse median overall survival in comparison to gemcitabine (11.9 versus 13.6 at the second interim analysis. Collectively, these results suggest the absence of convincing evidence to suggest erlotinib has a role in the treatment of pancreas cancer. Nonetheless, the role of novel signal transduction inhibitors remains an area of interest in the adjuvant treatment [49,50].

The emerging role of immunotherapeutic approaches

Checkpoint inhibitors—As opposed to other solid tumor malignancies, the role for immunotherapy in pancreas cancer remains undefined. Pancreatic cancer has been considered a non-immunogenic malignancy, largely in part due to its immunosuppressive microenvironment. The interaction and communication between the dense stroma and pancreas cancer cells leads to the production of inflammatory cells (fibroblasts and pancreatic stellate cells) that inhibit cytotoxic T and NK cells through immunomodulatory factors (interleukin-6) and myeloid-derived suppressor cells [51,52]. As a result, CD4 effector T cells are not representative in its histopathology [53,54] and therapeutic approaches focusing on overcoming T-cell immunologic checkpoints with anti-CTLA-4 and anti-PD1 monoclonal antibodies have not demonstrated any meaningful clinical activity in pancreatic cancer [55,56].

Several strategies are proposed to overcome the resistance and improve the efficacy of immune checkpoint inhibitors, including in the adjuvant setting. One approach includes a multi-prong approach, combining cytotoxic therapy with checkpoint inhibitors, where the initial insult from chemotherapy or radiation will expose tumor antigens and cause upregulation of PDL-1, and subsequent blockade with immune checkpoint inhibitors can enhance T cell effector function and improve locoregional and distant disease control [57]. Studies utilizing this adjuvant combination strategy in the resected pancreas cancer are currently under consideration and in development.

Vaccine therapies—With the molecular identification of human tumor antigens, anti-tumor vaccines are emerging with increased interest as an alternative immunotherapeutic strategy in pancreas cancer. Exposure to tumor-specific antigens sensitizes the immune system to identify cancer cells as being foreign and potentially eliminating pancreas cancer's ability to evade the immune system. Several types of vaccinations are under investigation in pancreas cancer, (including whole-cell, DNA and vaccines with microorganisms), with several in the adjuvant setting.

Algenpantucel-L (NewLink Genetics Corporation, Ames, Iowa) is a whole-cell vaccine made of two human pancreatic cancer cell lines (HAPa-1, HAPa-2) that on injection, induces an immune response that parallels the hyperacute rejection that can occur with post-organ transplantation. An open-label phase II study examining the combination therapy of algenpantucel-L with adjuvant gemcitabine and 5-FU/radiation in resected pancreatic cancer demonstrated promising 1-year disease-free survival and overall survival rates (62% and 86%, respectively) [58]. On this basis, the IMPRESS trial, a phase III study was recently completed, evaluating standard adjuvant chemotherapy or CRT with or without algenpantucel-L in resected pancreas cancer (ClinicalTrials.gov NCT01072981), and its results should be presented by the end of the year.

Another class of vaccines are based on tarmogens® which are whole, heat-killed recombinant *Saccharomyces cerevisiae* yeast engineered to express target proteins, which stimulate immune responses against malignant cells expressing the target protein(s) [59–61]. GI-4000 (GlobeImmune Inc., Louisville, Colorado) is a vaccine consisting of four different yeast-based immunotherapy products that target the seven most common *RAS* mutations at codons 12 and 61. Given the prevalence and central role of *RAS* activation in pancreatic cancer proliferation, a phase II randomized, placebo controlled trial examining the combination GI-4000 with adjuvant gemcitabine in *RAS* mutated resected pancreas cancer was recently completed [62]. While the findings did not demonstrate an overall survival benefit for all patients, patients with R1 resection who were treated with GI-4000 experienced a survival benefit and increase in *RAS*-specific T cell responses. These findings suggest that in the R1 resected group, patients may demonstrate a certain proteomic signature which would allow them receive a clinical benefit from GI-4000 [62].

While these recent findings have led to a renewed interest in the immunotherapeutic approaches in adjuvant therapy for resected pancreas cancer, further confirmatory studies are needed, and are currently in development.

Tailoring personalized therapy—Personalization of therapy or "precision medicine" is an increasingly important emerging strategy in managing cancer. Prognostic biomarkers that predict outcome following surgical resection regardless of therapy may have significant implications for patient and physician decisions. Furthermore, predictive biomarkers that can estimate response to a particular therapy can potentially be utilized to determine whether a patient should one therapy versus an alternative one. For example, human equilibrative nucleoside transporter (hENT1), a nucleoside transporter, was recently been shown to predict benefit from gemcitabine therapy in the ESPAC-3 trial, which randomized patients post-operatively to gemcitabine or 5-fluorouracil/folinic acid. In the gemcitabine arm,

patients with high hENT1 expression by immunohistochemistry had a median survival of 26.2 versus 17.1 months, which remained significant on multivariate analysis [63]. These data suggest that patients with low hENT1 expression may be considered for alternative therapy such as 5-fluorouracil. However, factors, including disease stage and antibody may affect hENT1 levels, and its role as a predictive marker for response should be prospectively investigated in future studies.

Another example of a potential prognostic and predictive bio-marker in pancreatic cancer is the secreted protein acidic and rich in cysteine (SPARC)/osteonectin which is a cell matrix protein that modulates migration, proliferation, and angiogenesis. A number of reports have demonstrated that SPARC stromal and tumor overexpression portends a worse prognosis [64,65]. Furthermore, initial data suggested that SPARC, by virtue of binding albumin, might predict benefit from gemcitabine/nab-paclitaxel [66]. Unfortunately, a recent analysis of SPARC levels in tumor tissue from the MPACT trial that established gemcitabine/nab-paclitaxel as a new standard of care in advanced or metastatic pancreas cancer did not corroborate this finding [67]. Most recently, high SPARC expression in the stroma and tumor of patients on the CONKO-001 trial both predicted worse patient survival, which was restricted to the patients randomized to the gemcitabine arm. Surprisingly, this finding suggests that SPARC expression may serve as a predictive biomarker for adjuvant gemcitabine, but needs further validation in prospective trials [68].

Another potential biomarker with potential clinical applicability is SMAD4/DPC4 which is a gene commonly inactivated in pancreatic cancer that is associated with poor prognosis when inactivated [69,70]. Interestingly, in a rapid autopsy series from Johns Hopkins, patterns of failure indicated that 30% of patients died of locally destructive pancreatic cancer, whereas 70% succumbed to widespread metastases, suggesting that local control is still important. SMAD4 inactivation was associated with the widespread metastatic phenotype, compared to the locally destructive phenotype [71]. Other studies attempting to validate SMAD4 as a biomarker in pancreatic cancer have shown mixed results [72,73]. Thus, prospective validation of SMAD4 is warranted, and is being investigated in ongoing trials including RTOG 1201 (NCT01921751), a phase II trial investigating the role of added chemoradiation to chemotherapy in patients with locally advanced pancreatic adenocarcinoma. Correlative studies include examining the role of SMAD4 as a marker for disease progression and therapy response. Ultimately, identifying a molecular signature which predicts for a more locally aggressive disease recurrence pattern after resection bears significant implications for deciding which patients might derive the most benefit from more aggressive local therapies such as radiation.

Conclusions

In conclusion, it is difficult to justify the routine utilization of CRT in the adjuvant setting in pancreas cancer given the lack of added benefit, the added direct costs, the likely added indirect costs (including risk of toxicities) and the possible impact on quality of life over CT alone. Investigational studies that are underway will help elucidate the role of radiation (including novel modalities such as SBRT or proton therapy), immunotherapies and other tailored approaches with the hope to improve outcomes of patients in this desperate disease.

Finally, the value of existing and emerging approaches should be fully integrated into our clinical decision making tree.

References

1. Weir HK, Thun MJ, Hankey BF, Ries LA, Howe HL, Wingo PA, et al. Annual report to the nation on the status of cancer, 1975–2000, featuring the uses of surveillance data for cancer prevention and control. J Natl Cancer Inst. 2003; 95:1276–99. [PubMed: 12953083]

2. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014; 64:9–29. [PubMed: 24399786]

3. Cameron JL, Riall TS, Coleman J, Belcher KA. One thousand consecutive pancreaticoduodenectomies. Ann Surg. 2006; 244:10–5. [PubMed: 16794383]

4. Lim JE, Chien MW, Earle CC. Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients. Ann Surg. 2003; 237:74–85. [PubMed: 12496533]

5. Wagner M, Redaelli C, Lietz M, Seiler CA, Friess H, Buchler MW. Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg. 2004; 91:586–94. [PubMed: 15122610]

6. National Comprehensive Cancer Network. [Accessed November 10, 2014] Pancreatic Adenocarcinoma. http://nccn.org

7. Oettle H, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA, J Am Med Assoc. 2007; 297:267–77.

8. Oettle H, Neuhaus P, Hochhaus A, Hartmann JT, Gellert K, Ridwelski K, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA, J Am Med Assoc. 2013; 310:1473–81.

9. Ueno H, Kosuge T, Matsuyama Y, Yamamoto J, Nakao A, Egawa S, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. Br J Cancer. 2009; 101:908–15. [PubMed: 19690548]

10. Neoptolemos JP, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA, J Am Med Assoc. 2010; 304:1073–81.

11. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. New Engl J Med. 2004; 350:1200–10. [PubMed: 15028824]

12. Gastrointestinal Tumor Study Group. Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Cancer. 1987; 59:2006–10. [PubMed: 3567862]

13. Klinkenbijl JH, Jeekel J, Sahmoud T, van Pel R, Couvreur ML, Veenhof CH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999; 230:776–82. discussion 82–4. [PubMed: 10615932]

14. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA, J Am Med Assoc. 2008; 299:1019–26.

15. Tummala P, Howard T, Agarwal B. Dramatic survival benefit related to R0 resection of pancreatic adenocarcinoma in patients with tumor $\leq$25 mm in size and $\leq$1 involved lymph nodes. Clin Transl Gastroenterol. 2013; 4:e33. [PubMed: 23515131]

16. Hsu CC, Herman JM, Corsini MM, Winter JM, Callister MD, Haddock MG, et al. Adjuvant chemoradiation for pancreatic adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. Ann Surg Oncol. 2010; 17:981–90. [PubMed: 20087786]

17. Corsini MM, Miller RC, Haddock MG, Donohue JH, Farnell MB, Nagorney DM, et al. Adjuvant radiotherapy and chemotherapy for pancreatic carcinoma: the Mayo Clinic experience (1975–2005). J Clin Oncol. 2008; 26:3511–6. [PubMed: 18640932]

18. Herman JM, Swartz MJ, Hsu CC, Winter J, Pawlik TM, Sugar E, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: results of a large, prospectively collected database at the Johns Hopkins Hospital. J Clin Oncol. 2008; 26:3503–10. [PubMed: 18640931]

19. Ahn, D.; Ahn, C.; Krishna, K.; Krishna, S.; Muscarella, P.; Bloomston, M., et al. Risk factors associated with overall survival in pancreatic adenocarcinoma following curative resection. Abstract #437, 2015 GI ASCO Symposium;

20. Schnipper LE, Davidson NE, Wollins DS, Tyne C, Blayney DW, Blum D, et al. American society of clinical oncology statement: a conceptual framework to assess the value of cancer treatment options. J Clin Oncol. 2015

21. Goldstein DA, Chen Q, Ayer T, Howard DH, Lipscomb J, El-Rayes BF, et al. First-and second-line bevacizumab in addition to chemotherapy for metastatic colorectal cancer: a United States-based cost-effectiveness analysis. J Clin Oncol. 2015; 33:1112–8. [PubMed: 25691669]

22. Goldstein DA, Chen Q, Ayer T, Howard DH, Lipscomb J, Harvey RD, et al. Cost effectiveness analysis of pharmacokinetically-guided 5-fluorouracil in FOLFOX chemotherapy for metastatic colorectal cancer. Clin Colorectal Cancer. 2014; 13:219–25. [PubMed: 25306485]

23. Goldstein DA, Chen Q, Ayer T, Howard DH, Lipscomb J, Ramalingam SS, et al. Necitumumab in metastatic squamous cell lung cancer: establishing a value-based cost. JAMA Oncol. 2015

24. Goldstein DA, Ahmad BB, Chen Q, Ayer T, Howard DH, Lipscomb J, et al. Cost-effectiveness analysis of regorafenib for metastatic colorectal cancer. J Clin Oncol. 2015

25. Goldstein DA, Zeichner SB, Bartnik CM, Neustadter E, Flowers CR. Metastatic colorectal cancer: a systematic review of the value of current therapies. Clin Colorectal Cancer. 2015

26. Goldstein DA, Shaib WL, Flowers CR. Costs and effectiveness of genomic testing in the management of colorectal cancer. Oncology (Williston Park). 2015; 29:175–83. [PubMed: 25783977]

27. Goldstein DA, El-Rayes BF. Considering efficacy and cost, where does ramucirumab fit in the management of metastatic colorectal cancer? Oncologist. 2015; 20:981–2. [PubMed: 26265225]

28. Natarajan N, Putnam W, Van Aarsen K, Beverley Lawson K, Burge F. Adherence to antihypertensive medications among family practice patients with diabetes mellitus and hypertension. Canadian Family Physician Medecin de Famille Canadien. 2013; 59:e93–e100. [PubMed: 23418264]

29. Gaudet MM, Kuchenbaecker KB, Vijai J, Klein RJ, Kirchhoff T, McGuffog L, et al. Identification of a BRCA2-specific modifier locus at 6p24 related to breast cancer risk. PLoS Genet. 2013; 9:e1003173. [PubMed: 23544012]

30. [Accessed: July 1] Medicare Physician Fee Schedule. 2014. https://http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/PhysicianFeeSched/index.html?redirect=/PhysicianFeeSched/

31. Herman JM, Chang DT, Goodman KA, Dholakia AS, Raman SP, Hacker-Prietz A, et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2015; 121:1128–37. [PubMed: 25538019]

32. Mahadevan A, Jain S, Goldstein M, Miksad R, Pleskow D, Sawhney M, et al. Stereotactic body radiotherapy and gemcitabine for locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2010; 78:735–42. [PubMed: 20171803]

33. Mahadevan A, Miksad R, Goldstein M, Sullivan R, Bullock A, Buchbinder E, et al. Induction gemcitabine and stereotactic body radiotherapy for locally advanced nonmetastatic pancreas cancer. Int J Radiat Oncol Biol Phys. 2011; 81:e615–22. [PubMed: 21658854]

34. Trakul N, Koong AC, Chang DT. Stereotactic body radiotherapy in the treatment of pancreatic cancer. Sem Radiat Oncol. 2014; 24:140–7.

35. Chuong MD, Springett GM, Freilich JM, Park CK, Weber JM, Mellon EA, et al. Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated. Int J Radiat Oncol Biol Phys. 2013; 86:516–22. [PubMed: 23562768]

36. Moningi S, Marciscano AE, Rosati LM, Ng SK, Teboh Forbang R, Jackson J, et al. Stereotactic body radiation therapy in pancreatic cancer: the new frontier. Expert Rev Anticancer Ther. 2014; 14:1461–75. [PubMed: 25183386]

37. Hong TS, Ryan DP, Blaszkowsky LS, Mamon HJ, Kwak EL, Mino-Kenudson M, et al. Phase I study of preoperative short-course chemoradiation with proton beam therapy and capecitabine for resectable pancreatic ductal adenocarcinoma of the head. Int J Radiat Oncol Biol Phys. 2011; 79:151–7. [PubMed: 20421151]

38. Nichols RC Jr, George TJ, Zaiden RA Jr, Awad ZT, Asbun HJ, Huh S, et al. Proton therapy with concomitant capecitabine for pancreatic and ampullary cancers is associated with a low incidence of gastrointestinal toxicity. Acta Oncol. 2013; 52:498–505. [PubMed: 23477361]

39. Hong TS, Ryan DP, Borger DR, Blaszkowsky LS, Yeap BY, Ancukiewicz M, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. Int J Radiat Oncol Biol Phys. 2014; 89:830–8. [PubMed: 24867540]

40. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. New Engl J Med. 2011; 364:1817–25. [PubMed: 21561347]

41. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. New Engl J Med. 2013; 369:1691–703. [PubMed: 24131140]

42. Hosein PJ, Macintyre J, Kawamura C, Maldonado JC, Ernani V, Loaiza-Bonilla A, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer. 2012; 12:199. [PubMed: 22642850]

43. Faris JE, Blaszkowsky LS, McDermott S, Guimaraes AR, Szymonifka J, Huynh MA, et al. FOLFIRINOX in locally advanced pancreatic cancer: the Massachusetts General Hospital Cancer Center experience. Oncologist. 2013; 18:543–8. [PubMed: 23657686]

44. Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, et al. Neoadjuvant Modified (m) FOLFIRINOX for Locally Advanced Unresectable (LAPC) and Borderline Resectable (BRPC) Adenocarcinoma of the Pancreas. Ann Surg Oncol. 2014

45. Sadot E, Doussot A, O'Reilly EM, Lowery MA, Goodman KA, Do RK, et al. FOLFIRINOX induction therapy for stage 3 pancreatic adenocarcinoma. Ann Surg Oncol. 2015; 22:3512–21. [PubMed: 26065868]

46. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2007; 25:1960–6. [PubMed: 17452677]

47. Sinn M, Liersch T, Gellert K, Messmann H, Bechstein W, Waldschmidt D, et al. CONKO-005: adjuvant therapy in R0 resected pancreatic cancer patients with gemcitabine plus erlotinib versus gemcitabine for 24 weeks—A prospective randomized phase III study. J Clin Oncol. 2015; 33(Suppl) abstr 4007.

48. Huguet F, Hammel P, Vernerey D, Goldstein D, Van Laethem JL, Glimelius B, et al. Impact of chemoradiotherapy (CRT) on local control and time without treatment in patients with locally advanced pancreatic cancer (LAPC) included in the international phase III LAP 07 study. J Clin Oncol. 2014; 32(5s Suppl) abstr 4001.

49. Berlin J, Catalano P, Lowry AM, et al. ECOG 2204: An intergroup randomized phase II study of cetuximab (Ce) or bevacizumab (B) in combination with gemcitabine (G) and in combination with capecitabine (Ca) and radiation (XRT) as adjuvant therapy (Adj Tx) for patients (pts) with completely resected pancreatic adenocarcinoma (PC). J Clin Oncol. 2010; 28(15s Suppl) abstr 4034.

50. Wong HH, Lemoine NR. Pancreatic cancer: molecular pathogenesis and new therapeutic targets. Nat Rev Gastroenterol Hepatol. 2009; 6:412–22. [PubMed: 19506583]

51. Mace TA, Bloomston M, Lesinski GB. Pancreatic cancer-associated stellate cells: a viable target for reducing immunosuppression in the tumor microenvironment. Oncoimmunology. 2013; 2:e24891. [PubMed: 24073373]

52. Apte M, Pirola RC, Wilson JS. Pancreatic stellate cell: physiologic role, role in fibrosis and cancer. Curr Opin Gastroenterol. 2015

53. von Bernstorff W, Voss M, Freichel S, Schmid A, Vogel I, Johnk C, et al. Systemic and local immunosuppression in pancreatic cancer patients. Clin Cancer Res. 2001; 7:925s–32s. [PubMed: 11300493]

54. Clark CE, Beatty GL, Vonderheide RH. Immunosurveillance of pancreatic adenocarcinoma: insights from genetically engineered mouse models of cancer. Cancer Lett. 2009; 279:1–7. [PubMed: 19013709]

55. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother. 2010; 33:828–33. [PubMed: 20842054]

56. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. New Engl J Med. 2012; 366:2443–54. [PubMed: 22658127]

57. Deng L, Liang H, Burnette B, Beckett M, Darga T, Weichselbaum RR, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. J Clin Investig. 2014; 124:687–95. [PubMed: 24382348]

58. Rossi GHJ, Mulcahy M, et al. Effect of algenpantucel-L immunotherapy for pancreatic cancer on anti-mesothelin antibody (Ab) titers and correlation with improved overall survival. J Clin Oncol. 2013; 31(Suppl) abstr 3007.

59. Stubbs AC, Martin KS, Coeshott C, Skaates SV, Kuritzkes DR, Bellgrau D, et al. Whole recombinant yeast vaccine activates dendritic cells and elicits protective cell-mediated immunity. Nat Med. 2001; 7:625–9. [PubMed: 11329066]

60. Bernstein MB, Chakraborty M, Wansley EK, Guo Z, Franzusoff A, Mostbock S, et al. Recombinant *Saccharomyces cerevisiae* (yeast-CEA) as a potent activator of murine dendritic cells. Vaccine. 2008; 26:509–21. [PubMed: 18155327]

61. Remondo C, Cereda V, Mostbock S, Sabzevari H, Franzusoff A, Schlom J, et al. Human dendritic cell maturation and activation by a heat-killed recombinant yeast (*Saccharomyces cerevisiae*) vector encoding carcinoembryonic antigen. Vaccine. 2009; 27:987–94. [PubMed: 19110021]

62. Richards DA, Muscarella P, Bekaii-Saab T. A phase 2 adjuvant trial of GI-4000 plus Gem vs. Gem alone in ras mutation + resected pancreas cancer: R1 subgroup and proteomic analysis. Ann Oncol. 2012; 23(Suppl 4):IV5. [PubMed: 22774231]

63. Greenhalf W, Ghaneh P, Neoptolemos JP, Palmer DH, Cox TF, Lamb RF, et al. Pancreatic cancer hENT1 expression and survival from gemcitabine in patients from the ESPAC-3 trial. J Natl Cancer Instit. 2014; 106:djt347.

64. Miyoshi K, Sato N, Ohuchida K, Mizumoto K, Tanaka M. SPARC mRNA expression as a prognostic marker for pancreatic adenocarcinoma patients. Anticancer Res. 2010; 30:867–71. [PubMed: 20393008]

65. Infante JR, Matsubayashi H, Sato N, Tonascia J, Klein AP, Riall TA, et al. Peritumoral fibroblast SPARC expression and patient outcome with resectable pancreatic adenocarcinoma. J Clin Oncol. 2007; 25:319–25. [PubMed: 17235047]

66. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol. 2011; 29:4548–54. [PubMed: 21969517]

67. Hidalgo M, Plaza C, Illei P, Brachmann C, Heise C, Pierce D, et al. SPARC analysis in the phase III MPACT trial of nab-paclitaxel (NAB-P) plus gemcitabine (gem) vs gem alone for patients with metastatic pancreatic cancer (PC). Ann Oncol. 2014; 25(Suppl 2):ii106.

68. Sinn M, Sinn BV, Striefler JK, Lindner JL, Stieler JM, Lohneis P, et al. SPARC expression in resected pancreatic cancer patients treated with gemcitabine: results from the CONKO-001 study. Ann Oncol. 2014; 25:1025–32. [PubMed: 24562449]

69. Jiang H, He C, Geng S, Sheng H, Shen X, Zhang X, et al. RhoT1 and Smad4 are correlated with lymph node metastasis and overall survival in pancreatic cancer. PLoS ONE. 2012; 7:e42234. [PubMed: 22860091]

70. Oshima M, Okano K, Muraki S, Haba R, Maeba T, Suzuki Y, et al. Immunohistochemically detected expression of 3 major genes (CDKN2A/p16, TP53, and SMAD4/DPC4) strongly predicts survival in patients with resectable pancreatic cancer. Ann Surg. 2013; 258:336–46. [PubMed: 23470568]

71. Iacobuzio-Donahue CA, Fu B, Yachida S, Luo M, Abe H, Henderson CM, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. J Clin Oncol. 2009; 27:1806–13. [PubMed: 19273710]

72. Crane CH, Varadhachary GR, Yordy JS, Staerkel GA, Javle MM, Safran H, et al. Phase II trial of cetuximab, gemcitabine, and oxaliplatin followed by chemoradiation with cetuximab for locally advanced (T4) pancreatic adenocarcinoma: correlation of Smad4(Dpc4) immunostaining with pattern of disease progression. J Clin Oncol. 2011; 29:3037–43. [PubMed: 21709185]

73. Winter JM, Tang LH, Klimstra DS, Liu W, Linkov I, Brennan MF, et al. Failure patterns in resected pancreas adenocarcinoma: lack of predicted benefit to SMAD4 expression. Ann Surg. 2013; 258:331–5. [PubMed: 23360922]

Table 1

Summary of randomized post-operative adjuvant therapy trials in pancreas cancer.

Study	No. of patients	Treatment	% R1	% LN +	% Locoregional recurrence	Median OS	P Value	Median DFS	P Value	% G3–4 toxicity
ESPAC-1[a] [11]	289	5-FU	19	53	35	20.1	0.009	15.2	0.04	4
		CRT	19	50		15.9		10.7		6
ESPAC-3[b] [10]	1149	5-FU	14	62	NR	23	0.39	14.1	0.53	14
		G	15	60	NR	23.6		14.3		7.5
RTOG 9704[c,^] [14]	451	5-FU/CRT	33	65	30	16.9	0.15	11.1	NR	62
		G/CRT	35	68	31	18.8		11.2		79
CONKO-001[d,*] [7,8]	354	G	19	71	34	22.8	0.01	13.4	<0.001	5
		Observation	15	73	41	20.2		6.7		1
JSAP-02[e,*] [9]	378	G	19	67	23	22.3	<0.001	11.4	0.01	26
		Observation	8	70	32	18.4		5		NR
GITSG[f] [12]	43	CRT	19	29	15	20	0.03	11	0.01	7
		Observation	24	27	15	11		9		
CONKO-005[g]	436	G	0	66	NR	26.5	0.406	11.6	0.291	45.4
		G + E	0	64	NR	24.6		11.6		63

G-gemcitabine, E-erlotinib, 5-FU (5-fluorouracil), CRT-chemoradiation, CT-chemotherapy.

[^] Findings in RTOG 9704 presented local recurrence and lymph recurrences separately, which we combined for conformity.

[*] In addition to adenocarcinoma, they included other histology.

[a] 5-FU (425 mg/m^2) + LV (20 mg/m^2 bolus) × 5 days (every 28 days × 6 courses). 20 Gy in 10 daily fx with IV bolus 5-FU (500 mg/m^2 days 1–3 of RT and again after planned 2 week break).

[b] (143) 5-FU-LV (20 mg/m^2 bolus), followed by 425 mg/m^2 5-FU days 1–5 every 28 days × 6 courses. (141) Gemcitabine 1 gm/m^2 IV once a week for 3 of every 4 weeks × 6 courses.

[c] 5-FU (continuous infusion 250 mg/m^2) or Gemcitabine (1 gm/m^2 once a week) for 3 weeks prior to CRT. CRT continuous infusion of 5-FU (250 mg/m2 per day) with 50.4 Gy (in 28 fx).

[d] Gemcitabine 1 gm/m^2 once a week for 3 of every 4 weeks × 6 courses.

[e] Gemcitabine (1 gm/m^2 once a week for 3 of every 4 weeks × 6 courses).

[f] CRT-5-FU (500 mg/m^2 IV bolus daily × 3d) with 2D RT (split course radiation, 40 Gy (20 Gy × 2 separated by interval of 2 weeks)), followed by 5-FU (500 mg/m^2 IV bolus once weekly × 2 years or until recurrence.

[g]Gemcitabine (1 gm/m^2 once a week for 3 of every 4 weeks × 6 courses). Erlotinib (100 mg/d p.o. daily) × 6 courses.

Table 2

Costs of adjuvant chemotherapy, radiation and chemoradiation.[*]

Treatment modality	Chemotherapy	Radiation	Chemotherapy + chemoradiation
3D Radiation Therapy (Non-IMRT)[a]		15161.79	
Intensity-Modulated Radiation Therapy[a]		18703.88	
Stereotactic Body Radiation Therapy[b]		9229.00	
Adjuvant gemcitabine[c]	2989.11		
Concurrent chemoradiation[d]			18,078.79

[*]
All costs were calculated in US dollars ($).

[a]Based on 28 fractions.

[b]Based on 5 fractions.

[c]Based on 6 cycles of adjuvant gemcitabine 1gm/m2 per CONKO-001.

[d]Based on RTOG 9704 (4 months of gemcitabine followed by 28 fractions of 3D radiation therapy with concurrent 5-flurouracil).

Table 3

Ongoing or Completed phase III clinical trials in adjuvant pancreas cancer.

Trial	Control Arm	Experimental Arm	Phase	Comment	NCT	Status
APACT	Gemcitabine	nab-paclitaxel + gemcitabine	III		NCT01964430	Ongoing
PRODIGE	Gemcitabine	mFOLFIRINOX	III		NCT01526135	Ongoing
IMPRESS	Gemcitabine or with 5-FU/RT	Algenpantucel	III		NCT01072981	Completed
RTOG0848	Gemcitabine	CRT with capectabine or 5-FU	III	After 5 cycles of gemcitabine	NCT01013649	Ongoing