

## HIGHLIGHT ARTICLE

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# Adjuvant Therapy for Pancreatic Cancer

## Highlights from the "2014 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 16-18, 2014

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### Summary

Survival for patients with pancreas cancer is correlated to stage. Only 20% of patients present with localized disease amenable to potentially curative resection but, despite resection, the 5-year survival rate for early stage patients remains less than 25%. Current accepted standard of care is adjuvant gemcitabine following curative resection but there have been no conclusions regarding the role or timing of adjuvant chemoradiation. Although systemic disease represents the major risk for failure following resection, there are patients who would benefit from adjuvant local therapy that remain difficult to identify at present. This year at 2014 ASCO Gastrointestinal Cancers Symposium, Cho *et al.* (Abstract #325) presented the results of adjuvant gemcitabine with the addition of docetaxel followed by 5-FU chemoradiation for patients with resected pancreatic cancer. Kumar *et al.* (Abstract #330) compared adjuvant chemoradiation to adjuvant chemotherapy. Lastly Heestand *et al.* (Abstract #176) used a novel way to look at different biomarkers in serum of patients in the RTOG 9407 study and evaluated the survival depending on the type of chemotherapy used. A lower serum CEA and CA 19-9 gave a better overall survival in all patients which has already been established. Low levels of matrix metalloproteinase-7 (MMP-7) predicted an overall survival benefit from adjuvant gemcitabine, but not from 5-FU.

### Introduction

Pancreatic cancer continues to be an elusive disease with a 5-year overall survival of 4%. It is the 4<sup>th</sup> leading cause of cancer death in the United States. The American Cancer Society estimates in the United States for 2013 about 45,220 people (22,740 men and 22,480 women) will be diagnosed with pancreatic cancer. About 38,460 people (19,480 men and 18,980 women) will die of pancreatic cancer [1]. The only chance for a prolonged survival and cure is surgery. Unfortunately only 20% of all patients diagnosed with pancreatic cancer are surgical candidates due to the aggressive biology of this disease. The optimal adjuvant treatment approach remains unclear. Despite improvements in radiation, systemic therapies, and targeted

agents, the 5-year survival rate for early stage resected patients remains less than 25%.

### What We Knew Before the 2014 ASCO Gastrointestinal Cancers Symposium

There have been multiple studies looking to improve survival in the adjuvant setting; however, there remains considerable controversy regarding the optimal adjuvant treatment. The use adjuvant radiation to chemotherapy is the issue of some debate regarding adjuvant therapy. Although systemic disease represents the major risk for failure following resection, there are patients who would benefit from adjuvant local therapy that remain difficult to identify at present. Current accepted standard of care is adjuvant gemcitabine following curative resection, but there have been no conclusions regarding the role or timing of adjuvant chemoradiation [2].

The randomized trials evaluating adjuvant therapy in pancreatic cancer are summarized in Table 1.

### What We Learned at the 2014 ASCO Gastrointestinal Cancers Symposium

Pancreatic cancer remains a substantial public health problem internationally. This disease has been used for testing new therapies with very little progress. More innovative treatment options are

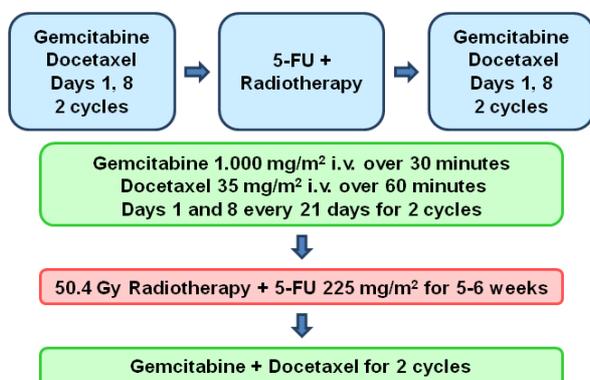
**Kew words** Chemotherapy, Adjuvant; Pancreatic Neoplasms  
**Abbreviations** CONKO: Charité Onkologie Clinical; ECM: extracellular matrix; EORTC: European Organisation for Research and Treatment of Cancer; ESPAC: European Study Group for Pancreatic Cancer; GITSG: Gastrointestinal Study Group; MMP-7: matrix metalloproteinase-7; RTOG: Radiation Therapy Oncology Group  
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**Table 1.** Randomized trials evaluating adjuvant therapy in pancreatic cancer.

Study	Treatment	Impact of adjuvant therapy
GITSG [3]	Observation vs. 5-FU plus radiation therapy	Median survival improvement from 11 to 20 months
EORTC [4]	Observation vs. 5-FU plus radiation therapy	A trend toward median survival improvement from 19 to 24.5 months (P=0.208)
ESPAC-1 [5]	5-FU/leucovorin vs. chemoradiation vs. chemoradiation + 5-FU/leucovorin vs. observation	Median survival of 5-FU/leucovorin vs. observation: 20.1 vs. 15.5 months (P=0.009). Chemoradiation alone vs. observation showed worse median survival: 15.9 vs. 17.9 months (P=0.05)
RTOG 9704 [6]	5-FU with radiation vs. gemcitabine plus 5-FU with radiation	Median survival of 5-FU alone vs. gemcitabine: 16.7 vs. 18.8 months (P=0.047) (pancreatic head tumors only)
CONKO-001 [7]	Gemcitabine vs. observation	Disease-free survival doubled: 13.4 months vs. 6.9 months Trend toward overall survival benefit: 22.1 vs. 20.2 months (P=0.06)
ESPAC-3 [8]	Gemcitabine vs. 5-FU vs. observation	No difference in survival advantage between gemcitabine and 5-FU. However, safety and dose intensity favored gemcitabine
JASPAC-01 [9]	S-1 vs. gemcitabine	The two-year survival rates were 70% and 53% for S-1 and gemcitabine. The two-year relapse free survival rates were 49% and 29% for S-1 and gemcitabine

JASPAC: Japanese Adjuvant Study Group of Pancreatic Cancer

needed to improve survival in this patient population. This year in ASCO Gastrointestinal Cancer Symposium, Cho *et al.* (Abstract #325) presented the results of adjuvant gemcitabine with the addition of docetaxel followed by 5-FU chemoradiation for patients with resected pancreatic cancer [10]. The primary objective was to evaluate the feasibility and safety of this regimen with the secondary aims to describe the toxicities, disease-free and overall survival. Kumar *et al.* (Abstract #330) presented the results of two different adjuvant treatments on survival. They compared adjuvant chemoradiation to adjuvant chemotherapy [11]. Lastly, Heestand *et al.* (Abstract #176) used a novel way to look at different biomarkers in serum of patients in the Radiation Therapy Oncology Group (RTOG) 9407 and evaluated the survival depending on the type of chemotherapy used [12]. A lower serum CEA and CA 19-9 gave a better overall survival in all patients which has already been established. Low levels of matrix metalloproteinase-7 (MMP-7) predicted an overall survival benefit from adjuvant gemcitabine, but not 5-FU.



**Figure 1.** Schema of the treatment with gemcitabine plus docetaxel followed by 5-FU and radiation, then followed by two more cycles of gemcitabine and docetaxel for patients with curatively resected pancreaticobiliary cancers [10].

Adjuvant Gemcitabine Plus Docetaxel Followed by 5-FU Chemoradiation for Patients with Resected Pancreaticobiliary Cancers: A Single Institution Phase II Study (Abstract #325 [10])

The aim of this study was to evaluate the feasibility and safety of adjuvant gemcitabine plus docetaxel followed by radiation with 5-FU after curative resection of pancreatic and biliary adenocarcinomas (Figure 1). They enrolled 50 patients with 30 patients completing therapy. Grade 3-4 non-hematologic toxicities include diarrhea (12%), fatigue (4%), renal failure (2%), hepatic toxicity (4%). Grade 3-4 hematologic toxicities include neutropenia (30%), anemia (2%) and thrombocytopenia (10%). The median overall survival and disease free survival for patients with pancreatic cancer was 17 and 9 months, respectively. They concluded that adjuvant gemcitabine plus docetaxel followed by concurrent 5-FU chemoradiation is feasible and tolerable.

Adjuvant Chemoradiation to Improve Survival Compared to Adjuvant Chemotherapy in Selected Patients with Pancreatic Cancer (Abstract #330 [11])

This was a single institution review of 343 patients from 2000 to 2012 that underwent a pancreaticoduodenectomy for pancreatic cancer. Patients were placed in 1 of 3 categories. Surgery alone, adjuvant chemotherapy with gemcitabine, or adjuvant 5-FU chemoradiation. Median follow-up and median survival for all patients was 17.5 and 19.5 months, respectively. One-hundred and thirty patients had resection alone, 84 had adjuvant chemotherapy, and 129 had adjuvant chemoradiation. Median survival for were 13, 23 and 26 months for surgery, adjuvant chemotherapy and adjuvant chemoradiation, respectively. Locoregional recurrence was 60%, 63%, and 38% and distant failure was 64%, 65%, and 66%. Chemoradiation group had significantly lower local regional recurrence compared to adjuvant

chemotherapy (P=0.01); however, survival between adjuvant chemotherapy and adjuvant chemoradiation was not statistically significant (P=0.23). Median survival of patients with lymph node ratio less than 0.2 and equal to, or greater than, 0.2 was 18 and 27 months, respectively. However, when compared to adjuvant chemotherapy alone, adjuvant chemoradiation improved survival for patients with a positive surgical margin and/or lymph node involvement when the ratio of lymph node positivity to the number of lymph nodes removed was less than 0.2

*A Novel Biomarker Panel Examining Response to Adjuvant Pancreatic Cancer Therapy in RTOG 9704 (Abstract #176 [12])*

RTOG 9704 was an adjuvant trial in patients with resected disease, randomized to receive 5-FU or gemcitabine chemotherapy given pre- and post-5-FU chemoradiotherapy. Serum levels were drawn on all patients prior to adjuvant therapy as stored. A probe panel of available antibodies capable of quantifying 42 key proteins was used in a proximity ligation assay. They were looking if any of these proteins linked with survival or response. As seen in prior studies, decreased levels of CEA and CA 19-9 were prognostic for improved overall survival in all patients. Low levels of matrix metalloproteinase-7 (MMP-7) predicted an overall survival benefit from adjuvant gemcitabine, but not 5-FU (Table 2). This suggests that patients with low MMP-7 serum levels were most likely to benefit from adjuvant gemcitabine and not 5-FU.

**Discussion**

Adjuvant treatment options for pancreatic adenocarcinoma include fluorouracil (including S-1), gemcitabine, chemoradiation, and chemoradiation plus fluorouracil or gemcitabine. The Charité Onkologie Clinical (CONKO)-001 and European Study Group for Pancreatic Cancer (ESPAC)-03 studies have shown that chemotherapy can almost double the disease free survival with an improved overall survival compared to observation. Gastrointestinal Study Group (GITSG), ESPAC-1, European Organisation for Research and Treatment of Cancer (EORTC), and RTOG 9407, have shown that the addition of chemoradiation compared to observation alone can improve survival. However, what is the best adjuvant treatment? Which gives

the best results is still for debate. To try and answer this question Liao *et al.* did a meta-analysis of all controlled randomized trials for adjuvant therapy for resected pancreatic cancer [13]. They concluded that fluorouracil or gemcitabine is the most favorable adjuvant treatment, which reduces mortality from cancer after surgery. Chemoradiation plus chemotherapy, either fluorouracil or gemcitabine, is more toxic and less effective in prolonging survival compared to chemotherapy alone.

Cho *et al.* (Abstract #325 [10]) evaluated a novel approach. Systemic gemcitabine and docetaxel for two treatments followed by 5-FU sensitized radiotherapy and then three more treatments of systemic chemotherapy. Docetaxel is a taxane that is a mitotic inhibitor that affects the microtubules. It is most commonly used for ovarian, breast, prostate and lung cancers. The protocol is shorter than the standard systemic regimens. The study has only 30 patients so it is difficult to come to any conclusions except that it is a tolerable protocol. This novel approach has inferior overall and disease free survival (17 months, and 9 months) compared to the CONKO-001 with single agent chemotherapy (22.1 months, and 13.4 months) or RTOG 9704 with single agent chemotherapy with or without 5-FU based radiotherapy (median survival: 16.8 and 18.8 months).

Kumar *et al.* (Abstract #330 [11]) tried to clarify what adjuvant therapy would have the most benefit. This retrospective study from a single institution compared observation to two different adjuvant therapy protocols of systemic chemotherapy or chemoradiation after surgical resection. The two adjuvant treatment modalities had an increased survival advantage compared to the observation group. Local recurrence rates were improved with chemoradiation however survival did not change compared to systemic chemotherapy.

One way to address the controversy of different combinations of systemic chemotherapy and chemoradiation is personalized treatment. The follow up RTOG 9704 study used a novel technique to evaluate what combination of biomarkers and adjuvant therapy has the best survival advantage. A protein called matrix metalloproteinase-7 (MMP-7) at lower levels in the serum of patients with resected pancreatic cancers had a better overall

**Table 2.** Univariate analysis: overall survival.

Biomarker	All patients HR (99.88% CI)	5-FU HR (99.88% CI)	Gemcitabine HR (99.88% CI)
CA 19-9	1.20 (1.11-1.30); P<0.0001	1.20 (1.08-1.33); P<0.0001	1.21 (1.06-1.39); P<0.0001
CEA	1.19 (1.04-1.38); P<0.0001	1.43 (1.12-1.83); P<0.0001	1.12 (0.90-1.38); P=0.094
MMP-7	1.15 (0.98-1.34); P=0.0054	0.96 (0.73-1.25); P=0.58	1.39 (1.05-1.83); P=0.0001

HR: hazard ratio

survival with systemic gemcitabine than with 5-FU. MMP-7, also known as matrilysin, is frequently overexpressed in human cancer tissues and is associated with cancer progression [14]. MMP-7 has been shown not only in the breakdown of extracellular matrix (ECM) proteins, but also in the regulation of several biochemical processes such as activation, degradation, and shedding of non-ECM proteins to promote cancer progression.

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**Conflict of interest** The authors have no potential conflicts of interest

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