# Definitive chemoradiation therapy with capecitabine in locally advanced pancreatic cancer

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**We evaluated safety and efficacy of concurrent chemoradiotherapy (CCRT) with capecitabine in patients with locally advanced pancreatic cancer (LAPC). Between January 2004 and January 2008, 39 patients with LAPC treated with capecitabine CCRT were reviewed. Capecitabine was administered at 850 mg/m$^2$ twice daily every day with 5 days per week radiotherapy (1.8 Gy fractions) over the 5 weeks. Thirty-seven (94.8%) patients completed CCRT. Of the 36 evaluable patients, 15 (41.7%) and 13 (36.1%) patients achieved partial response and stable disease, and eight (28.6%) among them received gemcitabine-based post-CCRT chemotherapy without dose reduction or delay. The overall survival was 14.3 months [95% confidence interval (CI): 10.6–17.9 months]. Median progression-free survival was 11.1 months for all patients, and 7.9 months for those patients who had not received post-CCRT chemotherapy. Eight patients (21.6%) had severe grade 3 toxicities, seven (18.9%) with gastrointestinal toxicity, and one (2.7%) with hematologic toxicity. Prognostic factors for survival were serum albumin ($P$=0.014; relative risk: 3.4; 95% CI: 1.4–9.7), and adjuvant gemcitabine treatment ($P$=0.005; relative risk: 3.5; 95% CI: 1.2–10.6). Combined therapy with capecitabine CCRT was well tolerated and seems to be a promising regimen, in terms of response, survival, and adverse effects.** ***Anti-Cancer Drugs*** **21:107–112 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Pancreatic cancer is diagnosed in over 37 000 people and considered the fourth leading cause of cancer-related death in the United States [1]. Although there have been improved diagnostic and therapeutic techniques, the survival and mortality of this disease has been remained relatively dismal. Therefore, it has the lowest 5-year survival rate with less than 5% during the past 20 years. Surgery is the only curable therapeutic option, but even patients who received complete resection have less than 5% of 5-year survival rate with 50–85% of local relapse rate [2]. High mortality rate of pancreatic cancer is because of high incidence of metastatic disease at the time of diagnosis, a dismal course, and the lack of adequate treatment modality.

More than half of all the patients were diagnosed as locally advanced pancreatic cancer (LAPC). It is considered unresectable because of local invasion of adjacent structures without distant metastases. Concurrent chemoradiotherapy (CCRT) and chemotherapy improved median survival to 9–13 months, and continuous infusion of 5-fluorouracil (5-FU) has been regarded as the mainstay therapy for patients with LAPC [3,4]. However, continuous 5-FU infusion requires indwelling catheters or ambulatory pumps. Despite this combined therapy, the majority of patients still experience either local or distant recurrence. Therefore, other new radiosensitizers have been tried for the CCRT in LAPC patients.

Capecitabine (N4-pentyloxycarbonyl-5′-deoxy-5-fluorocytidine, Xeloda; Roche, Inc., Nutley, New Jersey, USA) is an oral fluoropyrimidine. Capecitabine is activated selectively more in tumor cells because more thymidine phosphorylase (TP) is present in tumors than in healthy tissues [5,6]. Radiation therapy (RT) has been shown to increase the efficacy of capecitabine through the induction of TP [7]. In addition, this oral agent can be administered more conveniently in the outpatient setting without complications of intravenous treatment.

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This favorable pharmacokinetics with comparable advantage as a radiosensitizer makes capecitabine a particularly appealing agent for the combination with RT, and several studies were carried out to show potential therapeutic advantage of capecitabine in combination with RT [7–9]. Therefore, some retrospective and prospective studies showed that oral capecitabine is more active than 5-FU in terms of survival, progression, and favorable adverse events [5,10].

With these considerations, we have used capecitabine concurrently with RT for the LAPC patients. We evaluated clinical outcome with regard to treatment intensity, toxicity, tolerability, and survival in this study.

## Patients and methods

All patients underwent pretreatment multidetector contrast-enhanced computed tomography (CT) of the abdomen and were required to have locally advanced unresectable disease on the basis of NCCN guideline and following CT criteria: (i) evidence of tumor extension to the superior mesenteric artery or celiac axis; (ii) evidence of occlusion of superior mesenteric vein or portal vein; (iii) no evidence of distant metastasis. The disease was also staged according to the 2002 American Joint Committee on Cancer Classification [11]. Patients who had received previous chemotherapy were excluded. Patients were also required to have an Eastern Cooperative Oncology Group performance status 0–1, an absolute neutrophil count more than 1500 cells/mm$^3$, a platelet count of at least 100 000 cells/mm$^3$, a serum creatinine level less than 1.5 mg/dl, and a serum bilirubin level less than 2 mg/dl. When necessary, biliary decompression was accomplished either endoscopically or percutaneously. Patients were excluded if they had evidence of fever, active infection, hepatic transaminases (alanine aminotransferase and aspartate aminotransferase) greater than five times the upper limits of normal or significant comorbid illness. Chest CT was performed to determine the presence of pulmonary metastases. Tumor evaluation was performed on the basis of Response Evaluation Criteria in Solid Tumors criteria at baseline, 4 weeks after CCRT therapy, and then repeated every 2 months thereafter. This study was approved by the Samsung Medical Center Institutional Review Board.

### Study design and treatment

The primary objective of this study was to evaluate the response and efficacy of capecitabine with CCRT in patients with LAPC. We also tested the safety and tolerability of capecitabine combined with RT. Patients received CCRT with capecitabine referenced from regimen of the locally advanced rectal cancer [12]. Patients were irradiated once daily, 5 days/week, at 1.8 Gy/fraction, over the 5 weeks. Capecitabine was administered daily at 850 mg/m$^2$ twice a day for 5 weeks. The first daily dose was administered 2 h before RT, with the second dose given 12 h after the first. If the grade 3 toxicity that is related to capecitabine treatment occurred, capecitabine treatment was interrupted and appropriate prophylactic management was administered. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Radiotherapy was performed with three-dimensional conformal radiotherapy techniques to all patients. All target volumes were contoured slice-by-slice on the treatment planning images. The thickness of slide was 5 mm and the gross tumor volume was defined as the volume of primary tumor and adjacent visible lymph nodes. The clinical target volume was determined with a 1 cm margin of the gross tumor volume plus regional lymph nodal areas. The planning target volume had expanded by 0.5 cm of the clinical target volume. The extra margin (1–1.5 cm) in the craniocaudal direction was added to cover the respiratory motion. Radiation (range: 44–54 Gy) was delivered using 1.8- to 2-Gy daily fractions. All patients were scheduled to receive $\geq$ 44 Gy through a coplanar three-field or four-field technique. An additional 10 Gy with 2-Gy daily fractions was delivered in accordance with each patient's general performance and gross tumor volume.

In addition to the above therapy administered concurrently with RT, eight patients received gemcitabine/capecitabine post-CCRT chemotherapy among those who achieved stable disease (SD) or partial response (PR). The health insurance reimbursement program in Korea did not cover gemcitabine-based chemotherapy. Therefore, we could select eligible cases after discussing benefit and cost with the patients.

### Statistical analysis

Overall survival (OS) was calculated from the date of first administration of CCRT to death. The progression-free survival was calculated from the first day of chemoradiation to the date of evidence of increased primary tumor size, the appearance of distant metastasis on serial CT scans, or death from any cause. Survival curves were constructed using the Kaplan–Meier method and differences between survival curves were evaluated by the log-rank test. Cox proportional hazard analysis using the forward stepwise method was performed to explore the effect of each variable on survival. Differences were considered significant if the $P$ value was less than 0.05. The percent change between the pre- and post-CCRT CA 19-9 was calculated as follows: (pre-CCRT CA19-9 – post-CCRT CA19-9) $\times$ 100/pre-CCRT CA 19-9.

## Results

### Response to treatment

From January 2004 to January 2008, a total of 39 patients, including 24 men and 15 women, were retrospectively reviewed. The patients' demographic characteristics are shown in Table 1. Of the 39 patients enrolled in this study, 36 were included for response analysis. Two patients

**Table 1 Characteristics of patients**

| Characteristic | Value |
|---|---|
| Patients (*n*) | 39 |
| Sex, *n* (%) | |
| Male | 24 (61.5) |
| Female | 15 (38.5) |
| Age (years) | |
| Median | 61 |
| Range | 37–77 |
| ECOG performance status, *n* (%) | |
| 0–1 | 33 (87.2) |
| ≥ 2 | 5 (12.8) |
| Presenting symptoms, *n* (%) | |
| Abdominal pain | 20 (51.3) |
| Jaundice | 6 (15.4) |
| Dyspepsia | 5 (12.8) |
| Body weight loss | 4 (10.2) |
| Asymptomatic | 4 (10.2) |
| Albumin | |
| Median | 3.9 |
| Range | 2.5–4.6 |
| CEA, *n*=22, median (range) | 2.3 (0.5–17.8) |
| CA 19-9, median (range) | |
| Pre-CCRT (*n*=39) | 317 (5–12381) |
| Post-CCRT (*n*=37) | 54.9 (1–8357) |
| Changes (%, *n*=37) | 69 (−770 to 96.3) |
| Histology (*n*=18) | |
| Well differentiated | 1 |
| Moderately differentiated | 7 |
| Poorly differentiated | 6 |
| Adenocarcinoma, undifferenditated | 4 |
| T stage, *n* (%) | |
| T3 | 2 (5.1) |
| T4 | 37 (94.9) |
| Tumor location, *n* (%) | |
| Head | 26 (66.7) |
| Head/body | 1 (2.6) |
| Body | 11 (28.2) |
| Tail | 1 (2.6) |
| Tumor size (cm) | |
| Median | 3 |
| Range | 1.3–10.0 |
| Lymph node stage, *n* (%) | |
| N0 | 18 (46.2) |
| N1 | 21 (53.8) |
| Mean capecitabine (range) (days) | 33.5 (7–35) |
| Mean radiation dose, *n*=37, (SD) | 46 (±0.4) |

Changes: percent change between the pre-and post-CCRT CA 19-9.
CCRT, concurrent chemoradiotherapy; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group.

could not complete CCRT because of severe gastrointestinal toxicities, and the third patient completed CCRT, but died before the evaluation. The median interval from the date of CCRT completion to the date of the response assessment was 22.5 days (range: 4–41 days).

After the CCRT, 15 (41.7%) patients achieved PR. Of the remaining 21 patients, 13 (36.1%) had a SD and eight (22.2%) had a progressive disease. The disease control rate (PR or SD) was 77.8%. None of the patients with a PR underwent surgical resection because of persistent tumor infiltration of the adjacent vessels. Among the 28 patients who had achieved disease control, eight patients had received subsequent gemcitabine-based therapy. Of the eight patients, six had received six cycles of sequential gemcitabine–capecitabine chemotherapy, and two had each received two and 10 cycles of gemcitabine–erlotinib-based chemotherapy.

During the follow-up, 29 patients showed tumor progression. Of the 28 patients with an initial response (15 patients with PR and 13 with SD), 20 had disease progression during the subsequent follow-up period, with local progression in seven patients, and distant metastasis in 13 patients. Eighteen patients received subsequent salvage treatment after progression.

The median pre-CCRT ($n = 39$) and post-CCRT ($n = 37$) CA 19-9 values were 317 (range: 5–12 381) and 54.9 (range: 1–8 357), respectively. The percent changes from pre-CCRT to post-CCRT CA 19-9 values ($n = 37$) were also analyzed, being the median −69.6% (range: −96 to +770%). Patients who had established more than 30% changes showed significantly higher PR than the others (93.3 vs. 52.4%, $P = 0.009$).

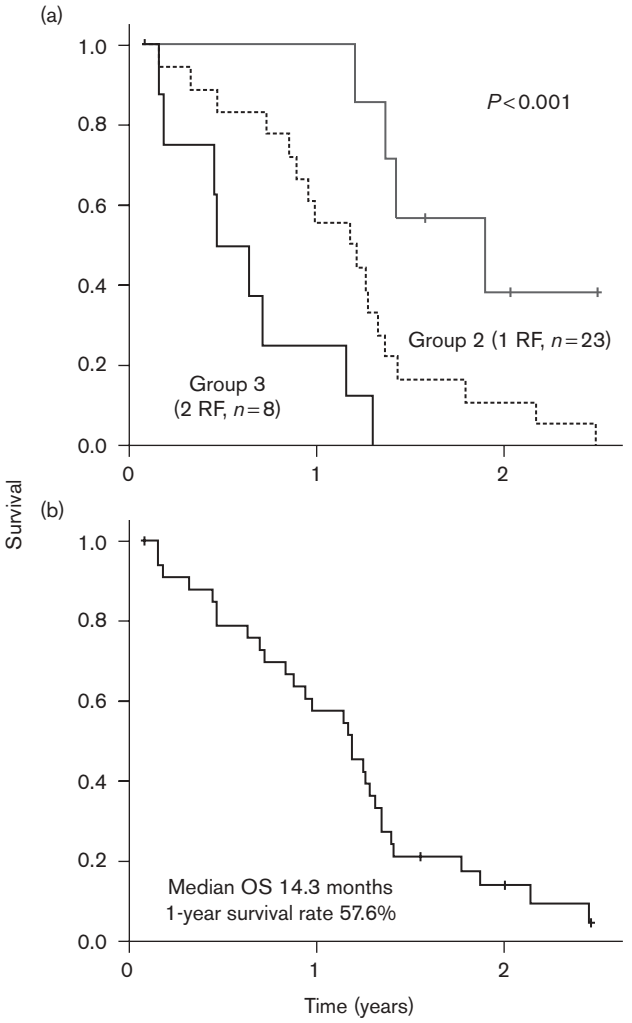
### Overall survival and time to progression

With a median 22.6 months of follow-up duration (range: 0.5–4.4 years), there were 30 (76.9%) events, and nine patients (23.1%) are still alive with diseases. The median OS duration was 14.3 months [95% confidence interval (CI): 10.6–17.9 months], with a 1-year and 2-year survival rate of 57.6 and 14.1%, respectively (Fig. 1a). Eight patients who completed post-CCRT chemotherapy (gemcitabine-based) showed median 22.5 (95% CI: 10.1–34.2) months of OS compared with those without post-CCRT chemotherapy (median 11.3 months, 95% CI: 6.7–15.9). Median progression-free survival was 5.1 months (95% CI: 1.0–9.2) for all patients. Patients established more than 30% of changes showed significantly better OS than the others (median 15.1 vs. 10.0 months, $P = 0.04$). For those with distant recurrence, the peritoneum was the most frequent metastatic site observed in seven patients, followed by liver in seven, and metastatic lymph node in one patient.

### Toxicity/tolerability

All the patients were evaluable for toxicity according to the maximum National Cancer Institute Common Toxicity Criteria as shown in Table 2. No patient had grade 4 hematologic or nonhematologic toxicity. Two patients could not complete the scheduled chemoradiation because of gastrointestinal complications: one patient refused because of grade 3 anorexia, and the other patient because of grade 3 diarrhea. Radiotherapy was discontinued at doses of 8 and 10 Gy. The median radiation dose for 37 patients who completed radiotherapy was 45 Gy (range: 36–54). Grade 3 enteritis occurred in one patient 2 weeks after the start of CCRT, and RT was discontinued for 1 month and then completed the remained course. Another patient had capecitabine held for 2 days because of nausea/vomiting during week 1 and completed the remainder of the course. Therefore, 35 (89.7%) patients completed the full combination of chemoradiation without dose reduction or delay.

**Fig. 1**




Kaplan–Meier overall survival (OS) curves for all patients (a), and patient according to prognostic factors (b). RF, risk factor.

Of the 37 patients who completed the full combination of chemoradiation, eight (21.6%) had severe grade 3 toxicities during chemoradiation, including seven (18.9%) with gastrointestinal toxicity and one (2.7%) with hematologic toxicity. For the eight patients who had received adjuvant gemcitabine-based chemotherapy, the most common nonhematologic toxicity was anorexia (four patients with grade 1, one with grade 2) followed by three patients with grade 1 nausea. There was only one patient who experienced hematologic toxicity (grade 2 neutropenia).

### Prognostic model

Clinical parameters predicting poor survival outcome included in the multivariate analysis were as shown in Table 3: age ( > 65 vs. ≤ 65 years), Eastern Cooperative Oncology Group performance status (0–1 vs. ≥ 2), radiation dose ( ≤ 4500 vs. > 4500), initial serum CA 19-9 ( ≤ 500 vs. > 500), initial serum albumin level ( ≤ 3.5 vs. > 3.5), adjuvant gemcitabine treatment or not. The cut-off value of CA 19-9 was obtained by applying every possible cut-off value and choosing the lowest *P* value. The Cox regression model was used to delineate independent prognostic factors. Prognostic factors for survival were initial serum albumin ($P = 0.014$; relative risk: 3.4; 95% CI: 1.4–8.6], and adjuvant gemcitabine treatment ($P = 0.005$; relative risk: 3.5; 95% CI: 1.2–10.6). The prognostic grouping of the 39 patients was performed according to the following criteria: group 1 ($n = 8$), no adverse factor; group 2 ($n = 23$), one adverse factor; and group 3 ($n = 8$), two adverse factors. The survival curves according to the prognostic index are shown in Fig. 1b. The prognostic model separated patients into three risk groups with different survival outcomes ($P < 0.001$). The median survival for group 1, 2, and 3 were 21.3, 14.0, and 5.6 months, and the 1-year OS rates for group 1, 2, and 3 were 87.5, 52.9, and 25.0%, respectively. Group 3 patients had an 11-fold (hazard ratio: 11.4, 95% CI: 3.3–39.5) increased risk of death compared with group 1.

**Table 2 Toxicity summary: worse toxicity experienced with capecitabine chemoradiotherapy per patient**

| | Grade | | |
|---|---|---|---|
| Toxicity | 1 | 2 | 3 |
| Hematologic | | | |
| Neutropenia | 3 | 7 | 0 |
| Anemia | 8 | 6 | 1 |
| Thrombocytopenia | 4 | 0 | 0 |
| Nonhematologic | | | |
| Nausea | 9 | 4 | 0 |
| Vomiting | 5 | 2 | 0 |
| Anorexia | 8 | 5 | 3 |
| Diarrhea | 1 | 0 | 3 |
| Enteritis | 0 | 0 | 1 |
| HFS | 1 | 0 | 0 |

HFS, hand–foot syndrome.

**Table 3 Prognostic factors for survival in multivariate analysis**

| | Univariate | Multivariate | |
|---|---|---|---|
| Variables | *P* value | HR (95% CI) | *P* value |
| Age ≤ 65 years | 0.06 | NA | 0.41 |
| ECOG PS 0–1 | 0.25 | NA | 0.07 |
| Radiation dose ( ≤ 4500 vs. >4500) | 0.19 | NA | 0.18 |
| CA 19-9 ( ≤ 500 vs. >500) | 0.04 | NA | 0.22 |
| Albumin ( ≤ 3.5 vs. >3.5) | <0.001 | 3.4 (1.4–8.6) | 0.014 |
| Adjuvant gemcitabine treatment | 0.005 | 3.5 (1.2–10.6) | 0.011 |

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NA, not applicable.

## Discussion

About half of the pancreatic cancer patients have locally advanced unresectable disease at the time of diagnosis, which is one of the most challenging fields in the treatment of pancreatic cancer. Until now, concurrent chemoradiation has been a standard treatment option for these patients and there has been significant interest in

developing new strategies for chemoradiotherapy [13]. However, systemic failure still remains as a major problem in improving the long-term survival in LAPC, although local control rates have been improved by current combined treatment modality. Therefore, many researchers have tried to incorporate new chemotherapeutic agents that provide both localized treatment as radiosensitizer and systemic control for patients, which might enhance both local control rate and OS.

As gemcitabine showed improvements in survival and clinical benefit compared with 5-FU for the treatment of patients with advanced pancreatic cancer, many attempts to improve survival in LAPC population have been made by combining gemcitabine with radiotherapy [14–18]. In early phase I trials, weekly 60–500 mg/m$^2$ of gemcitabine administered concurrently with various doses of radiation in pancreatic cancer patients has been previously evaluated with reports of significant toxicity problems [14,17,18]. Although these doses of gemcitabine are likely to be radiosensitizing, these are unlikely to be effective against systemic disease. Moreover, increased toxicity sometimes leads to the detriment of treatment outcome in pancreatic cancer patients. In a recent phase II trial, radiation with reduced field size encompassing only the gross tumor and involved nodes allows the concurrent delivery of full-dose gemcitabine, which should be further investigated [15].

Capecitabine is an oral fluoropyrimidine which shows single-agent activity in advanced pancreatic cancer with a similar response rate to that of single-agent gemcitabine [19]. Capecitabine mimics continuous intravenous infusion of 5-FU without the risk of a central venous catheter, and its tumor-preferential activation reduces systemic exposure to 5-FU and potentially improves efficacy and safety [5,20]. Preclinical studies have shown that irradiation can upregulate TP expression in tumor cells, resulting in a selective synergistic effect between RT and capecitabine [7]. In addition, the abscopal effect of capecitabine with radiation provides the rationale for this strategy. The abscopal effect is the theory that ionizing radiation can reduce tumor growth outside the radiation field [21,22]. Although the underlying mechanism is not fully understood yet, inflammatory signals generated by radiation may stimulate tumor-specific antigens. The transfer of those antigens from cancer cells to dendritic cells may enhance antitumor immunogenicity cascade. Therefore, capecitabine offers an interesting alternative to 5-FU, especially in combination with RT. In this study, we showed that the median survival was 14.3 months (patients with only capecitabine CCRT, median 11.3 months) with a 1-year survival rate of 57.6%, which was consistent with other studies of gemcitabine or capecitabine-based chemoradiation in LAPC [8,23,24]. An important concern about administering chemoradiation therapy as first-line treatment in patients with LAPC is that approximately 30% of them have occult metastatic disease at diagnosis and, thus, they would clearly not benefit from this locoregional treatment. The major benefit of capecitabine lies also in its favorable toxicity profiles, and capecitabine was generally well tolerated without significant toxicity in this study. The most common treatment-related adverse effects were anemia, nausea, vomiting, and anorexia. As it is absorbed as an inert drug, it produces little direct toxicity in the gastrointestinal tract. The incidence of myelosuppression was low: no grade 3 or 4 neutropenia or thrombocytopenia, and only one patient (3.1%) had grade 3 anemia. The hematologic toxicity profiles of capecitabine were relatively favorable compared with gemcitabine or 5-FU. Therefore, patients who had tolerated CCRT had the next opportunity with sequential gemcitabine-based chemotherapy. On the basis of earlier studies [25,26], additional systemic chemotherapy (especially gemcitabine-based) is recommended for patients with LAPC who are receiving chemoradiotherapy. By reducing toxicities of CCRT, capecitabine may possibly enable additional chemotherapy and results in better treatment outcome. However, this results should be interpreted cautiously and need to be validated in the future.

Other strategies to improve the outcomes of LAPC include combination chemotherapy with radiation, neoadjuvant approaches, and optimization of chemotherapy and CCRT sequence. Among them, combination regimens with radiation showed a significant amount of hematologic and nonhematologic toxicities with similar outcomes [17]. Therefore, reduced dose and fields of radiation with combination chemotherapy is now being investigated [13]. As surgical resection of the primary tumor remains as the only potentially curative treatment of pancreatic cancer, preoperative chemoradiaton therapy has also been studied to assess its ability converting LAPC to resectable disease. However, only a few patients with this strategy received curative resection in phase II trials [27,28]. Hence, it was unlikely that currently used neoadjuvant CCRT can convert unresectable lesions to resectable ones. Moreover, chemoradiation could significantly improve survival only in nonprogressive patients who remain in an acceptable condition. A retrospective study and a FFCD/SFRO study showed that an intensive induction schedule of chemoradiation therapy was more toxic and less effective than gemcitabine alone [26,29]. For these reasons, many researchers have questioned the value of local treatment such as radiation therapy or surgery in this subset of patients, which should be further evaluated in a randomized trial.

We also tried to devise a prognostic model for LAPC undergoing definitive CCRT to improve risk-based stratification. At multivariate analyses, initial serum albumin, and adjuvant gemcitabine treatment retained statistical significance. The grouping was based on a scoring system

of the adverse factors and yielded distinctive sets of three groups with different survival outcome (1-year OS rates for groups 1, 2, and 3 were 87.5, 52.9, and 25.0%, respectively). In some studies, neoadjuvant or adjuvant chemotherapy showed better survival outcome with minimal toxicity [25,30]. Patients who received adjuvant gemcitabine-based chemotherapy in our study also showed prolonged OS, and there were few treatment-related toxicities. Although there were relatively small cases with adjuvant chemotherapy, a further prospective study will be needed to validate those patients who may benefit from adjuvant chemotherapy.

In conclusion, we evaluated the efficacy and toxicity of capecitabine-based CCRT for the patients with LAPC. We suggest that capecitabine seems to be an appealing regimen in the treatment of LAPC, in terms of response, survival, and tolerable adverse effects. However, well-designed randomized trials evaluating capecitabine monotherapy or in combination with other drugs are warranted for the patients with LAPC. In addition, the value of local treatment in this subset of patients should be further evaluated as well.

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