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A Phase II Trial of Gemcitabine, 5-Florouracil, and Radiation Therapy in Locally Advanced Non-Metastatic Pancreatic Adenocarcinoma: Cancer and Leukemia Group B (CALGB) 80003

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Abstract

Purpose—To assess the efficacy and safety of 5-fluorouracil (5FU) and gemcitabine administered concurrently with radiation in patients with locally advanced, non-metastatic pancreatic cancer.

Patients and Methods—Eligible patients had histologically confirmed pancreatic adenocarcinoma, deemed locally unresectable without evidence of metastatic disease. In addition, all patients underwent laparoscopy or laparotomy prior to study entry to rule out peritoneal carcinomatosis. Patients received radiation therapy (50.4 Gy) with concurrent infusional 5FU (200 mg/m^2, 5 days per week) and weekly gemcitabine (200 mg/m^2). After a three-week break, patients received weekly gemcitabine at 1000 mg/m^2 for 3 of 4 weeks, for four cycles. The primary endpoint of the trial was the proportion of patients surviving nine months from study entry. Secondary endpoints included objective tumor response, CA19-9 response, overall survival (OS) time to progression (TTP) and toxicity.

Results—Between November 2001 and October 2004, 81 patients were enrolled, of whom 78 were eligible for analysis. With a median follow-up of 55.2 months, the median OS was 12.2 months (95% CI, 10.9 – 14.9 months) and median TTP was 10.0 months (95% CI 6.4 – 12.0 months). An objective tumor response was seen in 19 patients (25%) and among 56 patients with an elevated CA19-9 at baseline, 29 (52%) had a sustained CA19-9 response. Overall, 41% of patients had grade 3 or greater treatment-related GI adverse events.

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Conclusion—The combination of 5FU, gemcitabine and radiation is well-tolerated. Survival is comparable to the best results of other recent studies of 5FU and radiation or gemcitabine and radiation.

Keywords

pancreatic cancer; gemcitabine; 5-fluorouracil; radiation; combined modality therapy

INTRODUCTION

Pancreatic cancer, the fourth leading cause of cancer death in the United States1, remains one of the most treatment-refractory solid malignancies. Approximately 40% of patients with newly diagnosed pancreatic cancer present with locally advanced, non-metastatic disease.

In two randomized trials by the Gastrointestinal Tumor Study Group, the combination of fluorouracil and external beam radiation was shown to be more effective than either modality alone, with a median overall survival of approximately 42 weeks2–4. An Eastern Cooperative Oncology Group (ECOG) study, however, failed to demonstrate an advantage to combined modality therapy5. The French FFCD-SFRO trial suggested a detriment in survival when combined chemoradiation therapy was compared to gemcitabine alone6. However, in this intensive regimen increased toxicity may have contributed to the poor outcome. Despite these conflicting results, efforts over the past three decades have attempted to improve the efficacy of chemoradiation, largely by incorporating more active systemic therapy.

Among patients with metastatic or locally advanced pancreatic cancer, gemcitabine therapy has led to a superior clinical benefit when compared to 5-fluorouracil (5FU) 7. As gemcitabine has been shown to enhance the sensitivity of human pancreatic cancer cells to radiation8, 9 several investigators have assessed the impact of gemcitabine when combined with radiation. Most investigators combined lower doses of gemcitabine with conventional radiation10–20. An alternative approach has been to combine full-dose gemcitabine with a hypofractionated course of radiation21–23. Several groups have combined radiation and gemcitabine with additional agents, including cisplatin24–29, oxaliplatin30, taxanes31, 32, irinotecan33, mitomycin34 and inhibitors of EGFR and VEGF35–39.

As 5-FU and gemcitabine are both active radiation sensitizing agents and represent the two principal systemic agents for pancreatic cancer, we conducted a phase I/II trial combining 5FU, gemcitabine and radiation in patients with locally advanced disease. The regimen appeared well-tolerated with maximum tolerated doses of 200 mg/m^2/day for infusional 5FU and 200 mg/m^2/week for gemcitabine with 50.4 Gy of radiation. More recently, Wilkowski reported a similar experience in a group of 32 patients, with a median survival of over 13 months40. In contrast, a similar phase I study of concurrent 5-FU, gemcitabine and radiation led by ECOG reported unacceptable toxicity41. Five of the seven treated subjects experienced dose-limiting toxicities, three of which involved GI bleeding. To clarify the safety and efficacy of this combination, we conducted a multi-institutional phase II trial of 5FU, gemcitabine and external beam radiation therapy in patients with locally advanced pancreatic cancer.

PATIENTS AND METHODS

Patient Eligibility Criteria

Eligible patients had biopsy-proven, localized, unresectable adenocarcinoma of the pancreas and an ECOG performance score of 0 – 2. Criteria for unresectability and eligibility included one or more of the following: a tumor measuring greater than 5 cm, regional lymph nodes greater than 2 cm in size that could be included within the radiation port, involvement of major vessels including the superior mesenteric artery, superior mesenteric vein, portal vein or hepatic artery, and direct extension of tumor to adjacent organs. Staging studies included a chest x-ray and an abdominal/pelvic CT scan; patients underwent a laparotomy or laparoscopy to rule out the presence of occult peritoneal disease. Exclusion criteria included a prior malignancy other than non-melanoma skin cancer or in-situ cervical cancer within the past five years, or other major co-morbidities such as myocardial infarction within six months of study entry. Required laboratory values included a total bilirubin below 2.0 mg/dl, and AST ≤ 3x upper limits of normal, creatinine ≤ 2.0 mg/dl, WBC ≥ 3,000/mm^3 and platelets ≥ 100,000/mm^3. All patients signed a consent form, and the study was approved by the Human Investigations Committee of participating Cancer and Leukemia Group B (CALGB) institutions.

Study Design and Treatment Plan

This was an open-label, non-randomized phase II study. Cycle one consisted of radiation to 50.4 Gy in 28 fractions over 5.5 weeks, with 5FU given as a continuous infusion from Monday through Friday at 200 mg/m^2/day and gemcitabine given weekly at 200 mg/m^2, both given throughout the radiation therapy course. Three weeks following the completion of radiation, patients received gemcitabine at a dose of 1000 mg/m^2 over 30 minutes weekly for three weeks, followed by a one-week rest, for four 4-week cycles.

Radiation was delivered on a linear accelerator with a minimum energy of 6 MV. Patients were simulated on a machine that reproduced the geometry of the treatment machine; multi-field techniques were mandatory. Doses were specified to isocenter. Patients were treated to 4500 cGy in 25 fractions to an initial tumor / nodal field, followed by a boost field for an additional 540 cGy in 3 fractions. The gross tumor volume (GTV) included the pancreatic mass and any lymph nodes measuring > 1.5 cm as visualized on CT scan. The clinical target volume (CTV) was defined by expanding the GTV for 1 to 1.5 cm, including the porta hepatic and pancreaticoduodenal nodes for head lesions, and the celiac axis for tumors of both the head and body/tail. The planning target volume (PTV) was based on a 1 cm expansion of the CTV. The boost volume consisted of the GTV with a 1 cm expansion for the boost PTV. Normal tissue constraints included no portion of the spinal cord receiving above 4500 cGy, no more than 50% of the combined renal volume receiving above 2000 cGy and no more than 1/3 of the total liver volume receiving above 3000 cGy. All treatment plans were reviewed by the Quality Assurance Review Center (QARC) in Providence, RI, and by the study chair.

Dose Modifications for Adverse Events

Adverse events were scored using version 2.5 of the Common Terminology Criteria for Adverse Events. During cycle 1, a decrease in platelets to between 50,000–99,999/mm^3 and/or a decrease in the ANC to 500–999/mm^3 resulted in a 75% dose-reduction for gemcitabine and a 50% dose-reduction for 5FU. If the ANC decreased below 500/mm^3 or the platelets decreased below 50,000/mm^3, then chemotherapy and radiation were held until the ANC was greater than or equal to 1,000/mm^3 and the platelet count was above 100,000/mm^3. If treatment was held for greater than three weeks, the patient was removed from protocol treatment.

For non-hematologic events, both gemcitabine and 5FU were reduced to 75% of the dose for grade 3 toxicity and to 50% of the dose for grade 4 toxicities. Reduced doses of chemotherapy were not re-escalated. Owing to concerns about GI bleeding raised by ECOG 229742 stopping rules dictated study termination if more than 10 cases of grade 3 or higher GI bleeding were observed among the first 35 patients. The incidence of bleeding was followed in cohorts of seven patients, with plans to stop accrual if any of the following proportions of patients had grade 3 or higher GI bleeds: 5 of 7, 6 of 14, 7 of 21, 9 of 28 or 11 of 35.

During cycles 2–5 (gemcitabine alone), the dose of gemcitabine was reduced by 25% for an ANC between 500 and 999/mm^3 and held for an ANC below 500/mm^3. For grade 3 non-hematologic toxicities gemcitabine was held and re-started at a 25% dose reduction when the toxicity had resolved. For grade 4 non-hematologic adverse events, the gemcitabine was held and re-started at a 50% dose reduction when the toxicity had resolved. Dose reductions were continued through all subsequent cycles of gemcitabine.

Patient Monitoring

Patients were assessed weekly by history and physical examination. Laboratory studies, including blood counts, BUN, creatinine, bilirubin, AST, alkaline phosphatase and CA19-9 were obtained weekly during combined chemoradiation and prior to each subsequent cycle of gemcitabine. Blood counts were assessed prior to each weekly administration of gemcitabine.

Statistical Considerations

The primary endpoint was the proportion of patients surviving nine months. Secondary endpoints included overall survival (OS), measured from study entry to death from any cause, time-to-tumor progression (TTP) measured from study entry to documented progression of disease or death from any cause, CA19-9 response defined as ≥ 75% decrease from the baseline maintained for two consecutive measurements at least four weeks apart among patients with an elevated baseline CA19-9, and toxicity. The prior protocol for patients with locally advanced pancreatic cancer, CALGB 89805, studied concurrent gemcitabine (40 mg/m^2 twice weekly) and radiation therapy in a similar patient population. Based on the median survival of 8 months in that study17, it was determined that a median survival of 9 months or less in the current protocol would be considered unworthy of further investigation. An accrual goal of 78 evaluable patients to be followed for a minimum of 9 months was targeted resulting in 80% power to distinguish between median survival rates of 9 and 13 months. If the 90% lower confidence bound estimate (90% LCB) for the proportion of patients surviving 9 months were to exceed 0.5, the regimen would be considered for further investigation.

Patient registration and data collection were managed by the CALGB Statistical Center. Data quality was ensured by careful review of data by CALGB Statistical Center staff and by the study chairperson. All analyses were based on the study database frozen on March 3, 2009 and performed by CALGB statisticians using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Eighty-one patients from 15 U.S. institutions were accrued between November 2001 and October 2004, of whom 78 were eligible for analysis. Three patients who canceled their registration prior to starting any protocol treatment were excluded from the analysis. Pre-treatment characteristics of the eligible patients are shown in Table 1. Thirty-six percent of

patients underwent palliative bypass surgery prior to starting treatment, 47% underwent the placement of a biliary stent. The majority of patients had T4 tumors with vascular involvement.

Efficacy

The median survival of the 78 eligible patients was 12.2 months (Table 2, Fig. 1) with four patients reported alive at 39, 52, 58 and 60 months of follow-up. The estimated one-year survival was 51% (95% CI 0.4 – 0.62). The 90% lower confidence bound for the proportion of patients surviving 9 months was 0.64. The Kaplan-Meier survival estimate at 9 months was 73% (95% CI 0.62 – 0.82). The probability of being progression free (Table 2, Fig. 2) was 0.54 (95% CI 0.42 – 0.64) at 9 months and 0.40 (95% CI 0.29 – 0.50) at 1 year. Median TTP was 10 months (95% CI 6.4 – 12.0).

Of the 56 patients with an elevated serum CA19-9 level at study baseline, 29 (52%) experienced a sustained CA19-9 response, defined as a greater than 75% decrease lasting for at least two measurements more than four weeks apart. When compared to patients who did not experience a sustained CA19-9 response, subjects with a sustained response exhibited a trend toward improved OS (median, 13 vs. 9 months; $P = 0.11$) and a statistically significant improvement in TTP (median, 12.3 vs. 5.7 months, $P = 0.007$) (Figs. 3–4). Based on RECIST criteria, 19 patients (24%) experienced an objective response, of whom 5 (6%) had a complete response and 14 (18%) had a partial response. The median response duration was 5.5 months, with a minimum and maximum duration of 1 and 52.2 months, respectively (including 12 patients with progressive disease and 4 patients who died without documented progression). In addition, 41 (53%) had stable disease as their best response, 14 (18%) had progressive disease and 4 patients (5%) were unevaluable. The median time to objective response was 3.6 months (range 1.7 – 9.0).

Patterns of Failure

Twenty-eight (36%) of the patients had local progression in the pancreas as the first site of failure. The next most common site of disease progression was in the liver, which occurred in 23 (30%) of patients, followed by the lung (10%) and peritoneum (9%).

Treatment Modifications

Twenty-seven patients (35%) completed all protocol therapy. The most common reason for stopping treatment was progressive disease, which occurred in 21 (27%) patients. Nine (12%) discontinued treatment because of adverse events. Other common reasons for discontinuing protocol treatment included being switched to non-protocol therapy (9%) and patient refusal (9%).

A total of 64 patients (82%) had at least one treatment modification during the course of therapy at a mean of 22 days after starting protocol treatment. Twenty-two patients had a single dose modification. The maximum number of dose adjustments was 5 in two patients.

Radiotherapy Quality Assurance

All of the radiation therapy treatment plans were reviewed by QARC (Quality Assurance in Radiation Oncology) in Providence, RI, and by the study chair. Major deviations were defined as field borders that transected the gross tumor (GTV) or potentially tumor bearing areas (CTV). In addition, a dose discrepancy of more than 10% above or below the recommended dose at the prescription point, or exceeding the recommended dose to adjacent critical organs was considered a major deviation. Of the 78 patients who started radiation therapy, 65 cases were scored as appropriate, three had major deviations and seven had minor deviations. The remaining 3 cases were unevaluable due to insufficient data

provided. Sixty-eight patients (87%) completed the planned 28 fractions to a total dose of 5040 cGy. Ten patients discontinued radiation, one each after 3, 4, 13, 21, 22, and 24 fractions, two each after 25 and 26 fractions.

Adverse Events

Among the 78 patients, 55 (71%) experienced grade 3 or higher non-hematological adverse events possibly attributed to treatment and 50 (64%) patients experienced grade 3 or higher related hematologic adverse events (Table 3). The most common non-hematologic events were gastrointestinal in 32 (41%) subjects, and constitutional and metabolic/laboratory each in 19 (24%).

Without regard to attribution, 11 patients (14%) had at least one episode of gastrointestinal bleeding during the study or follow-up period, of which five were considered grade 3 or higher and possibly related to treatment. Neither a palliative surgical bypass nor placement of a stent correlated with an increased risk of GI bleeding. Five of these 11 gastrointestinal hemorrhages were localized within the radiation field.

Sixty-five (88%) of the deaths in the study population were secondary to disease progression. Two deaths (2%) were considered to be treatment-related, resulting from gastrointestinal bleeding in one subject and sepsis without neutropenia in the second. Three deaths resulted from causes other than treatment or disease.

DISCUSSION

The benefit for treating locally advanced, non-metastatic pancreatic cancer remains limited, with median survival ranging from eight to ten months43. In the current study of 78 patients, a combination of gemcitabine and 5FU with radiation therapy conferred a median OS of 12.2 months and a median TTP of 10 months. In a previous phase I/II trial of gemcitabine, 5-FU and concurrent radiation therapy, we similarly observed a median survival of 12 months in patients with locally advanced disease. These results compare favorably to prior studies of 5-FU with radiation, which reported a median OS of nine months and a median TTP of eight months or less.

Following the initial studies of 5-FU and radiation therapy in locally advanced pancreatic cancer, subsequent studies have also yielded median survivals well above the historical level of nine months. This gradual improvement in outcome over the past several years is apparent for both studies of radiation with gemcitabine10, 11, 14, 15, 17–23, 44 and for other chemoradiation combinations3, 27, 39, 40, 45–50. The reasons for this improvement are speculative, but may include slightly improved treatment regimens, improved staging which excluded patients with not easily apparent metastatic disease, improved supportive care, and improved salvage chemotherapy.

The current trial found the combination of 5FU and gemcitabine with concurrent radiation to be tolerable, though toxicity was moderate. Twelve percent of patients discontinued protocol therapy due to adverse events and 82% had at least one treatment modification. Our incidence of adverse events was comparable to other recent cooperative group trials in this patient population including a study of radiation with concurrent capecitabine and bevacizumab39 and a trial of radiation with concurrent gemcitabine and cisplatin29. In contrast to a prior ECOG trial51, the incidence and severity of gastrointestinal bleeding was manageable.

Our trial met its target of 50% of patients surviving for at least 9 months; 9-month survival was 73% and median overall survival was 12.2 months. A similarly designed trial of 32

patients combining higher doses of weekly gemcitabine and infusional 5-FU with radiation, followed by gemcitabine and cisplatin, observed a median OS of 13.6 months, although toxicity in that trial was considerable40.

The merits of combined chemoradiation as initial treatment for locally advanced pancreatic cancer have been questioned by the results of a recent randomized trial that demonstrated a superior outcome for patients receiving gemcitabine alone compared to chemoradiation followed by gemcitabine6. An alternative approach has been examined in which patients receive initial chemotherapy, with chemoradiation offered only to those patients without disease progression. In one retrospective study of 188 patients who had received three months of initial chemotherapy, 128 patients who did not demonstrate progressive disease received either further chemotherapy or combined chemoradiation. Although such non-randomized data must be interpreted with caution, the median progression free survival and OS for the patients receiving chemoradiation were 10.8 and 15 months, respectively, compared to 7.4 and 11 months for those treated with chemotherapy alone52. Other investigations have similarly suggested a benefit to selecting patients for combined chemoradiation following induction chemotherapy53–55. Such an approach potentially avoids radiation in patients who are destined to manifest metastatic disease, limiting local therapy to those who are most likely to derive a benefit. One promising strategy for future studies may be to build on this schedule of induction chemotherapy followed by chemoradiation with the addition of targeted agents emerging from an improved understanding of pancreatic cancer biology56–59.

We have demonstrated the feasibility of combining both 5-FU and gemcitabine with radiation, with several long term survivors and a superior overall survival compared to historical levels of eight to ten months. Although this regimen has achieved the pre-defined goals of improving median survival beyond nine months with acceptable morbidity, the observed median survival of 12 months is similar to the results of other recent phase II trials in patients with locally advanced pancreatic cancer. Given the multiple other treatment regimens that similarly appear to confer a 12-month median survival, we do not recommend further study of this treatment combination in future trials.

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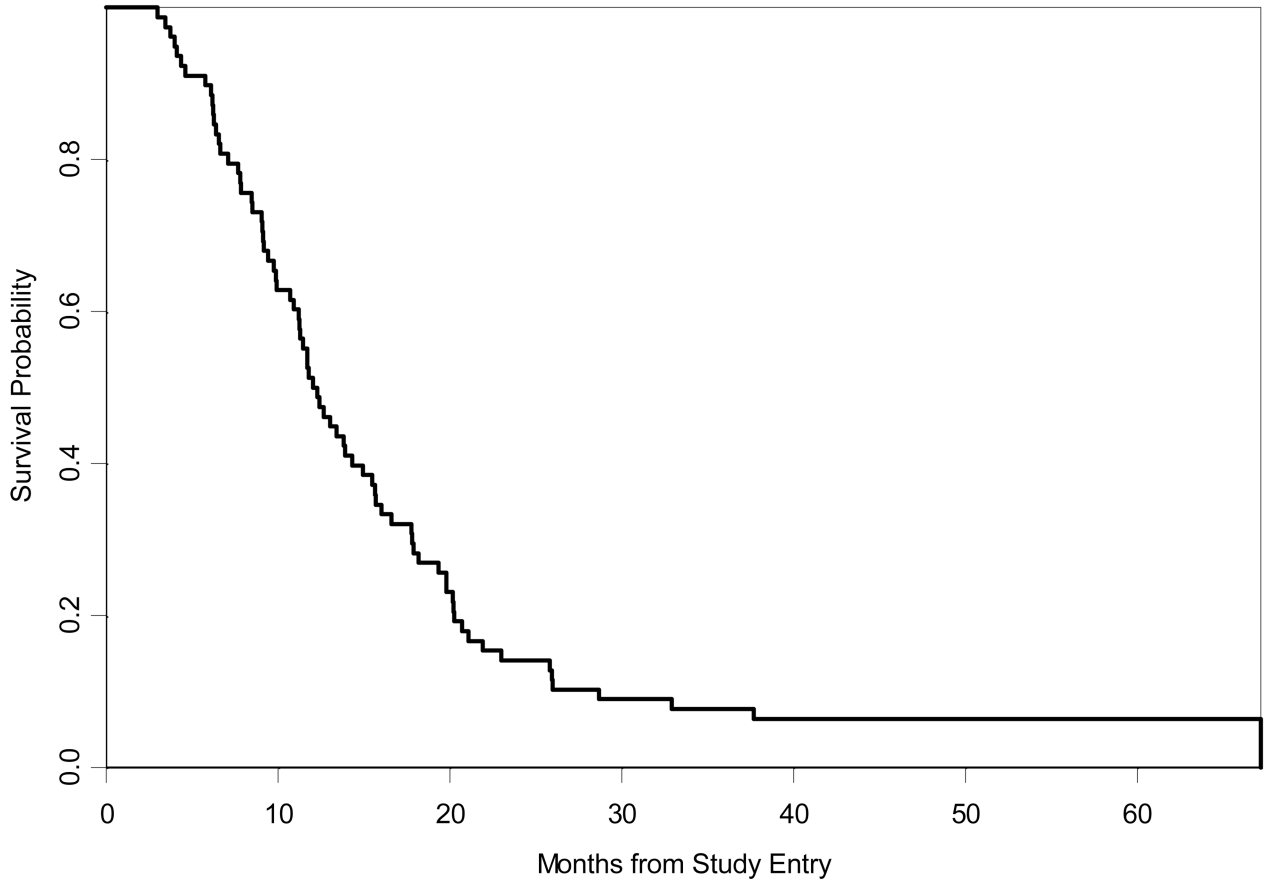
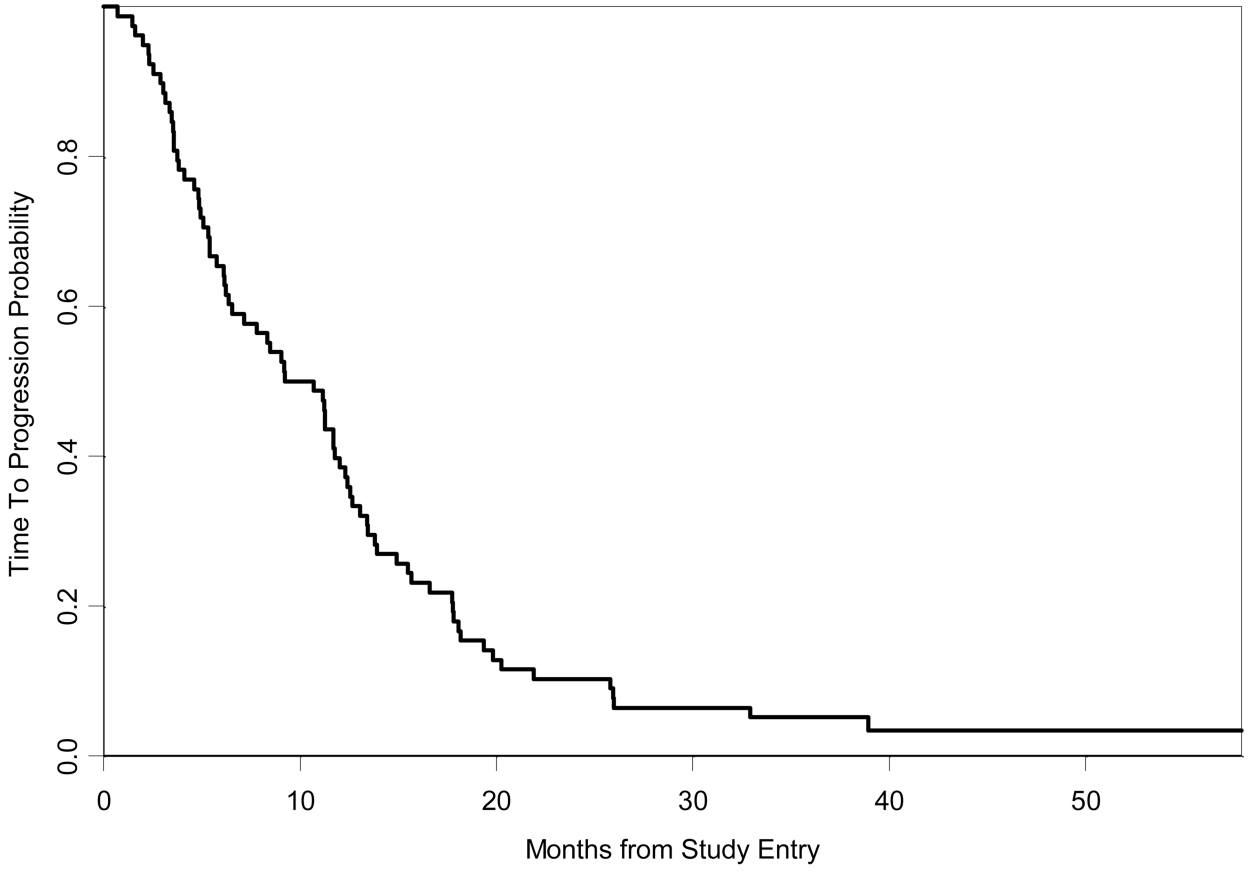


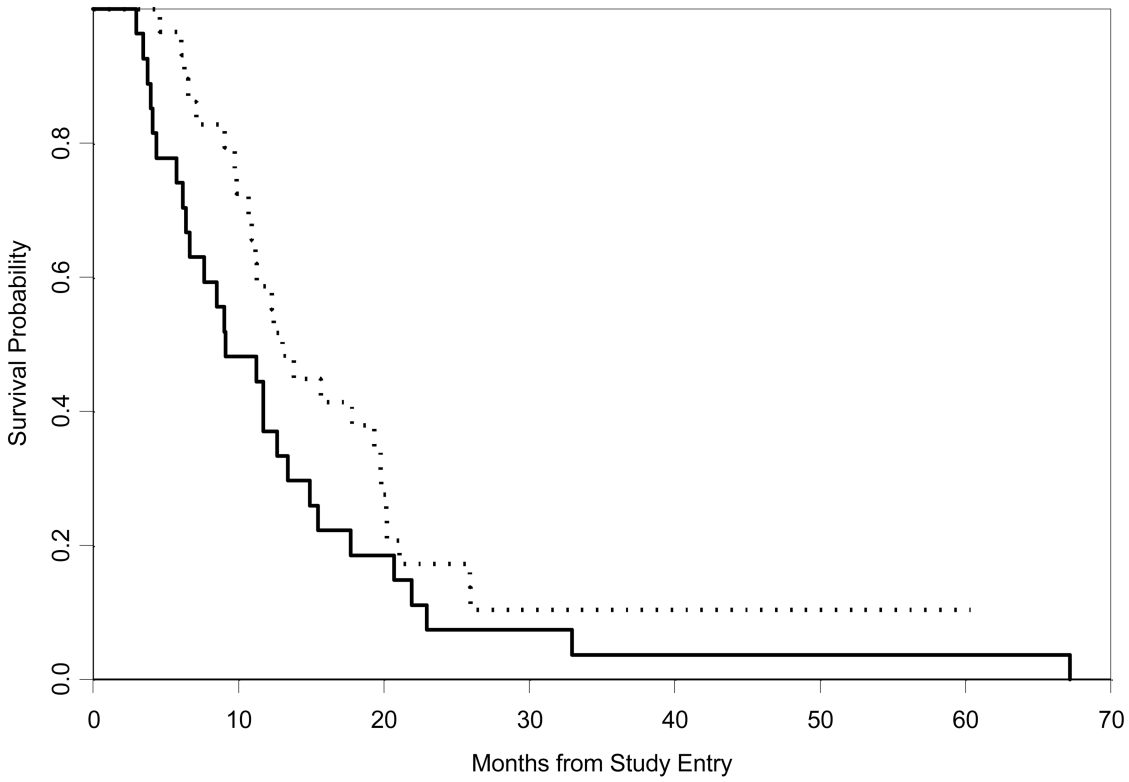
No. of Subjects	Event	Censored	Median Survival (95% CL)
78	95% (74)	5% (4)	12.2 (10.9, 14.9)

Figure 1.
Overall Survival for all patients



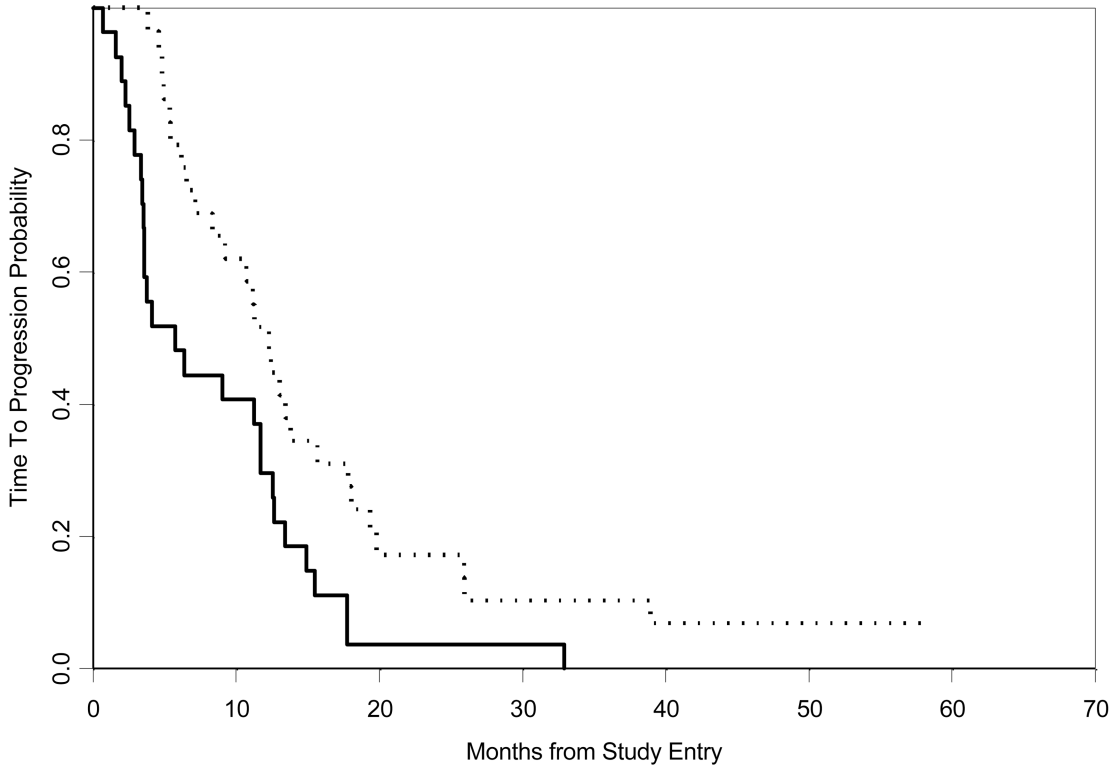
No. of Subjects	Event	Censored	Median TTP (95% CL)
78	96% (75)	4% (3)	10.0 (6.4, 12.0)

Figure 2.
Time to Progression for all patients



	No. of Subjects	Event	Censored	Median Survival (95% CI)	p-value
—— No sustained CA 19-9	27	100% (27)	0% (0)	9.1 (6.4, 13.4)	0.1147
····· Sustained CA 19-9	29	90% (26)	10% (3)	13.0 (10.9, 19.8)	

Figure 3.
Overall Survival analyzed according to CA19-9 response



	No. of Subjects	Event	Censored	Median TTP (95% CL)	p-value
——No sustained CA 19-9	27	100% (27)	0% (0)	5.7 (3.5, 11.7)	0.0071
····· Sustained CA 19-9	29	93% (27)	7% (2)	12.3 (8.3, 15.7)	

Figure 4.
Time to Progression analyzed according to CA19-9 response

Table 1

Patient characteristics

Gender	M	39(50%)
	F	39(50%)
Race	White	70(90%)
	Hispanic American	1(1%)
	African American or Black	6(7%)
	Asian	1(1%)
Age	Mean (Std. Dev.)	62.3(9.8)
Performance Status	0	27(34%)
	1	4 (58%)
	2	6(8%)
Size (cm)	Mean (Std. Dev.)	3.7(1.7)
	Median (Range)	3.8(0 – 8.8)
Grade	Well differentiated	8(10%)
	Moderately differentiated	19(24%)
	Poorly differentiated	17(22%)
	Undifferentiated	2(3%)
	Unknown	32(41%)
T	2	13(17%)
	3	14(18%)
	4	51(65%)
N	0	50(64%)
	1	21(27%)
	X	7(9%)
Location	Head	67(87%)
	Body	16(21%)
	Tail	5(7%)
Vessel involvement		69(89%)
Baseline CA19-9	Mean(Std. Dev.)	1288(2130)
	Median(Range)	402(3,10854)

Table 2

Survival and time to progression

Proportion Surviving 9 Months		
	Proportion	0.731
	90% Lower Confidence Bound	0.64
Median Follow-up Time		
	N alive	4
	Median (range)	55.2(38, 60) months
Overall Survival		
	N	78
	Number Censored (%)	4 (5.1%)
	Kaplan-Meier Estimate, 9-months (95% CI)9-month Survival Estimate (95% CI)	0.73(0.62, 0.82)
	Kaplan-Meier Estimate, 12-months (95% CI)12-month Survival Estimate (95% CI)	0.51(0.40, 0.62)
Median Follow-up Time		
	N alive	4
	Median	55.2 months
Time to Progression		
	N	78
	Number Censored (%)	3 (3.8%)
	3-month Survival Estimate (95%CI)	0.90(0.81, 0.95)
	Kaplan-Meier Estimate, 9-months Survival Estimate (95% CI)	0.54(0.42, 0.64)
	Kaplan-Meier Estimate, 12-month Survival Estimates (95% CI)	0.40(0.29, 0.50)

Table 3

Commonly observed treatment related adverse events, grade 3 and higher

Category	Grade 3 N (%)	Grade 4 N (%)	Grade 5 N (%)
Blood / bone marrow	40(51)	10(13)	0
Hemoglobin	6(8)	1(1)	0
Total WBC	30(38)	6(8)	0
Lymphopenia	20(26)	0	0
Neutropenia	16(21)	7(9)	0
Thrombocytopenia	11(14)	1 (1)	0
Transfusion: platelets	1(1)	0	0
Transfusion: pRBCs	4(5)	0	0
Non-hematological	47(60)	21(27)	2(3)
Cardiovascular (general)	3(4)	1(1)	0
Constitutional symptoms	17(22)	2(3)	0
Gastrointestinal	29 (37)	3(4)	0
Hemorrhage	2(3)	2(3)	1(1)
Hepatic	7(9)	0	0
Infection / febrile neutropenia	8(10)	0	1(1)
Metabolic / laboratory	17(22)	2(3)	0
Neurology	5(6)	0	0
Pain	8(10)	1(1)	0