

Clinical Investigation: Gastrointestinal Cancer

Survival After Chemoradiation in Resected Pancreatic Cancer: The Impact of Adjuvant Gemcitabine

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Summary

There is no clear consensus on the role of adjuvant therapy for postoperative pancreatic cancer patients. We reviewed our institution's experience and compared survival among patients treated with adjuvant concurrent 5-fluorouracil-based radiotherapy alone, adjuvant 5-fluorouracil-based radiotherapy plus adjuvant gemcitabine, and concurrent full-dose gemcitabine with involved-field radiotherapy plus further adjuvant gemcitabine. With a median overall survival of 21.0 months, there was no survival difference among the three groups.

Purpose: To evaluate survival in patients with resected pancreatic cancer treated with concurrent chemoradiation with or without adjuvant gemcitabine (Gem).

Methods and Materials: From 1998 to 2010, 86 patients with pancreatic adenocarcinoma who underwent resection were treated with adjuvant concurrent chemoradiation. Thirty-four patients received concurrent 5-fluorouracil-based chemoradiation (5-FU/RT) with traditional field radiation (range, 45–61.2 Gy; median, 50.4 Gy) without further adjuvant therapy. Thirty patients received traditional field 5-FU/RT (range, 45–60.4 Gy; median, 50.4 Gy) with Gem (1,000 mg/m² weekly) either before and after radiotherapy or only after radiotherapy. Twenty-two patients received concurrent full-dose Gem (1,000 mg/m² weekly)-based chemoradiation (Gem/RT), consisting of involved-field radiation (range, 27–38 Gy; median, 36 Gy) followed by further adjuvant Gem.

Results: The median age of the cohort was 65 years (range, 40–80 years). Of the patients, 58 had T3 tumors (67%), 22 had T2 tumors (26%), and 6 had T1 tumors (7%). N1 disease was present in 61 patients (71%), whereas 18 patients (21%) had R1 resections. Performance status, lymph node status, and margin status were all similar among the treatment groups. Median follow-up was 19.0 months. Median overall survival (OS) (19.2 months, 19.0 months, and 21.0 months) and 3-year OS rates (26.5%, 27.2%, and 32.1%) were similar among patients with 5-FU/RT with no adjuvant Gem, those with 5-FU/RT with adjuvant Gem, and those with Gem/RT with adjuvant Gem, respectively ($p = 0.88$). Patients who received adjuvant Gem had a similar median OS (22.1 months) and 3-year OS rate (29%) compared to patients who did not (19.2 months and 26.5%, respectively) ($p = 0.62$). There was a trend for improved 3-year OS rates in patients with R0 vs. R1 resections (28.1% vs. 14.2%, $p = 0.06$) and in patients with T1 and T2 vs. T3 tumors (38% vs. 20%, $p = 0.09$). Node-negative patients had an improved 3-year OS rate (30.1%) when compared with patients with N1 disease (16.2%) ($p = 0.02$).

Conclusion: In our cohort of patients with resected pancreatic cancer, Gem chemotherapy did not improve OS after chemoradiotherapy. © 2012 Elsevier Inc.

Keywords: Pancreatic cancer, Radiotherapy, Adjuvant therapy, Gemcitabine, 5-Fluorouracil

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Introduction

Currently, there is no clear consensus on the role of adjuvant therapy for postoperative pancreatic cancer patients. Although many investigators have viewed the standard to be adjuvant 5-fluorouracil (5-FU) chemotherapy with radiotherapy (RT) based on the Gastrointestinal Tumor Study Group (GITSG) randomized trial (1), the controversial European Study Group for Pancreatic Cancer (ESPA) 1 trial has questioned this strategy, with supporters concluding that adjuvant RT is potentially detrimental (2).

With the arrival of gemcitabine (Gem), new treatment regimens have been investigated. The CONKO-001 (Charité Onkologie) trial showed that 6 months of adjuvant Gem was superior to observation in resected pancreatic cancer, with a median disease-free survival of 13.4 months vs. 6.9 months and a 5-year overall survival (OS) benefit of 21% vs. 9%; RT was not part of the trial design (3). However, the Radiation Therapy Oncology Group (RTOG) 9704 trial found that there was no survival difference between Gem before and after 5-FU/RT when compared with 5-FU before and after 5-FU/RT (4). Furthermore, the recent results of ESPA-3 showed no survival difference in patients receiving 5-FU/folinic acid vs. Gem at 2 years (5). Gem has also been found to be a strong radiosensitizer and has been studied in combination with RT (6). Two approaches have been developed in an attempt to maximize the therapeutic ratio: full-dose Gem with reduced-dose RT (7, 8) or low-dose Gem and full-dose RT (9).

Historically, at our institution, we treated our patients with 5-FU/RT alone as adjuvant treatment. With increasing data supporting the use of Gem as adjuvant therapy, we began to treat patients with 5-FU/RT plus adjuvant Gem. More recently, we introduced a series of Phase I/II protocols administering full-dose Gem with low-dose involved-field RT (7). We now have a current series of resected patients treated with three different adjuvant regimens. The purpose of this analysis was to examine survival outcomes among the three treatment groups at our institution and to examine the impact of adjuvant Gem.

Methods and Materials

After approval by the human investigation committee, all the records of patients diagnosed with pancreatic cancer who underwent resection followed by chemoradiotherapy from January 1998 to September 2010 at William Beaumont Hospital were retrospectively reviewed. Inclusion criteria included patients diagnosed with adenocarcinoma of the pancreas with gross total tumor resection and lymph node dissection (R0 and R1 resections only). Patients with metastatic disease (M1) were excluded. The selection of adjuvant chemotherapy and RT was based on medical and radiation oncologist preference; however, only patients who were treated with 5-FU-based or Gem-based chemotherapy were included.

Chemotherapy

Chemotherapy with 5-FU/RT consisted of a continuous infusion of 5-FU (250 mg/m²) administered Monday through Friday, bolus 5-FU (500 mg/m²) on Days 1 to 3 and Days 29 to 31 or oral capecitabine (1,300–1,600 mg/m² per day). Chemotherapy was initiated on Day 1 of RT. Sequential Gem was given either before or after 5-FU/RT at the discretion of the medical oncologist. When

initiated before RT, Gem was typically given for one cycle (3 weeks). When delivered after 5-FU/RT, Gem was usually given for a minimum of 3 months [(3 weeks on + 1 week off) × 3 cycles]. In patients who received Gem/RT, concurrent Gem was administered as a 30-minute intravenous infusion at a dose of 1,000 mg/m² given on Days 1, 8, and 15 of a 28-day cycle, with RT beginning on Day 1. The Gem/RT patients went on to receive approximately 6 months of Gem administration [(3 weeks on + 1 week off) × 6 cycles]. Chemotherapies given at the time of progression were at the discretion of the treating medical oncologist.

Radiotherapy

All patients were treated with three-dimensional conformal RT. Patients were virtually simulated in a supine position with an immobilizing foam cradle, with oral contrast given. Patients were treated with a 3- to 4-field approach with homogeneous dose calculations. Traditional field definitions were used in the 5-FU/RT groups. The clinical target volume encompassed the tumor bed, at least 3 cm of the pancreatic remnant, and the regional lymphatics, including the celiac axis, superior mesenteric vessels, duodenal and hepatoportal lymph nodes, and porta hepatis for pancreatic head tumors. The planning target volume (PTV) was typically treated to 45 Gy, and the tumor bed defined by the preoperative tumor volume was boosted to a cumulative dose of 50.4 to 61.2 Gy, depending on margin status. RT was delivered at 1.8 Gy per fraction given 5 days a week. The majority (72%) of these patients received 50.4 Gy.

In the Gem/RT group, an involved-field technique was used, which included covering the pancreatic bed, with a 1-cm margin around any pancreatic remnant (7). For tumors of the head of the pancreas, this included the celiac axis and superior mesenteric artery. A PTV margin of 0.5 cm was then included for daily patient setup variation. The median RT dose delivered was 36 Gy (range, 27–38 Gy). The majority of these patients (77%) received a dose of 36 Gy. Treatments were prescribed to the isocenter with the 95% isodose line encompassing the PTV.

Statistics

Differences in treatment groups were calculated with the unpaired Student *t* test. OS was calculated from the time of diagnosis. Rates of OS were estimated with Kaplan-Meier analysis and compared by use of the log-rank test. A *p* value of <0.05 was considered statistically significant. Statistical analyses were performed with SYSTAT, Version 11.0 (SPSS, Chicago, IL), and all statistical tests were two sided.

Results

A total of 86 patients were treated with either concurrent 5-FU or Gem chemoradiotherapy. The median follow-up was 19.0 months (range, 2.9–137.9 months). Sixty-four patients received concurrent 5-FU-based chemoradiation (5-FU/RT). Of these patients, 34 received only concurrent 5-FU/RT and no further adjuvant chemotherapy whereas 30 received adjuvant Gem either before and after 5-FU/RT (14 patients) or only after 5-FU/RT (16 patients). Twenty-two patients received concurrent full-dose Gem/RT followed by 6 months of additional Gem.

Table Patient and treatment characteristics				
	5-FU/RT alone	5-FU/RT + Gem	Gem/RT + Gem	<i>p</i> value
No. of patients	34	30	22	—
Age (y)				
Median	66	63	70	0.25
Range	41–83	48–82	40–82	
Performance status				
0	16 (47%)	12 (40%)	12 (54%)	0.15
1	16 (47%)	18 (60%)	7 (32%)	
2	2 (6%)	0 (0%)	3 (14%)	
T stage				
T1	3 (9%)	2 (7%)	1 (5%)	0.003
T2	16 (47%)	5 (17%)	1 (5%)	
T3	15 (44%)	23 (77%)	20 (91%)	
N stage				
N0	9 (26%)	10 (33%)	7 (32%)	0.77
N1	25 (74%)	20 (67%)	15 (68%)	
Location				
Head/neck	28 (82%)	27 (90%)	19 (86%)	0.68
Body/tail	6 (18%)	3 (10%)	3 (14%)	
Grade				
1	5 (15%)	2 (7%)	2 (9%)	0.44
2	14 (41%)	11 (37%)	4 (18%)	
3	13 (38%)	16 (53%)	15 (68%)	
Unknown	2 (6%)	1 (3%)	1 (5%)	
Margin status				
Negative	26 (76%)	24 (80%)	17 (77%)	0.78
Positive	8 (24%)	6 (20%)	4 (18%)	
Unknown	0 (0%)	0 (0%)	1 (5%)	
RT dose (cGy)				
Median	5,040	5,040	3,600	—
Range	4,500–6,120	4,500–6,040	2,700–3,800	
RT duration (d)				
Median	39	39	21	—
Range	30–58	31–54	18–31	

Abbreviations: 5-FU/RT = concurrent 5-fluorouracil or capecitabine radiotherapy; Gem = gemcitabine; Gem/RT = concurrent gemcitabine radiotherapy; RT = radiotherapy.

The median age of the cohort was 65 years (range, 40–80 years). Of the patients, 58 had pathologic T3 tumors (67%), 22 had T2 tumors (26%), and 6 had T1 tumors (7%). Positive lymph nodes were found in 61 patients (71%), and 18 patients (21%) had positive margins. The three treatment groups had similar baseline characteristics (Table), with the exception of T stage: the 5-FU/RT-alone group had fewer T3 tumors compared with the other two treatment groups (*p* = 0.003). There were no differences in Eastern Cooperative Oncology Group performance score, age, N stage, tumor location, grade, or margin status.

At last follow-up, 65 of 86 patients had died, with a median OS of 21.0 months and a 5-year OS rate of 18%. The median OS was similar among the three groups (Fig. 1), at 19.2 months, 19.0 months, and 21.0 months for the 5-FU/RT-alone group, 5-FU/RT-plus-Gem group, and Gem/RT group, respectively (*p* = 0.88). The 2-year survival rates were also similar, at 26.5%, 27.2%, and 32.1%, respectively. The 5-FU/RT group, which had the longest follow-up, had a 5-year OS rate of 21%.

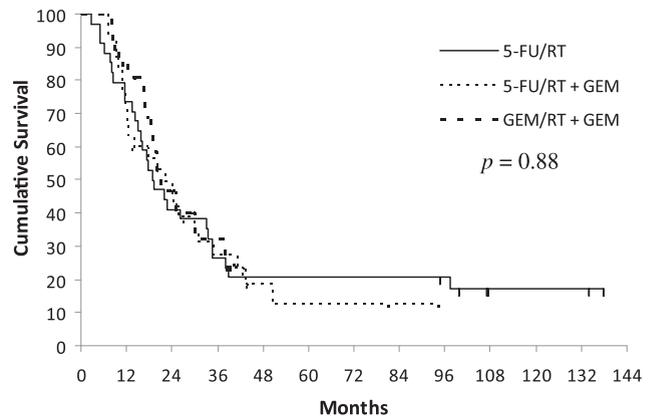


Fig. 1. Overall survival of patients treated with concurrent 5-fluorouracil or capecitabine radiotherapy (5-FU/RT alone), concurrent 5-fluorouracil or capecitabine radiotherapy plus adjuvant gemcitabine (5-FU/RT + Gem), or concurrent gemcitabine radiotherapy plus adjuvant gemcitabine (Gem/RT + Gem).

Patients who received adjuvant Gem after chemoradiotherapy had a similar median OS (22.1 months) and 3-year OS rate (29.0%) compared to patients who did not (19.2 months and 26.5%, respectively) (*p* = 0.62). There was a trend for improved 3-year OS rates (28.1% vs. 14.2%) in patients with R0 resections (*p* = 0.06) (Fig. 2). When we compared T3 with T1 and T2 tumors, there was a trend for better survival in patients with T1 and T2 tumors (*p* = 0.09) (Fig. 3). When we compared just the T3 tumors, there was no difference in survival among the three treatment groups (*p* = 0.6) (data not shown). Lymph node-negative patients had an improved 5-year OS rate (30.1%) when compared with patients with N1 disease (16.2%) (*p* = 0.02) (Fig. 4). Various radiation dose levels were also analyzed; however, no survival differences were found when stratified by dose.

Discussion

In our series of patients with resected pancreatic cancer, there was no survival difference among patients treated with adjuvant 5-FU/RT alone, 5-FU/RT plus Gem, or Gem/RT plus additional Gem. The median OS of our cohort was 21.0 months, which is similar to the median survival reported in other large randomized trials (1, 3–5, 10). For example, CONKO-001 found a median OS of 22.8 months with Gem alone (3), and the 5-FU/RT-plus-Gem arm of RTOG 9704 had a median OS of 20.5 months (4).

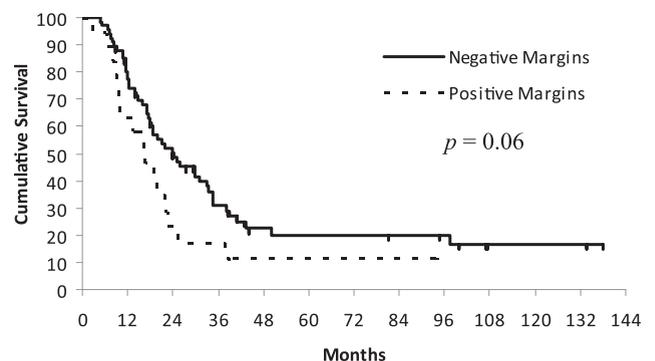


Fig. 2. Overall survival of patients with negative margins vs. positive margins.

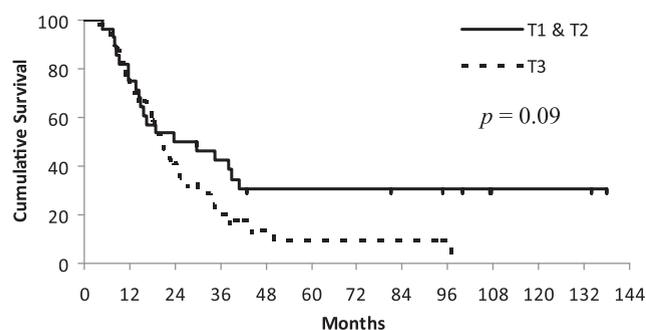


Fig. 3. Overall survival of patients with T1 and T2 tumors vs. T3 tumors.

At this time, there remains no consensus on what is the optimal adjuvant therapy after resection. The National Comprehensive Cancer Network guidelines currently state that adjuvant 5-FU/RT with Gem and adjuvant Gem alone are both acceptable options (Version 2.2011, www.nccn.org). The role of adjuvant chemoradiotherapy was established by the GITSG trial, which showed a survival advantage with 5-FU/RT followed by adjuvant 5-FU when compared with observation (1). The results of the GITSG trial have been confirmed with additional studies using updated RT techniques (11–13), and thus 5-FU/RT had been the standard adjuvant therapy for many years. Adjuvant Gem became incorporated into adjuvant therapy after the initial publication of the CONKO-001 study, which did not test the role of RT but did show a survival advantage of adjuvant Gem over observation (3).

More recently, the ESPAC-3 trial was designed to determine which adjuvant chemotherapy is superior, 5-FU/leucovorin or Gem; however, the results showed survival to be equivalent between the two arms. This trial did not include RT in the treatment schema, leaving the guidelines unclear at this time (5). RTOG 9704 also examined the role of adjuvant 5-FU vs. adjuvant Gem but included 5-FU/RT sandwiched within the chemotherapy schema and found no difference in survival between the two adjuvant regimens (4). Concurrent Gem/RT has been introduced as a way to optimize local control as well as systemic control at the same time. Gem is a potent radiosensitizer (6), and studies have shown that it can be delivered safely by use of involved-field RT (36 Gy) concurrent with full-dose Gem (7). This combination is considered advantageous because it eliminates the delay of administering adjuvant Gem.

Our study, which showed that the addition of adjuvant Gem provided no further benefit, may help explain the findings of RTOG 9704. In RTOG 9704 all patients received 5-FU/RT, and

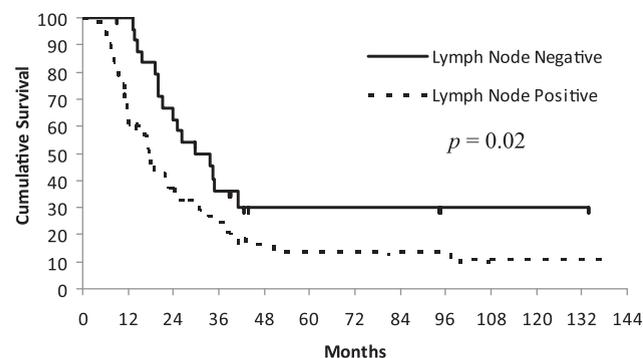


Fig. 4. Overall survival of patients with negative lymph nodes vs. positive lymph nodes.

the additional chemotherapy may not have given any added benefit over 5-FU/RT. Thus RTOG 9704 may have been a negative study not because an inadequate amount of chemotherapy was given, four cycles of Gem compared with six cycles in CONKO-001, but because the chemotherapy was of no further benefit in this irradiated group of patients. Our findings also contradict ESPAC-1, the controversial 2×2 randomized study that suggested that 5-FU/leucovorin alone was superior and that the addition of split-course RT was harmful (2). ESPAC-1 found a median OS of only 14 months in the 5-FU/RT-alone arm. This trial has been justifiably criticized, and its findings should not be used to support the omission of RT. The addition of RT is important for local control, given that the local failure rate after surgery alone is as high as 50% to 80% (2, 14, 15). In RTOG 9704, which used a centralized RT quality-control review, the local recurrence rate was as low as 28% (4). There is also a potential benefit of chemoradiotherapy in patients with R1 resections or positive lymph nodes (16).

The median OS in the 5-FU/RT-alone patients was 19.2 months compared with 17.0 months in the pancreatic head patients who also received 5-FU/RT alone in the European Organisation for Research and Treatment of Cancer 40891 trial (10). The European Organisation for Research and Treatment of Cancer trial used split-course RT techniques, which could explain the difference. Our 5-FU/RT-alone arm, which has the longest follow-up, also had a 5-year survival of 21%, which is comparable to other trials including those that use adjuvant Gem (3, 4). It is difficult to compare between studies, but our findings support the continued inclusion of 5-FU/RT in clinical trials with the consideration of including a 5-FU/RT-only group. If 5-FU/RT was found to be comparable to 6 months of Gem, this would offer patients a shorter treatment course and could potentially reserve Gem-based chemotherapy for progressive disease.

This study is limited by the fact that it is retrospective. Overall, the three groups were balanced except for T stage, with the 5-FU/RT group having fewer T3 tumors. This could explain the equivalence among the groups. When comparing T3 with T1 and T2 tumors, we found a trend for better survival in patients with T1 and T2 tumors ($p = 0.09$). However, when excluding the T1 and T2 tumors and examining just the T3 tumors, we found no survival difference among the three treatment groups. Lymph node involvement and positive margins, which were well balanced among the groups, are also considered risk factors and are shown in our data (Figs. 2 and 4).

Conclusion

In our series of patients from a single institution treated with 5-FU/RT alone, 5-FU/RT plus Gem, and full-dose Gem/RT plus Gem, there was no survival difference. The addition of adjuvant chemotherapy may not contribute to survival if traditional, non-split-course 5-FU/RT is given. Further randomized trials will be needed to determine the optimal adjuvant therapy for resected pancreas cancer.

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