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Perioperative Therapy for Surgically Resectable Pancreatic Adenocarcinoma

Lingling Du, M.D.[1,2], **Melissa DeFoe, M.D.**[3], **Marianna B. Ruzinova, M.D. Ph.D.**[4], **Jeffrey R. Olsen, M.D.**[5], and **Andrea Wang-Gillam, M.D. Ph.D.**[1,2]

[1]Division of Oncology, Department of Internal Medicine, Washington University School of Medicine

[2]Alvin J. Siteman Cancer Center, Washington University School of Medicine

[3]Department of Internal Medicine, Washington University School of Medicine

[4]Department of Pathology and Immunology, Washington University School of Medicine

[5]Department of Radiation Oncology, Washington University School of Medicine

Synopsis

It is estimated that 10–20% of patients with pancreatic cancer present with resectable disease. Although surgery offers curative intent, the median survival following curative resection is less than 2 years. To improve clinical outcomes in this patient population, clinical studies have investigated the role of perioperative therapy including neoadjuvant and adjuvant treatment in resectable pancreatic cancer. The role of adjuvant therapy has been well established by large randomized phase III studies, while benefit of the neoadjuvant approach remains inconclusive. Here, we review various treatment modalities and their clinical benefits in resectable pancreatic cancer.

Keywords

Resectable pancreatic cancer; adjuvant therapy; neoadjuvant therapy; predictive biomarkers; hENT1

Corresponding author: Andrea Wang-Gillam M.D. Ph.D., Division of Oncology, Campus Box 8056, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, Missouri 63110, USA. Telephone: 314-362-5740; Fax: 314-362-7086; awang@dom.wustl.edu.

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1. Introduction

Pancreatic cancer is a highly lethal disease with a 5-year survival rate of less than 5% [1]. It is the fourth leading cause of cancer-related mortality in the United States [2] and is projected to rise to the second leading cause by 2030 [3]. Surgical resection offers the only chance for cure in pancreatic cancer; unfortunately, only 10–20% of patients present with resectable disease at the time of diagnosis due to the lack of effective means of early detection and the presentation of only vague clinical symptoms. Even in patients who undergo curative surgical resections, the 5-year survival rate remains low at 10–20% [4,5]. Clinical studies have explored the role of perioperative therapy, including adjuvant and neoadjuvant treatment, and the survival benefits of adjuvant therapy have been well established over the last few years. The role of neoadjuvant therapy has been explored but remains largely undefined. Efforts to identify predictive and prognostic biomarkers have been intense with encouraging results. Moreover, promising novel therapies have been incorporated in the adjuvant and neoadjuvant settings that may potentially improve survival.

2. Definition of Resectable Pancreatic Adenocarcinoma

Traditionally, to better prognosticate patients with solid tumors, pathological staging with the TNM (tumor, node and metastases) classification system is commonly utilized. However, because the majority of patients with pancreatic cancer are not eligible for resection, clinical staging is more practical than TNM staging, in particular, for patients with localized disease, a group wherein the tumor's vascular involvement is the deciding factor for resection. An expert consensus group published its criteria on the resectability of pancreatic adenocarcinoma in 2009 [6]. Using multidetector computed tomography (CT) with triple phase study, patients without distant metastases or evidence of tumor extension to the superior mesenteric vein and portal vein, and with clear fat planes around the celiac axis, the hepatic artery, and superior mesenteric artery are categorized as resectable. These criteria have clearly distinguished resectable pancreatic cancer from borderline resectable and locally advanced disease, and they have been well recognized and incorporated into clinical trial design. The same criteria are adopted in the National Comprehensive Cancer Network (NCCN) guidelines [7].

3. Adjuvant Therapy

3.1 Major Phase III Trials of Adjuvant Therapy

Pancreatic cancer has a high rate of early metastases. Even in patients with resectable pancreatic cancer who undergo surgical resection, up to 70% of recurrence occurs at distant sites [8,9]. The rationale of adjuvant treatment is to administer therapy systemically with the intent of eradicating occult metastases. The benefits of adjuvant therapy have been validated in several large phase III clinical trials. (Table 1)

Gemcitabine was approved by the United States Food and Drug Administration (FDA) for its superior clinical benefit compared with 5-FU in advanced pancreatic cancer [10]. Since then, gemcitabine has become the cornerstone treatment for pancreatic cancer. The benefit of gemcitabine in the adjuvant setting was demonstrated in the CONKO-001 trial (Charite

Onkologie 001) [11]. This is the first phase III trial evaluating the role of adjuvant chemotherapy in patients with resectable pancreatic cancer, and it is a landmark study of this population [11,12]. In CONKO-001, 368 patients who underwent resection for pancreatic cancer in Germany and Austria were stratified by tumor stage, nodal status and resection status. Patients were randomly assigned to receive either 6 cycles of gemcitabine 1,000 mg/m^2 on days 1, 8, and 15 every 4 weeks or be observed without any treatment protocol. The primary endpoint was disease-free survival (DFS), and the secondary endpoints included overall survival (OS), toxicity, and quality of life. Results were first published in 2007 [11]. Gemcitabine was well tolerated with rare adverse events. Grade 3 or 4 hematologic side effects were experienced in 3.8% of patients, and 3.1% had grade 3 or 4 nonhematologic adverse events. Of 186 patients in the gemcitabine group, 111 (62%) patients completed all 6 cycles of treatment. The gemcitabine group had a superior median DFS over observation alone (13.4 vs. 6.9 months, p<.001). An updated result was later published in 2013, which not only confirmed the benefit in DFS, but more importantly, demonstrated a prolonged OS in the gemcitabine group (22.8 vs. 20.2 months; p=.01) [12]. The 5-year survival rate was 20.7% in the gemcitabine group compared with 10.4% in the observation group. The 10-year survival rate was 12.2% vs. 7.7%, respectively. This is the first time an actual 10-year survival outcome was reported in patients with resectable pancreatic cancer. This study also established the pivotal role of adjuvant gemcitabine in treating this patient population.

Although gemcitabine was superior to 5-FU in advanced pancreatic cancer [10], whether this survival advantage persisted in the adjuvant setting remained to be determined. The ESPAC-3 (European Study Group for Pancreatic Cancer 3) trial was initially designed to evaluate the survival benefit of adjuvant chemotherapy with either 5-FU and gemcitabine versus observation alone following resection for pancreatic cancer [13]. After the CONKO-001 trial demonstrated a survival benefit with gemcitabine in resectable pancreatic cancer [14], the observation group in the ESPAC-3 study was removed. Therefore, this study directly compared the clinical efficacy of gemcitabine to 5-FU in the adjuvant setting [13]. In the ESPAC-3 study, 1088 patients who underwent resection for pancreatic cancer from 159 centers in Europe, Australia, Canada and Japan were randomized to receive a 6-month course of adjuvant chemotherapy with 5-FU at 425 mg/m^2 plus leucovorin 20 mg/m^2 on days 1–5, or gemcitabine 1,000 mg/m^2 on days 1, 8, 15 every 28 days. 5-FU was associated with more grade 3 or 4 gastrointestinal side effects (e.g. stomatitis, diarrhea), while the gemcitabine arm had more grade 3 or 4 hematologic toxicities. Overall, gemcitabine was better tolerated with a severe adverse event rate of 7.5%, compared to 14% in the 5-FU group. It was speculated that the 5-FU schedule (bolus on days 1–5) was partially responsible for the higher rate of adverse events. There was no significant difference in DFS between the two groups. Median OS was 23.0 months for the 5-FU group and 23.6 months for the gemcitabine group, respectively, and this was not statistically significant. Therefore, this study demonstrated that adjuvant 5-FU is equally effective as gemcitabine in resectable pancreatic cancer. In a practical sense, patients with resectable pancreatic cancer who cannot tolerate gemcitabine may receive 5-FU as adjuvant therapy.

On the other side of the Pacific Ocean, Japanese researchers have been exploring the efficacy of S-1 in the treatment of pancreatic cancer. S-1 is an oral fluoropyrimidine that

results in survival outcomes similar to gemcitabine in patients with advanced pancreatic cancer [15]. The JASPAC 01 (Japan Adjuvant Study Group of Pancreatic Cancer 01) trial was designed to assess the efficacy of S-1 compared to gemcitabine in the adjuvant setting [16]. In this study, 385 patients were assigned to receive either adjuvant gemcitabine (1,000 mg/m^2, on days 1, 8, 15, every 4 weeks for 6 courses) or S-1 (80, 100, 120 mg/day depending on body surface area, days 1–28, every 6 weeks for 4 courses) after surgical resection for pancreatic cancer. The primary endpoint was OS. S-1 was well-tolerated and associated with fewer hematologic adverse events. Median OS was 25.9 months in the gemcitabine group and not mature in the S-1 group when the results were presented at the ASCO 2013 annual meeting. The 2-year survival rate was 53% for gemcitabine and 70% for S-1. S-1 demonstrated clear non-inferiority when compared to gemcitabine (HR 0.56, p<.0001), and was even superior to gemcitabine (p<.0001). This study showed the promising role of S-1 as the new standard adjuvant treatment for resected pancreatic cancer in Japan, and longer follow-up is needed to confirm the survival benefit of S-1.

The RTOG 9704 (Radiation Therapy Oncology Group 9704) trial has incorporated radiation into adjuvant therapy. The study was designed to compare the effectiveness of gemcitabine and 5-FU as adjuvant chemotherapy in combination with radiation. Both groups had 5-FU based chemoradiation as the backbone [17]. In this study, 451 patients with resected pancreatic cancer were treated with chemoradiation with 5-FU at 250 mg/m^2 per day concurrent with 50.4 Gy radiation after the surgery. In addition, they were assigned to receive either 5-FU at the same dose or gemcitabine (1,000 mg/m^2 once weekly), which was given for 3 weeks prior to, and for 12 weeks following chemoradiation. The median OS was 20.5 months in the gemcitabine group, and 17.1 months in the 5-FU group; the 5-year survival was 22% and 18% for these two groups, respectively. The difference in survival was not statistically significant. Multivariate analysis revealed a trend toward better survival outcomes with gemcitabine over 5-FU (p=.08). Subgroup analysis showed a survival benefit in patients with tumors in the head of the pancreas (HR 0.80, 95% C.I. 0.63–1.00; p=.05). Since the publication of this study, many institutions in the United States use this regimen of systemic gemcitabine plus 5-FU based chemoradiation in the adjuvant treatment of resectable cancer in the head of the pancreas.

In summary, several large phase III studies have established the survival benefit of adjuvant chemotherapy in pancreatic cancer. Gemcitabine has been the most commonly used adjuvant agent, while 5-FU was found to have equal efficacy. S-1 was recently found to be noninferior, and even superior to gemcitabine in patients with resectable pancreatic cancer in Japan. Chemoradiation can be used as part of adjuvant therapy in patients with tumors in the head of the pancreas.

3.2 Controversy over adjuvant radiation therapy

Although adjuvant chemotherapy was proven to improve survival in patients with resectable pancreatic cancer, the benefit of radiation therapy in the adjuvant setting remains debatable. In the 1980s, the GITSG (Gastrointestinal Tumor Study Group) first observed a survival benefit in 43 patients who received postoperative combined radiation therapy and 5-FU (n=21) compared to observation alone (n=22; OS 20 vs. 11 months, p=.03) [18]. This was

followed by an EORTC (European Organization for Research and Treatment of Cancer) study, in which 218 patients with pancreatic head and periampullary cancers were randomized to receive adjuvant radiation therapy and 5-FU vs. observation alone after resection [19]. The treatment group demonstrated a trend toward improved survival, but the data did not reach statistical significance (2-year survival rate of 34% vs. 26%; p=.099).

The ESPAC-1 trial was a phase 3 study assessing the roles of adjuvant chemoradiation and chemotherapy, in which 541 patients were randomized by a two-by-two design to receive no treatment (observation arm), chemoradiation, chemotherapy, or combined chemoradiation and chemotherapy [14,20]. This study demonstrated an improved survival in patients who received chemotherapy compared to those who did not receive chemotherapy (5-year survival rate was 21% vs. 8%, p=.009). In addition, adjuvant chemoradiation was found to be detrimental, with a 5-year survival rate of 10% in patients who received chemoradiation vs. 20% in patients who did not (p=.05). However, this study was criticized for its study design and confounding factors [21]. For example, due to allowed modifications in the study, a significant number of patients in the “no chemotherapy” group and “chemotherapy only” group received chemoradiation, which confounds the interpretation of the results. Regardless, the incorporation of radiation therapy in the adjuvant setting after resection of pancreatic cancer has fallen out of favor among European researchers. However, in the United States, adjuvant radiation therapy is largely considered to be part of the ideal adjuvant therapy. The ongoing RTOG 0848 trial, which directly compares patients treated with chemotherapy alone versus chemotherapy plus chemoradiation may offer a definitive answer on the benefit of radiation therapy in resectable pancreatic cancer.

4. Neoadjuvant Therapy

As adjuvant chemotherapy has demonstrated improved survival, multiple studies have also explored the role of neoadjuvant therapy as an alternative to the standard adjuvant approach. Neoadjuvant therapy offers all patients the opportunity of receiving full courses of chemotherapy and/or radiation without the potential delay secondary to surgical complications or prolonged postoperative recovery. Additionally, it helps identify patients who are unlikely to benefit from surgery due to futility in the setting of early, subclinical metastatic spread. Furthermore, the neoadjuvant approach provides an opportunity to examine predictive biomarkers for novel agents in pancreatic cancer.

Most of the early pancreatic cancer neoadjuvant studies used 5-FU as a radio-sensitizing agents. In a phase II trial published in 1992, 28 patients received preoperative chemoradiation with 5-FU, and 61% underwent resection [22]. No patients experienced a delay in surgery due to treatment toxicities. Evidence of tumor cell destruction was well appreciated on the resected specimens. Although the survival data was not reported, this study demonstrated the feasibility of preoperative chemoradiation. It was followed by several others studies incorporating a 5-FU based regimen, and a wide range of OS results were observed [23–27].

After gemcitabine demonstrated better survival over 5-FU in patients with advanced pancreatic cancer [10], most clinical trials for resectable pancreatic cancer patients switched to

studying gemcitabine-based regimens. The efficacy of neoadjuvant gemcitabine 400 mg/m^2 with concurrent radiation in patients with resectable pancreatic cancer was evaluated and published their in 2008 [28]. Seventy-four percent of these patients underwent resection; the median OS and 5-year survival rate were 34 months and 36%, respectively, for patients who underwent resection, and 22.7 months and 27%, respectively, for the overall cohort. A study of the same chemoradiation regimen with the addition of gemcitabine and cisplatin given prior to chemoradiation was published later in the same year, and it showed a resection rate of 66% among ninety patients with a median OS of 27.4 months for all patients and 31 months for those who underwent resection [29]. Direct comparison across the two studies was difficult given the slightly different patient population. However, the survival outcomes in both studies were quite encouraging, even compared to the CONKO-001 or ESPAC-3 studies.

Overall, most of the clinical studies of neoadjuvant therapy are phase II trials with small sample sizes. Several studies have demonstrated promising survival, but more consolidating evidence from large clinical studies using more effective treatment modalities is needed to validate the benefit of neoadjuvant therapy in resectable pancreatic cancer.

4. Biomarkers Predictive of Outcome

With the growing understanding of the genomic profile of pancreatic cancer [30], many studies have investigated molecular markers for their ability to predict treatment response and survival outcome. One of the most promising markers is the human equilibrative nucleoside transporter 1 (hENT1). hENT1 is a transmembrane glycoprotein that mediates the cellular uptake of cytotoxic nucleotides such as gemcitabine and capecitabine [31,32]. Early studies suggested that in patients treated with gemcitabine for pancreatic cancer, those with detectable hENT1 in their cancer cells had longer median survivals compared to those with absent hENT1 [32–34]. However, other studies failed to demonstrate the predictive or prognostic value of hENT1 in patients with pancreatic cancer [35,36]. The ESPAC study group recently published their results utilizing the tumor samples of 380 patients from the ESPAC-3 trial [37]. The expression of hENT1 on these tumor samples was analyzed. In the gemcitabine arm, patients with low hENT1 expression had a significantly worse median OS compared to those with high hENT1 expression (17.1 vs. 26.2 months, p=.002). In contrast, this predictive value of hENT1 expression was not observed in either the 5-FU or the observation group. These findings may help guide clinical decisions when considering adjuvant treatment regimens for patients with resectable pancreatic cancer; i.e., patients who have low hENT1 expression in their resected tumors might be better treated with chemotherapeutic agents other than gemcitabine.

5. What is on the Horizon

Recently, immunotherapy has emerged as a promising alternative treatment for pancreatic cancer. One approach is the “HyperAcute” immunotherapy using algenpantucel-L. Algenpantucel-L are allogeneic tumor cells modified to express the αGal xenoantigen, an antigen which is not normally present in humans. When these modified pancreatic tumor cells are introduced into patients with pancreatic cancer, they can trigger a profound immune

reaction leading to hyperacute rejection of the tumor cells. In a phase II study presented at the 2013 ASCO annual meeting, 69 patients who underwent resection for pancreatic cancer received adjuvant gemcitabine and chemoradiation with 5-FU as per the RTOG 9704 protocol, with the addition of algenpantucel-L vaccination every 2 weeks for 6 months [38]. Patients were randomized into two groups: the low dose arm (100 million cells) and the high dose arm (300 million cells). This vaccine was well tolerated with the most frequent adverse events being mild skin reactions at injection sites. Patients who had ≥25% increase in the anti-mesothelin antibody (anti –MSLN Ab) demonstrated better survival over those without significant anti-MSLN Ab increase (median OS 42 vs. 20 months). The 3-year disease free survival (DFS) rate for the whole cohort was 26%, and the 3-year OS rate was 39%. These results are encouraging. Algenpantucel-L is currently being further evaluated in the IMPRESS trial, which is a phase III study comparing standard adjuvant gemcitabine and 5-FU-based chemoradiation with or without the algenpantucel-L immunotherapy in patients with surgically resected pancreatic cancer (NLM identifier: NCT 01072981).

As discussed previously, the role of adjuvant chemoradiation in resectable pancreatic cancer remains controversial. The RTOG 0848 trial is designed to investigate whether the addition of adjuvant chemoradiation to chemotherapy improves survival (NLM Identifier: NCT01013649). This is a phase II/III study following a 2 × 2 randomization design. Patients who underwent resection for pancreatic cancer are first randomized to receive 6 cycles of chemotherapy with gemcitabine alone or gemcitabine plus erlotinib. The accrual to the gemcitabine plus erlotinib arm was closed in April 2014. Patients without progression at the end of 5 cycles of chemotherapy are further randomized to receive either 1 cycle of chemotherapy followed by capecitabine or 5-FU based chemoradiation or 1 cycle of chemotherapy alone. This study is estimated to complete data collection in August 2020, and hopefully will unveil the true role of adjuvant chemoradiation in resectable pancreatic cancer.

Recent advancements in the use of chemotherapeutic agents have shown an encouraging survival benefit in patients with advanced pancreatic cancer. In the metastatic setting, both gemcitabine plus nab-paclitaxel and FOLFIRINOX have demonstrated better survival over gemcitabine alone [39,40]. Large clinical trials incorporating these two regimens in the adjuvant treatment after resection for pancreatic cancer are ongoing. The APACT study is designed to evaluate the effect of gemcitabine plus nab-paclitaxel compared to gemcitabine alone as adjuvant chemotherapy in patients with resected pancreatic cancer (NLM identifier: NCT01964430). On the other hand, a randomized phase II/III study comparing FOLFIRINOX given in both the neoadjuvant and adjuvant settings versus adjuvant gemcitabine alone for patients with resectable pancreatic cancer is on the horizon (NLM identifier: NCT 02172976).

Overall, recent advancements in chemotherapy and immunotherapy have provided researchers new modalities in treating resectable pancreatic cancer. Several phase III studies with the incorporation of newer regimens are ongoing and hopefully can improve the survival of patients with resectable pancreatic cancer.

6. Conclusion

Resectable pancreatic adenocarcinoma represents 10–20% of all pancreatic adenocarcinomas. Although surgery offers the only opportunity for cure, treatment with surgery alone still provides poor survival outcomes. Adjuvant systemic chemotherapy has demonstrated improved survival over surgery alone. Whether the addition of chemoradiation in the adjuvant setting improves outcomes remains controversial. On the other hand, neoadjuvant therapy has shown survival improvements in several phase II studies, but more consolidating evidence is needed to demonstrate a true benefit. With the recent advancement in chemotherapeutic agent combinations and immunotherapy, large clinical studies with more effective treatment modalities should be explored in resectable pancreatic cancer.

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Key Points

1. Several landmark phase III studies have demonstrated a survival benefit with adjuvant systemic chemotherapy in patients with resected pancreatic cancer.
2. The benefit of adjuvant chemoradiation in this population remains controversial.
3. Understanding of the role of neoadjuvant treatment in resectable pancreatic cancer is largely limited by small early phase studies.
4. Predictive biomarkers such as the human equilibrative nucleoside transporter 1 (hENT1) are emerging in the adjuvant setting.

Table 1

Major Phase III Trials of Adjuvant Therapy in Resectable Pancreatic Cancer

Trial	Year	Pts	Treatment	≥T3 %	N+ %	R0 %	Failure		Median Survival (months)	Survival Rate (%)
							Local (%)	Distant (%)		
CONKO-001	2007, 2013	368	**a.** Gem **b.** Observation	86	72	83	38	53	22.8 vs. 20.2 (p=.01)	20.7 vs. 10.4 (5yr) 12.2 vs. 7.7 (10yr)
ESPAC3	2010	1,088	**a.** Gem **b.** 5-FU/LCV	NA	72	65	NA	NA	23.6 vs. 23.0 (p=.39)	49.1 vs. 48.1 (2yr)
RTOG 9704	2008	451	**a.** Gem→5-FU/RT→Gem **b.** 5-FU/LCV→5-FU/RT→5-FU/LCV	75	66	66	28	73	20.5 vs. 17.1 (p=.08)	22 vs. 18
JASPAC 01	2013	378	**a.** Gem **b.** S-1	87	63	87	21	47	25.9 vs. not matured (p<.0001)	53 vs. 70 (2yr)

Abbreviations: Pts: patients; gem: gemcitabine; yr: year; LCV: leucovorin; RT: radiation therapy