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Longer course of induction chemotherapy followed by chemoradiation favors better survival outcomes for patients with locally advanced pancreatic cancer

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Abstract

Objectives—At diagnosis, 30% of patients with pancreatic cancer are unresectable stage 3 locally advanced. The standard treatment for locally advanced pancreatic cancer (LAPC) is not defined. The current study was conducted to assess the roles of chemotherapy and chemoradiation for LAPC treatment.

Methods—Between June 2006-March 2011, 100 patients with LAPC were treated at Johns Hopkins Hospital. Retrospective analysis was performed to compare cumulative incidence of progression (CIP) and overall survival (OS) among different subgroups.

Results—For the 100 patients, median OS was 15.8 months and median CIP 8.4 months. The combination of chemotherapy and chemoradiation prior to disease progression was significantly associated with improved CIP (p=0.001) and improved OS when compared to chemoradiation alone (median OS 16.4 vs. 11.1 mo; p=0.03). Among patients receiving combination treatment, patients who received chemotherapy first followed by chemoradiation had a trend towards lower CIP (p=0.09) and improved OS (median OS: 18.1 vs. 11.0 mo, p=0.09). Patients who received >2 cycles of chemotherapy prior to chemoradiation had a significantly decreased CIP (p=0.008) and a trend toward better OS (median OS 19.4 vs. 15.7 mo, p=0.10). On multivariate analysis, receiving >2 cycles of chemotherapy prior to chemoradiation was associated with improved CIP.

Conclusions—While combination chemotherapy and chemoradiation is favored in the treatment of LAPC, longer induction chemotherapy may play a more important role in sensitization of tumors to subsequent chemoradiation. Our results support treating patients with induction chemotherapy for at least 3 cycles followed by consolidative chemoradiation. These results merit further validation by a prospective study.

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Keywords

pancreatic cancer; induction chemotherapy; radiation

INTRODUCTION

Pancreatic cancer is the 4th leading cause of cancer-related deaths in the United States.[1] The overall prognosis for pancreatic cancer is extremely poor: the five year survival rate is less than 5%.[2] At diagnosis, less than 20% of patients are considered resectable, and nearly two-thirds of patients have radiographic evidence of metastatic disease.[1] The subset of patients who do not have detectable metastatic disease at the time of diagnosis but who are also ineligible for surgery are identified as having stage III locally advanced pancreatic cancer (LAPC). LAPC accounts for about 30% of pancreatic cancers. The median survival for patients with locally advanced disease has previously been estimated to be 8–14 months.[3]

LAPC is less extensively studied compared to resectable or metastatic disease. The largest randomized study, published in 1981, found that radiation concurrently with 5-fluorouracil (5-FU) as a radiosensitizer (designated chemoradiation) improved overall survival outcomes for LAPC compared to radiation alone.[4] Subsequent studies have investigated the role of systemic chemotherapy in addition to chemoradiation. Patients with LAPC have a high risk of micrometastatic disease at the time of diagnosis and may rapidly develop metastases during radiation treatment. Low dose chemotherapy as a radiosensitizer in the form of chemoradiation is unlikely to be adequate for systemic disease control. Thus standard-dose systemic chemotherapy (designated chemotherapy) may play a pivotal role in the treatment of patients with LAPC. The role of chemotherapy, the length of systemic chemotherapy, and the sequence of chemotherapy with chemoradiation are all aspects of the treatment regimen for LAPC that have not been defined. Currently, there is no standard of care for LAPC and the roles of chemotherapy and chemoradiation are constantly evolving. We performed a retrospective analysis of patients treated at the Johns Hopkins Hospital (JHH) to assess the optimal roles of chemotherapy and chemoradiation therapy for LAPC.

MATERIALS AND METHODS

Study Design and Pretreatment Evaluation

The records of all pancreatic cancer patients seen at JHH between June 2006 and March 2011 were reviewed. Among them, 100 patients who met the American Hepato-Pancreato-Biliary Association (AHPBA)/Society of Surgical Oncology (SSO)/Surgical Society of Alimentary Tracts (SSAT) criteria[5] for LAPC and who were treated primarily at JHH with chemotherapy and/or chemoradiation were included in the retrospective analysis. All patients underwent routine pancreatic protocol computed tomography (CT) examination. Based on the review of CT images with three-dimensional reconstruction, tumors that encased the superior mesenteric artery or celiac artery or that occluded the superior mesenteric vein or portal vein without the possibility of reconstruction were deemed unresectable and locally advanced. Tumors that were deemed resectable, borderline resectable, or metastatic were excluded from the study. Patients who only sought a second

opinion and were not treated at JHH were excluded. The end date of the study was August 25, 2012.

Treatment

Patients included in this study received standard-dose systemic chemotherapy (chemotherapy regimens typically used for metastatic pancreatic cancer), chemoradiation (radiation in concurrence with low dose infusional 5-fluouracil, capcitabine, or gemcitabine), or both as part of their treatment regimen. Seventy patients (70%) received a combination of both chemotherapy and chemoradiation. Eighteen patients received chemotherapy alone (18%), and 10 patients (10%) received chemoradiation alone. Of the patients receiving combination therapy, 44 patients (63%) received induction chemotherapy followed by chemoradiation, and 25 patients (36%) received chemoradiation followed by chemotherapy. One patient received chemotherapy and chemoradiation concurrently. Of the patients who received standard-dose chemotherapy, 40 patients (45%) received single agent gemcitabine chemotherapy and 46 patients (52%) received a combination regimen that included gemcitabine and other chemotherapeutic agents. Two patients received a chemotherapy regimen that did not include gemcitabine.

Statistical Analysis

The primary analyses of this study were cumulative incidence of progression (CIP) and overall survival (OS). Progression was defined as the time from the first day of treatment to evidence of progression based on follow-up radiographic imaging. Patients who did not progress were censored at their last known follow-up date, and those who died before progressing were considered as having a competing event. OS was calculated from the first day of treatment until death or last known follow up. CIP was compared between groups of patients and summarized with cumulative incidence curves and hazard ratios calculated using Fine and Gray's method.[6,7] Median CIP is defined as the time at which CIP equals 50%. OS was estimated using the Kaplan Meier method and compared between groups with hazard ratios calculated using Cox proportional hazards models. All reported hazard ratios adjust for age and gender. Variables that were significantly associated with CIP and/or OS with an age- and gender-adjusted $p < 0.10$ were included in a multivariate analysis. Analyses were completed using statistical software R version 2.15.1.

RESULTS

Patient Characteristics

Between June 2006 and March 2011, 100 patients with LAPC were treated with chemotherapy and/or chemoradiation at JHH. All patients in this cohort were evaluated by a multidisciplinary team, and a diagnosis of locally advanced disease was made based on AHPBA/SSO/SSAT criteria. Demographic and baseline characteristics for the patients are summarized in Table 1. The median age of the study cohort was 62.5 years (range 40–88 years). There were 41 females and 59 males. The majority of patients (81%) had a baseline ECOG performance status of 0–1. Fifteen percent of patients did not have ECOG scores documented at their initial visit. Tumor marker CA 19-9 was also measured at the initial

clinic visit: 60 patients had a CA 19-9 ≤1000 U/mL and 25 patients had a CA 19-9 >1000 U/mL. The remaining 15 patients did not have CA 19-9 levels recorded at the initial visit.

Clinical Outcomes

The median follow-up for all 100 patients was 15.8 months (range 1.4–46.7). At the end of the study, there were 20 patients alive, and their median follow-up was 22.3 months (range 10.0–46.7). Eight of the surviving patients did not have any evidence of disease progression. Seven patients were able to undergo surgical resection of their tumors after treatment.

For the entire cohort, the cumulative incidence of progression was 61.2% at 1 year, and 86.7% at 2 years. The median CIP was 8.4 months (Fig. 1A). Median OS for the whole group was 15.8 months. The 1 and 2 year overall survival rates were 63.9% and 22.2%, respectively (Fig. 1B).

Baseline clinical characteristics

The association between baseline patient characteristics and CIP and OS are summarized in Tables 2 and 3. An ECOG score of 0, compared to an ECOG score of 1, was associated with trends towards both improved CIP (HR 0.70, 95% CI 0.44–1.11, p=0.13) and OS (HR 0.63, 95% CI 0.38–1.05, p=0.08). There was no significant difference between CA 19-9 ≤1000 U/mL and CA 19-9 >1000 U/mL in CIP or OS (CIP: HR 1.53, 95% CI 0.95–2.49, p=0.08; OS: HR 1.38, 95% CI 0.83–2.30, p=0.22).

Combination of chemotherapy and chemoradiation

We then wanted to determine if patients who received a combination of both chemotherapy and chemoradiation therapy prior to the development of progressive disease had better outcomes than patients who received only chemoradiation or only chemotherapy. Here, standard-dose chemotherapy was given either alone, as induction chemotherapy prior to chemoradiation, or as consolidation chemotherapy after chemoradiation. Chemoradiation refers to radiation in concurrence with low-dose chemotherapy as radiosensitizers. Patients who received both chemotherapy and chemoradiation therapy were compared with those who received chemoradiation alone. The median CIP was 2.2 months for chemoradiation alone and 11.7 months for combination therapy (Fig. 2A). Median OS was 11.1 months for chemoradiation alone and 16.4 months for combination therapy (Fig. 2B). Combination therapy was significantly associated with improved CIP (HR 0.23, 95% CI 0.10–0.55, p=0.001) and OS (HR 0.45, 95% CI 0.22–0.93, p=0.03), compared to chemoradiation alone. However, combination therapy was not associated with improved CIP or OS when compared to patients who received chemotherapy alone (Figs. 2C, D). The median CIP was 4.5 months for chemotherapy alone and 11.7 months for combination therapy (HR 0.59, 95% CI 0.29–1.21, p=0.15). Median OS for chemotherapy alone was 15.9 months and 16.4 months for combination therapy (HR 0.84, 95% CI 0.47–1.49, p=0.55). There were no significant differences in CIP or OS for patients treated with the single agent gemcitabine versus gemcitabine-based combinational chemotherapy (Tables 2, 3).

Sequence of chemotherapy and chemoradiation

Our next goal was to establish if, in those patients receiving combination therapy, the sequence of therapy – induction chemotherapy followed by chemoradiation or chemoradiation followed by chemotherapy – affected CIP or OS. Different from prior retrospective analyses[1,2], which compared patients who received induction chemotherapy followed by chemoradiation to those who only received a single modality prior to disease progression, we specifically excluded those patients in these subsets who progressed immediately following chemotherapy or chemoradiation, respectively, and thus were anticipated to have a worse outcome. Median CIP was 12.6 months for chemotherapy first and 8.3 months for chemoradiation first. Median OS was 18.1 months for chemotherapy first and 11.0 months for chemoradiation first. There were no significant differences in CIP or OS based on sequence of combination therapy (CIP: HR 0.63, 95% CI 0.37–1.08, p=0.09; OS: HR 0.61, 95% CI 0.34–1.08, p=0.09). However, among patients who received both therapies sequentially, patients who received chemotherapy first followed by chemoradiation had a trend towards better CIP and OS (Figs 3A, B).

Duration of induction chemotherapy

The optimal length of induction chemotherapy has not been determined. We thus examined if the number of chemotherapy cycles received prior to chemoradiation therapy had an effect on survival outcomes. Patients who received 0–2 cycles of chemotherapy before chemoradiation had a median CIP of 8.2 months and a median OS of 15.7 months. Patients who received >2 cycles of chemotherapy prior to chemoradiation had a median CIP of 15.0 months and a median OS of 19.4 months. Receiving >2 cycles of chemotherapy before chemoradiation was significantly associated with a decreased CIP (Fig. 4A) (HR 0.46, 95% CI 0.26–0.82, p=0.008) and was associated with a trend toward better OS (Fig. 4B), although the trend was not a significant difference from patients who received 0–2 chemotherapy cycles (HR 0.56, 95% CI 0.28–1.12, p=0.10). The multivariate analysis showed that receiving >2 cycles of chemotherapy prior to chemoradiation was associated with improved CIP, while adjusting for CA 19-9 level, age and gender (Table 4).

DISCUSSION

This study has examined the effects of the combination of chemotherapy and chemoradiation therapy, sequence of therapy, as well as length of induction therapy on treatment outcomes for LAPC at a single institution. We observed that a combination of chemotherapy and chemoradiation therapy is superior to chemoradiation alone, and that longer cycles of induction chemotherapy followed by chemoradiation therapy may result in more favorable clinical outcomes.

We analyzed the sequence of chemotherapy and chemoradiation in patients receiving combination therapy and found that induction chemotherapy before chemoradiation demonstrates a trend towards more favorable clinical outcomes. This association is consistent with previous retrospective analyses that reported better clinical outcomes with induction chemotherapy followed by chemoradiation compared to chemoradiation alone or chemotherapy alone for LAPC. Huguet et al. found that LAPC patients who were treated

with at least 3 months of induction chemotherapy followed by chemoradiation had better progression-free survival (PFS) and OS compared to those patients who continued with chemotherapy after 3 months.[2] Rana et al. reported more favorable survival outcomes in LAPC patients treated with chemotherapy followed by chemoradiation compared with chemoradiation alone.[8] Similar results favoring induction chemotherapy and consolidation chemoradiation over chemoradiation alone were also reported by Krishnan et al.[1] Several phase II trials have demonstrated acceptable toxicity profile for induction chemotherapy followed by chemoradiation.[9–11]

Radiation is currently considered to be part of the standard of care for LAPC. Although the role of radiation has been supported by previous studies[1,2,8], these studies were either retrospective or small prospective ones. The randomized, phase III, LAP07 clinical trial in LAPC treatment recently conducted by Hammel et al. showed that there was no additional benefit of adding chemoradiation after induction chemotherapy compared to maintenance chemotherapy alone.[12] By far, this is the only randomized study adequately powered to assess the role of radiation in treating locally advanced pancreatic cancer; and its results questioned the previously accepted notion of radiation as a standard of care for LAPC. Consistently, our present study's findings support the idea that chemotherapy plays a more important role than chemoradiation in the treatment of LAPC. Although our study showed that the combination of chemoradiation and chemotherapy trended toward lower cumulative incidence of progression compared to chemotherapy alone, we should point out that this analysis may have selected for those patients who did not progress systemically prior to receiving chemoradiation.

To our knowledge, there have been few randomized or retrospective studies showing the advantage of chemoradiation first followed by chemotherapy in the treatment of LAPC. A small randomized study conducted in the 1980's showed improved overall survival for LAPC patients who received chemoradiation followed by multidrug chemotherapy (streptozocin, mitomycin, and 5-fluorouracil; SMF) compared to patients receiving SMF chemotherapy alone (42 weeks vs. 32 weeks, $p<0.02$).[13] A more recent Phase III study of chemoradiation followed by chemotherapy showed inferior survival outcomes compared to chemotherapy alone.[14]

Our results and most of the aforementioned studies support the use of combination therapy for LAPC, but more importantly the sequence of combination therapy – induction chemotherapy followed by chemoradiation – may be the key factor in combination treatment. Our study is unique in that we compared the sequence of chemotherapy first followed by chemoradiation to the sequence of chemoradiation first followed by chemotherapy among patients who had a chance of receiving both modalities before they had disease progression. This is different from all previous studies mentioned, which compared patients who received induction chemotherapy followed by chemoradiation to those who only received a single modality prior to disease progression. Our analysis specifically excluded those patients who progressed immediately following chemoradiation and thus were anticipated to have a worse outcome. Our analysis thus provides a stronger rationale for induction chemotherapy in LAPC treatment and suggests that the sequence of

chemotherapy plays a larger role beyond the selection for patients to receive chemoradiation.

The results of our study further suggest that LAPC has a high incidence of occult micrometastatic disease that cannot be identified by radiographic imaging tests; thus systemic chemotherapy may be beneficial for these patients to prevent progression to frank metastatic disease. There may be other advantages to induction chemotherapy prior to chemoradiation. Chemotherapy can reduce tumor size prior to chemoradiation, making the local therapy more effective. Induction chemotherapy can suppress occult metastatic disease early in the course of treatment. For those patients receiving chemoradiation first, the occult metastatic disease may have disease progression during radiation treatment that is not evident clinically or radiographically such that by the time systemic chemotherapy is given, the metastatic disease will be unresponsive to treatment or the patient will be in a more unfavorable condition for chemotherapy to be effective. Additionally, delivery of chemotherapeutic drugs to the tumor is postulated to be more effective in tumors not yet treated by local radiation therapy.[1]

On multivariate analysis, our results also showed that induction chemotherapy with at least 3 cycles was associated with improved cumulative incidence of progression and a trend towards more favorable overall survival. One explanation is that fewer cycles of chemotherapy may not render the tumor more responsive to chemoradiation therapy; longer courses of induction chemotherapy may have a strong effect on selecting patients who are more likely to benefit from radiation. Another explanation may be that more induction chemotherapy has a better effect on stabilizing micrometastatic disease before chemoradiation treatment.

In a previous study we analyzed baseline patient characteristics for locally advanced pancreatic cancer at our institution between 1997 and 2009.[15] That study demonstrated an OS of 12.1 months and a median PFS of 6.7 months. Our current study identified LAPC patients from 2006 to 2011, with median OS of 15.8 months and median CIP of 8.4 months. The superior survival outcomes demonstrated in our current study may be explained by the improvements in treatment regimens for LAPC in recent years. Additionally, in the previous study only 5% of patients identified had received induction chemotherapy followed by chemoradiation; our current study likely has superior survival outcomes due to the adoption and success of induction chemotherapy as part of the treatment regimen. Our previous study showed that pretreatment Karnofsky performance status and CA19-9 levels may be important prognostic factors for patients with LAPC treated with chemoradiation.[15] KPS >80 and CA19-9 ≤1000 U/mL were independently associated with improved progression-free survival and overall survival. In our current study, we found a similar trend of an association between initial ECOG performance status with CIP and OS outcomes. However, we did not observe the same association of CA19-9 with either survival or cumulative incidence of progression on univariate analysis. It could be due to the smaller sample size in this current study. However, the more likely explanation is that induction chemotherapy may have improved the outcome of patients whose CA19-9 was >1000 U/mL prior to the initiation of treatment. In our current study, 40% of patients whose CA19-9 was >1000 U/mL received induction chemotherapy, whereas 24% of those patients received

chemoradiation as the first treatment. It is possible that patients who had a higher CA19-9 were more likely recommended induction chemotherapy. Consistently, we found CA19-9 >1000 U/mL is still a predictor for poorer OS on multivariate analysis, where either CA19-9 or cycles of chemotherapy prior to chemoradiation was assessed for its capability of predicting clinical outcomes independently. It remains interesting to explore whether patients who have higher versus lower CA19-9 equally benefit from receiving induction chemotherapy when a larger patient population is available for analysis in the future.

Our study is limited in its retrospective nature, its small sample size, and the unbalanced distribution of patients in the different treatment arms due to inclusion of only patients treated at our institution. Additionally, we did not identify the factors that may have contributed to providers' clinical decisions; although all patients were seen and discussed by a multidisciplinary team at our institution. While our results favor induction chemotherapy of at least 3 cycles, we still do not know the optimal length of chemotherapy cycles prior to radiation that results in the best survival outcomes. Additionally, we did not see a difference in outcomes between chemotherapy cycles <2 or ≥2 (data not shown). Our study also showed no difference between single agent gemcitabine or gemcitabine-containing combination chemotherapy. There is a need to further investigate the optimal chemotherapy regimens for LAPC, such as exploring the use of newer regimens typically used for metastatic disease (for example, FOLFIRINOX, modified FOLFOX-6, or gemcitabine plus nab-paclitaxel).[16–19] A recent phase II trial found that gemcitabine may have more hematologic and non-hematologic toxicity compared to capecitabine, which may be more effective and safer as a chemotherapy arm for LAPC.[20] More recently, another phase II study showed that a triple combination for induction chemotherapy (gemcibatine, oxaliplatin, and 5-FU/leucovorin) followed by gemcitabine-based chemoradiation produced encouraging survival results for LAPC.[21] A different approach that is currently being investigated is the concurrent application of full-cycle chemotherapy with radiotherapy.[22] Additionally, while the role of traditional chemoradiation in LAPC remains debatable, it will be intriguing to explore the role of more innovative forms of radiation such as stereotactic body radiation.[23,24]

In conclusion, our current study highlights a novel aspect of treatment for LAPC. We believe that longer courses of chemotherapy may allow tumors to become more sensitive to chemoradiation therapy, thus potentially increasing the benefit of consolidation chemoradiation. Our results support treating patients with LAPC with at least 3 cycles of induction chemotherapy followed by consolidation with chemoradiation. This retrospective analysis merits further validation by prospective studies, where both newer forms of combinational chemotherapy and innovative forms of radiation should be considered.

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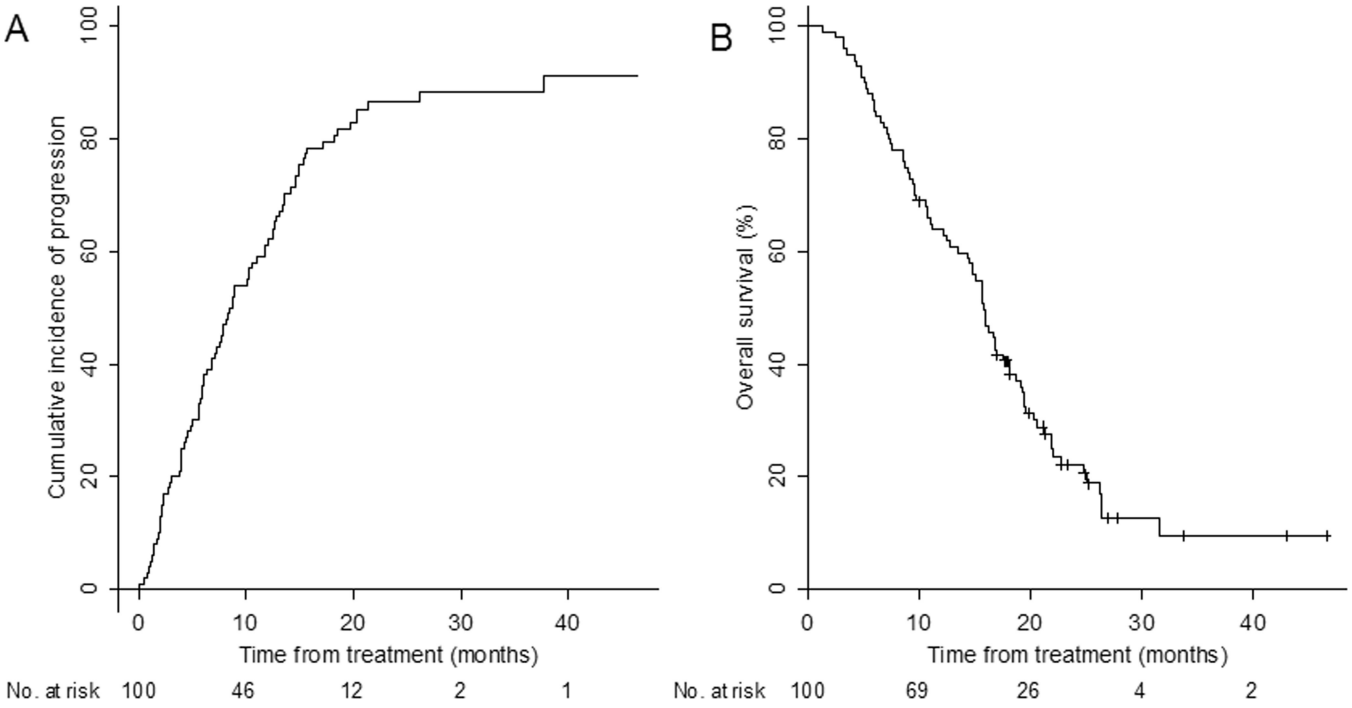

Figure 1. Plots of cumulative incidence of progression and Kaplan-Meier curve of overall survival

A. Median CIP was 8.4 months. **B.** Median OS was 15.8 months. (CIP indicates cumulative incidence of progression; OS, overall survival)

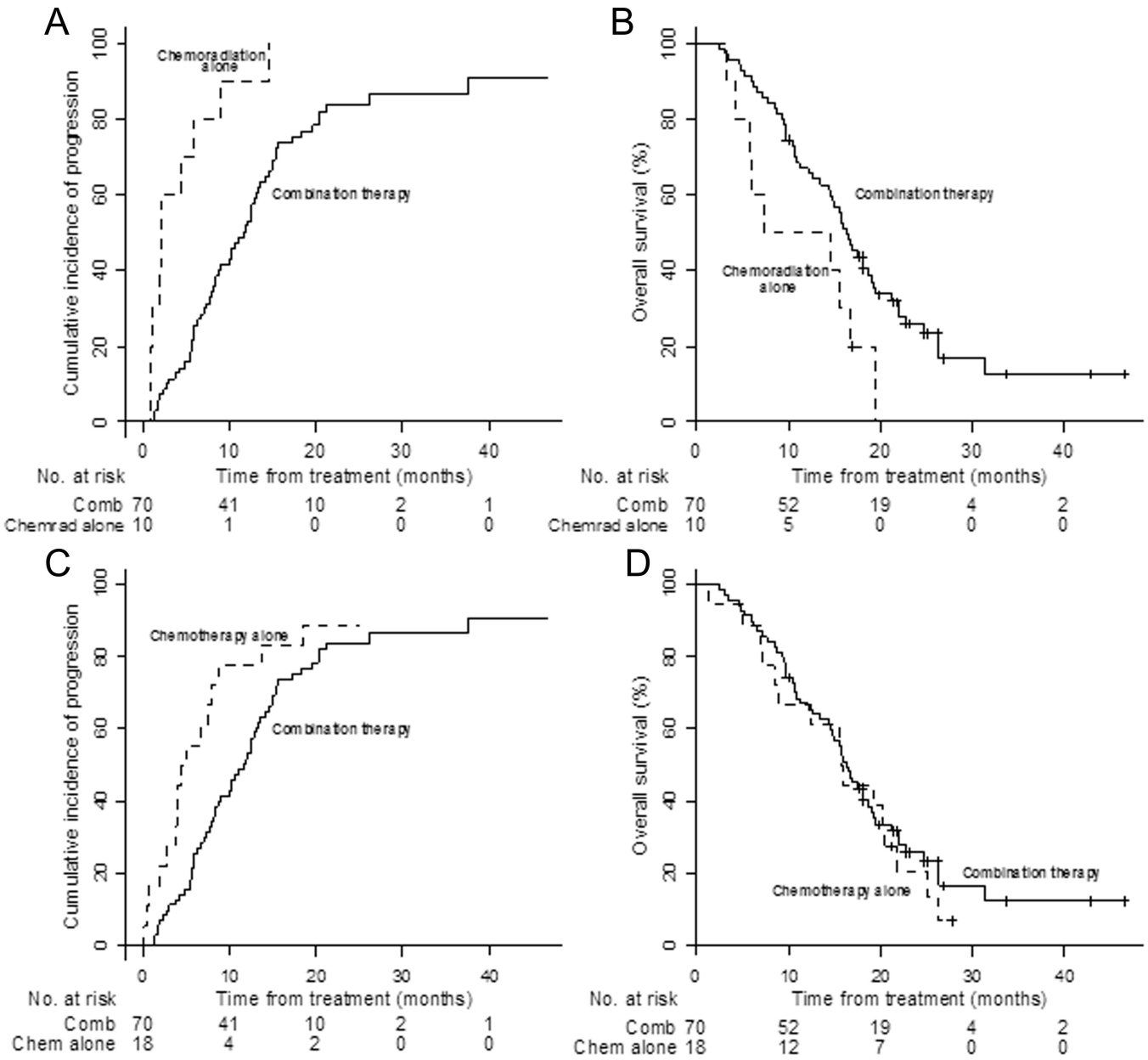

Figure 2. Plots of cumulative incidence of progression and Kaplan-Meier curve of overall survival by therapeutic types: combination therapy vs. chemoradiation alone, or vs. chemotherapy alone

A. Patients who received combination therapy had a significantly better CIP compared to patients who received chemoradiation alone (median CIP, 11.7 vs. 2.2 mo, p=0.001). **B.** Patients who received combination therapy had a significantly better OS compared to patients receiving chemoradiation alone (16.4 vs. 11.1 mo, p=0.03). **C.** There was no difference in CIP between patients receiving combination therapy and patients receiving chemotherapy alone (11.7 vs. 4.5 mo, p=0.15). **D.** There was also no difference in OS between patients receiving combination therapy and patients receiving chemotherapy alone (16.4 vs. 15.9 mo, p=0.55). (CIP indicates cumulative incidence of progression; OS, overall survival)

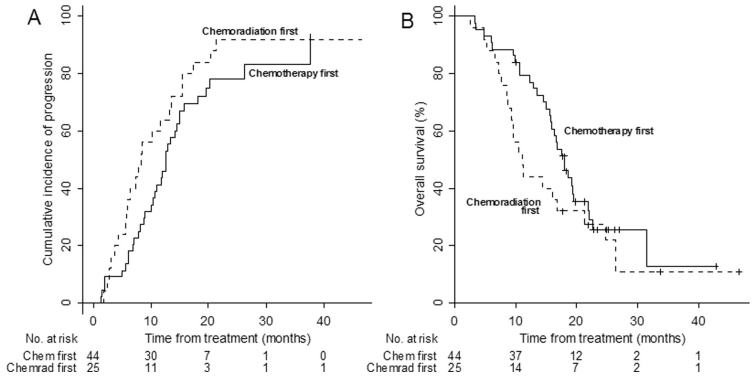

Figure 3. Plots of cumulative incidence of progression and Kaplan-Meier curve of overall survival by sequence of chemotherapy or chemoradiation therapy within patients who underwent combination therapy

A. Patients who received chemotherapy first followed by chemoradiation had a trend towards improved CIP compared to those who received chemoradiation first followed by chemotherapy (12.6 vs. 8.3 mo, p=0.09). **B.** Patients who received chemotherapy first also had a trend towards improved OS outcomes compared to those who received chemoradiation first (18.1 vs. 11.0 mo, p=0.09). (CIP indicates cumulative incidence of progression; OS, overall survival; chemotherapy first/Chem first, chemotherapy followed by chemoradiation; chemoradiation first/chemrad first, chemoradiation first followed by chemotherapy)

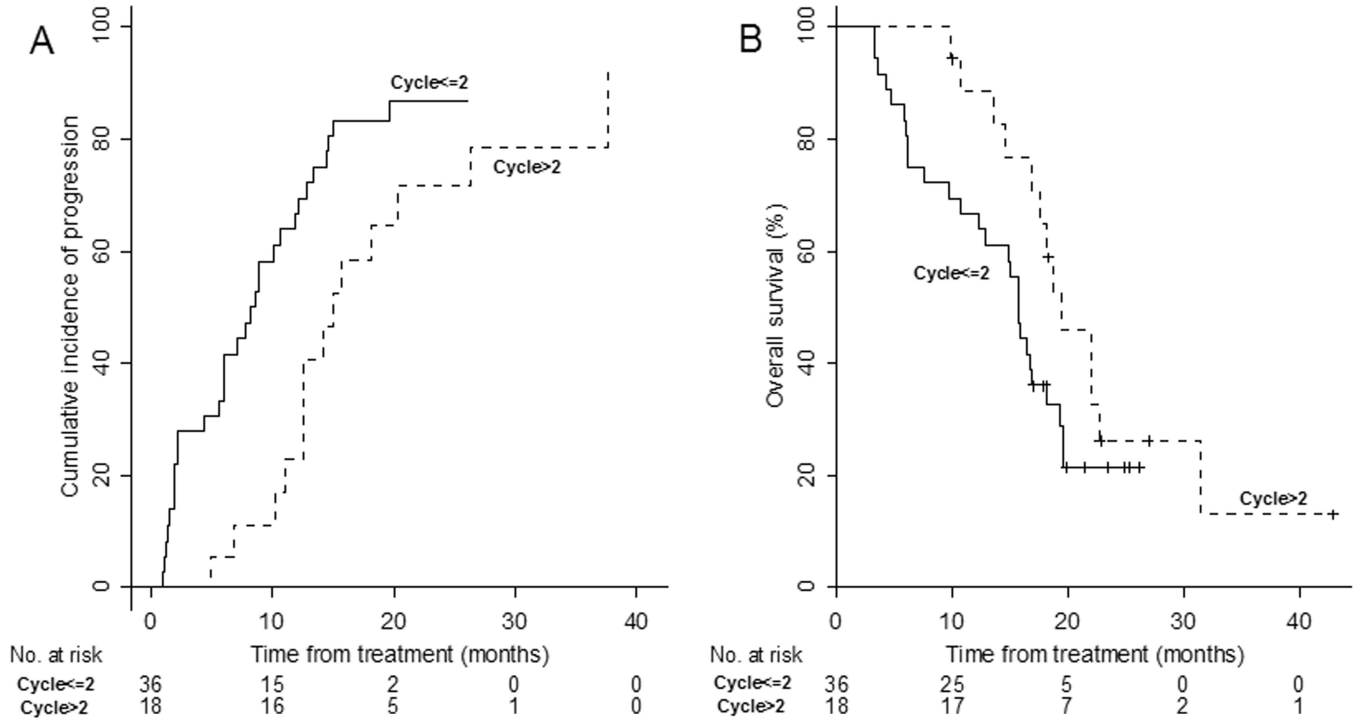

Figure 4. Plots of cumulative incidence of progression and Kaplan-Meier curve of overall survival by cycles of chemotherapy received before radiation

A. Patients who received >2 cycles of chemotherapy prior to chemoradiation had a significantly better CIP compared to those who received ≤2 cycles of induction chemotherapy (15.0 vs. 8.2 mo, p=0.008). **B.** Patients who received >2 cycles of chemotherapy prior to chemoradiation had a trend towards better OS compared to patients receiving ≤2 cycles of induction chemotherapy (19.4 vs. 15.7 mo, p=0.10). (CIP indicates cumulative incidence of progression; OS, overall survival; cycle ≤2, 0–2 cycles of induction chemotherapy prior to chemoradiation; cycle >2, >2 cycles of induction chemotherapy prior to chemoradiation)

Table 1

Patient characteristics at baseline.

Patient characteristics at baseline	N = 100
Sex – no. (%)	
Females	41 (41)
Males	59 (59)
Age, years – no. (%)	
Median	62.5
Range	40–88
ECOG performance status – no. (%)	
0	42 (42)
1	39 (39)
2	4 (4)
Missing	15 (15)
CA 19-9, U/mL – no. (%)	
≤ 1000	60 (60)
> 1000	25 (25)
Missing	15 (15)
Resectability – no. (%)	
Resectable	7 (7)
Not respectable	92 (92)
Missing	1 (1)

Table 2

Factors associated with cumulative incidence of progression.

Predictors	No. of Patients (%)	Median CIP (months)	1 yr CIP (%)	2 yr CIP (%)	HR (95% CI)	P
Overall	100 (100)	8.4	61.2	86.7	--	--
Chemoradiation alone	10 (10)	2.2	90.0	100.0	1	0.001
Combination chemotherapy and chemoradiation	70 (70)	11.7	52.9	92.9	0.23 (0.10–0.55)	
Chemotherapy alone	18 (18)	4.5	77.8	94.4	1	0.15
Combination chemotherapy and chemoradiation	70 (70)	11.7	52.9	92.9	0.59 (0.29–1.21)	
Chemoradiation followed by chemotherapy	25 (25)	8.3	64.0	96.0	1	0.09
Chemotherapy followed by chemoradiation	44 (44)	12.6	45.5	90.9	0.63 (0.37–1.08)	
0–2 cycles of chemotherapy prior to chemoradiation	36 (36)	8.2	66.7	97.2	1	0.008
>2 cycles of chemotherapy prior to chemoradiation	18 (18)	15.0	27.8	83.3	0.46 (0.26–0.82)	
Gemcitabine alone chemotherapy	40 (40)	8.7	60.0	92.5	1	0.82
Gemcitabine combination chemotherapy	46 (46)	11.0	54.3	93.5	1.06 (0.66–1.68)	
ECOG 1	39 (39)	7.9	69.2	100.0	1	0.13
ECOG 0	42 (42)	8.3	61.9	90.5	0.70 (0.44–1.11)	
CA 19–9 ≤ 1000 U/mL	60 (60)	11.0	55.0	93.3	1	0.08
CA 19–9 > 1000 U/mL	25 (25)	7.1	76.0	100.0	1.53 (0.95–2.49)	

(CIP, cumulative incidence of progression; HR, age and gender adjusted hazard ratio; CI, confidence interval. Median CIP is the time at which the CIP equaled 50%.)

Table 3

Factors associated with overall survival.

Predictors	No. of patients (%)	Median OS (months)	1 yr OS (%)	2 yr OS (%)	HR (95% CI)	p value
Overall	100 (100)	15.8	63.9	22.2	--	--
Chemoradiation alone	10 (10)	11.1	50.0	0	1	0.03
Combination chemotherapy and chemoradiation	70 (70)	16.4	65.7	14.3	0.45 (0.22–0.93)	
Chemotherapy alone	18 (18)	15.9	61.1	16.7	1	0.55
Combination chemotherapy and chemoradiation	70 (70)	16.4	65.7	14.3	0.84 (0.47–1.49)	
Chemoradiation followed by chemotherapy	25 (25)	11.0	44.0	20.0	1	0.09
Chemotherapy followed by chemoradiation	44 (44)	18.1	77.3	13.6	0.61 (0.34–1.08)	
0–2 cycles of chemotherapy prior to chemoradiation	36 (36)	15.7	66.7	8.3	1	0.10
>2 cycles of chemotherapy prior to chemoradiation	18 (18)	19.4	83.3	11.1	0.56 (0.28–1.12)	
Gemcitabine alone chemotherapy	40 (40)	15.7	62.5	17.5	1	0.30
Gemcitabine combination chemotherapy	46 (46)	17.6	69.6	15.2	0.77 (0.48–1.25)	
ECOG 1	39 (39)	14.5	56.4	5.1	1	0.08
ECOG 0	42 (42)	16.1	61.9	16.7	0.63 (0.38–1.05)	
CA 19–9 ≤ 1000 U/mL	60 (60)	16.75	70.0	13.3	1	0.22
CA 19–9 > 1000 U/mL	25 (25)	10.67	48.0	12.0	1.38 (0.83–2.30)	

(OS, overall survival; HR, age and gender adjusted hazard ratio; CI, confidence interval)

Table 4

Multivariate model of cumulative incidence of progression and overall survival

Outcome	HR	95% CI	p value
Cumulative incidence of progression			
CA 19–9 (>1000 U/mL vs. ≤1000 U/mL)	1.73	0.68–4.42	0.25
Cycles of chemotherapy prior to chemoradiation (>2 vs. 0–2)	0.46	0.23–0.93	0.03
Age	1.00	0.97–1.04	0.82
Gender (M vs. F)	0.77	0.39–1.49	0.43
CA 19–9 (>1000 U/mL vs. ≤1000 U/mL)	1.47	0.84–2.56	0.17
Combination chemotherapy and chemoradiation vs. Chemoradiation alone	0.54	0.26–1.13	0.10
Age	0.99	0.97–1.02	0.51
Gender (M vs. F)	1.07	0.67–1.73	0.77
CA 19–9 (>1000 U/mL vs. ≤1000 U/mL)	2.04	1.13–3.71	0.019
Chemoradiation followed by chemotherapy vs. Chemotherapy followed by chemoradiation	0.60	0.35–1.03	0.063
Age	1.01	0.99–1.04	0.30
Gender (M vs. F)	0.75	0.43–1.32	0.32
Overall survival			
ECOG (1 vs. 0)	1.61	0.78–3.31	0.19
Cycles of chemotherapy prior to chemoradiation (>2 vs. 0–2)	0.59	0.27–1.30	0.19
Age	1.02	0.98–1.07	0.26
Gender (M vs. F)	0.84	0.42–1.71	0.64
ECOG (1 vs. 0)	1.81	1.02–3.23	0.04
Combination chemotherapy and chemoradiation vs. Chemoradiation alone	1.05	0.51–2.15	0.90
Age	1.01	0.98–1.04	0.50
Gender (M vs. F)	0.78	0.45–1.36	0.39
ECOG (1 vs. 0)	2.22	1.18–4.19	0.014
Chemoradiation followed by chemotherapy vs. Chemotherapy followed by chemoradiation	0.52	0.28–0.99	0.045
Age	1.02	0.99–1.06	0.17
Gender (M vs. F)	0.74	0.40–1.37	0.34

(HR, hazard ratio; CI, confidence interval)