

Concurrent radiotherapy with oral fluoropyrimidine versus gemcitabine in locally advanced pancreatic cancer: a systematic review and meta-analysis

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Background: Gemcitabine (GEM) is the most widely utilized systemic agent in combination with radiation therapy (RT) for treating locally advanced pancreatic cancer (LAPC) in the concurrent setting. Despite recent interest in using two novel oral fluoropyrimidines (FUs), capecitabine and S-1, in this setting, there is a lack of randomized controlled trials (RCTs) to support this approach.

Methods: Trials published between 1994 and 2014 were identified by an electronic search of public databases (Medline, Embase, and the Cochrane Library). All prospective studies were independently identified by two authors for inclusion. Demographic data, treatment response, objective response rate (ORR), progression-free and overall survival (PFS and OS, respectively), and toxicities were extracted and analyzed using comprehensive meta-analysis software (version 2.0).

Results: Twenty-three cohorts with 843 patients were included: 497 patients were treated with GEM and 346 patients were treated with oral FU. Pooled OS was significantly higher at 1 and 2 years for S-1 plus RT than for GEM plus RT (relative risk [RR] 1.27; 95% confidence interval [CI], 1.00–1.65; $P=0.03$; and RR 1.75; 95% CI, 1.18–2.60, $P=0.002$, respectively), while 1-year PFS and ORR were not significantly different between S-1 and GEM-based chemoradiotherapy ($P=0.37$ and $P=0.06$, respectively). Additionally, comparable efficacy was found between capecitabine and GEM-based chemoradiotherapy in terms of OS, PFS, and ORR. As for grade 3 and 4 acute toxicity, oral FU plus RT significantly reduced the risk of developing hematologic toxicities, nausea, and vomiting when compared to GEM plus RT ($P<0.001$).

Conclusions: Oral FU plus RT may be a safe and feasible regimen for patients with LAPC, with similar efficacy and low rate of toxicities compared with GEM plus RT. Our findings support the need to compare S-1 with GEM in the concurrent setting in large prospective RCTs due to its potential survival benefits.

Keywords: pancreatic cancer, chemoradiotherapy, oral fluoropyrimidine, gemcitabine, meta-analysis

Introduction

Pancreatic cancer (PC) is the 12th most commonly diagnosed malignancy, yet it is the eighth leading cause of cancer-related mortality worldwide, with an estimated 266,000 deaths in 2008.¹ Of all treatment modalities available for PC, only resection offers an opportunity for a cure. However, only 10%–15% of patients have localized and resectable disease at diagnosis. Approximately 50% of PC patients present with distant metastatic disease, and 30% present with localized and unresectable disease. For these patients, both chemotherapy alone and chemoradiotherapy (CRT) are regarded as acceptable treatment options.^{2–4} However, randomized controlled trials that compared

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the two strategies have had conflicting results^{4,5} and therefore have not been able to define a preferred standard of care.

Currently, both fluoropyrimidines (FU) and gemcitabine (GEM) have been used concurrently with radiation therapy (RT) in patients with locally advanced pancreatic cancer (LAPC). FU drugs including 5-fluorouracil, capecitabine and S-1 have proven to be effective in LAPC treatment. In 1981, a modest prolongation of survival and a median survival of 10 months in LAPC patients treated with 5-fluorouracil-based CRT was reported by the Gastrointestinal Tumor Study Group (GITSG).⁶ Thus, 5-fluorouracil-based CRT is the most widely used treatment for LAPC.

During the past decades, GEM radiosensitization has been used in some studies because of its systemic activity in pancreatic cancer and its potent radiosensitizing properties.⁷⁻¹⁰ In addition, a recent meta-analysis based on three small randomized controlled trials (RCTs) and one retrospective study suggested a survival benefit of GEM compared with 5-fluorouracil-based CRT,¹¹ but at the cost of greater toxicity. Therefore, the optimal regimen for CRT remains elusive. Recently, two novel oral FU drugs, capecitabine and S-1, have been widely used in conjunction with radiotherapy for LAPC patients due to their improved therapeutic index, more favorable pharmacokinetics (similar to those of protracted infusion of 5-fluorouracil), and their convenient oral administration without the need for central venous access and an ambulatory infusion pump. However, whether oral FU-based CRT is better than GEM-based CRT for LAPC remains uncertain. Due to the controversy of the effect of oral FU-based CRT in LAPC, we conducted the present systematic review and meta-analysis to evaluate the efficacy and toxicities of oral FU-based CRT compared with GEM-based CRT for the treatment of LAPC.

Materials and methods

Study design

We developed a protocol that defined inclusion criteria, search strategy, outcomes of interest, and analysis plan. The reporting of the current systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.¹²

Identification and selection of studies

To identify studies for inclusion in our current systematic review and meta-analysis, we did a broad search of four databases, including Embase, Medline, the Cochrane Central Register of Controlled Trials, and the Cochrane Database

of Systematic Reviews, from the date of inception of every database to August 2014. The search included the following terms: “pancreatic neoplasms”, “pancreatic cancer”, “pancreatic carcinoma”, “pancreatic adenocarcinoma”, “gemcitabine”, “gemzar”, “oral fluoropyrimidines”, “capecitabine”, “xeloda”, “S-1”, “radiotherapy”, and “chemotherapy”. Additional references were searched through manual searches of the reference lists and specialist journals. No language restrictions were applied.

To be eligible for inclusion in our present systematic review and meta-analysis, study populations (referred to hereafter as cohorts) had to meet all the following criteria: 1) patients with LAPC; 2) treatment with GEM-based CRT, capecitabine-based CRT, or S-1 based CRT, while combined chemotherapy plus RT were excluded for analysis in our current study; 3) reported outcomes of interest (ie, objective response rate, survival, and complications); and 4) from an original study (ie, RCT, non-randomized clinical trial, observational studies, or case series).

Data extraction

Two investigators screened the titles and abstracts of potentially relevant studies. We retrieved the full text of relevant studies for further review by the same two reviewers. A third senior investigator resolved any discrepancies between reviewers. If reviewers suspected an overlap of cohorts in a report, they contacted the corresponding author for clarification; we excluded studies with a clear overlap.

The same pair of reviewers extracted study details independently, using a standardized pilot-tested form. A third investigator reviewed all data entries. We extracted the following data: author, study design, study period, median age, interventions (concurrent chemotherapy, radiation dose, and fractionation schedule), sample size, and outcomes of interest. We defined outcomes of interest as overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and toxic effects. We assessed survival outcomes at 1 and 5 years, while we also assessed 1-year PFS, ORR, and toxicities.

To assess quality, since we included non-comparative (uncontrolled) studies in our current systematic review and meta-analysis, we used the Newcastle–Ottawa quality assessment scale.¹³ We selected items that focused on representativeness of study patients, demonstration that the outcome of interest was not present at the start of the study, adequate assessment of outcome, sufficient length of follow-up to allow outcomes to arise, and adequacy of follow-up (Table S1).

Statistical analysis

We pre-specified the analysis plan in the protocol. We analyzed all patients who started GEM or oral FU-based CRT, regardless of their adherence to treatment. We calculated event rates of outcome (the proportion of patients who developed outcomes of interest) from the included cohorts for both GEM and oral FU-based CRT. We pooled log-transformed event rates with DerSimonian and Laird random-effect models and assessed heterogeneity using the Mantel–Haenszel test.¹⁴ We used the test of interaction proposed by Altman to compare log-transformed rates of outcomes between GEM and oral FU-based CRT.¹⁵ A statistical test with a P -value <0.05 was considered significant. To account for the potential effect of publication bias, we used the Duval and Tweedie non-parametric trim-and-fill method.¹⁶ To measure overall heterogeneity across the included cohorts, we calculated the I^2 statistic, with $I^2 > 50\%$ indicating high heterogeneity. We assessed potential publication bias by visual inspection of the symmetry of funnel plots and with the Egger regression asymmetry test. We did all statistical analyses with Stata version 12.1 (StataCorp LP, College Station, TX, USA) and comprehensive meta-analysis software version 2.0 (Biostat Inc, Englewood, NJ, USA).

Results

Search results

A total of 317 studies were identified from the database search, of which 51 reports were retrieved for full-text evaluation. Exactly 23 cohorts from 22 trials^{4,7,9,17–35} met the inclusion criteria and were included in the present systematic review (Figure 1). We only found one phase II RCT that directly compared GEM-based CRT with capecitabine-based CRT. Table 1 shows the characteristics of the included studies. Overall, 843 patients were included, with a median age of 64.7 years (range, 59–68.5 years) for the GEM-based group and 63.1 years (range, 58–67.5 years) for the oral FU group. The median OS was longer in oral FU-based CRT than GEM-based CRT (Table 2), while median radiation dose or median PFS did not differ between groups.

Methodological quality of the included studies was fair; most studies provided adequate outcome ascertainment, enrolled a representative sample of patients, and had an acceptable length of follow-up (Figure 2). However, comparative evidence was at high risk of bias, because we compared data across studies, not within them, and selection bias was likely to be present. Assessment of publication bias was not done because data would be unreliable in view of

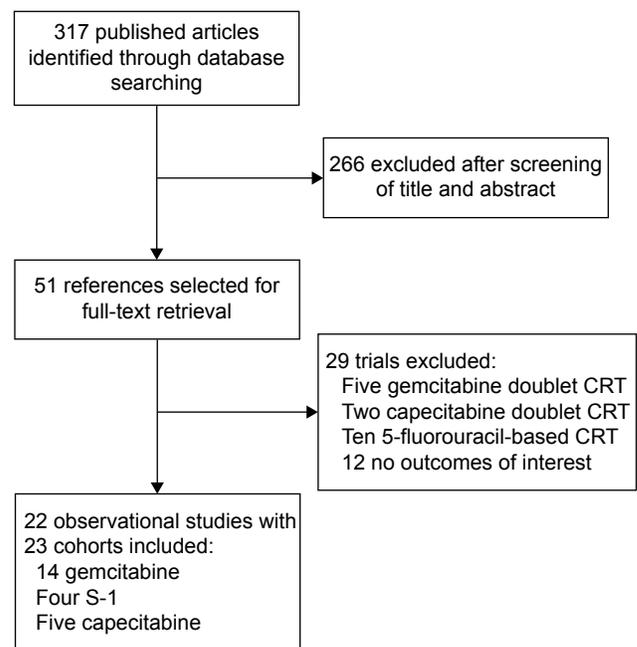


Figure 1 Selection process for clinical trials included in the meta-analysis.

Abbreviation: CRT, chemoradiotherapy.

the few studies included for each treatment group and their high heterogeneity ($I^2 > 50\%$) in most analyses.

Pooled results of primary outcomes

The pooled event rate of OS for S-1-based CRT was significantly higher than that for GEM-based CRT at 1 year (relative risk [RR] 1.27; 95% CI, 1.00–1.65; $P=0.03$), and at 2 years (RR 1.75; 95% CI, 1.18–2.60; $P=0.002$; Table 3). ORR and 1-year PFS were not significantly different between S-1 and GEM-based CRT ($P=0.06$ and $P=0.37$, respectively). Additionally, comparable efficacy was found between capecitabine and GEM-based CRT in terms of OS, PFS, and ORR (Table 3).

Pooled high-grade acute toxicities

Table 4 shows the overall acute occurrence of high-grade (\geq grade 3) toxic effects with oral FU versus GEM-based CRT. The incidence of high-grade acute hematologic toxicities, nausea, and vomiting was significantly lower in the oral FU-based CRT group than in the GEM-based CRT group (Table 4). Additionally, equivalent frequencies of high-grade diarrhea and fatigue were found between oral FU and GEM-based CRT ($P=0.07$ and $P=0.05$, respectively).

Discussion

LAPC has a poor prognosis, and treatment advances have evolved slowly. Until now, the optimal therapy for patients with LAPC remains elusive. Since a series of seminal studies

Table 1 Baseline characteristics of 23 cohort groups for meta-analysis

Author	Year	Study design	Patients, n	Concurrent chemotherapy	Median age, years	Radiation dose, Gy/Fx	Radiation dose/Fx	Radiation technique	Median OS, months	Median PFS, months	ORR, %
de Lange et al ⁷	2002	P	24	GEM 300 mg/m ²	63	24 Gy/8 Gy/3 Fx		3D-CRT	10	7	29.20%
Epelbaum et al ³⁵	2002	P	20	GEM 400 mg/m ²	66	50.4 Gy/1.8 Gy/28 Fx		3D-CRT	8	NR	15%
Blackstock et al ³⁴	2003	P	43	GEM 40 mg/m ² twice	59	50.4 Gy/1.8 Gy/28 Fx		NR	8.2	NR	NR
Okusaka et al ³³	2004	P	42	GEM 250 mg/m ²	59	50.4 Gy/1.8 Gy/28 Fx		NR	9.5	4.4	21%
Li et al ⁹	2003	P	18	GEM 600 mg/m ²	68.5	50.4–61.2 Gy/1.8 Gy/28–34 Fx		3D-CRT	14.5	7.1	50%
Magnino et al ³²	2005	R	23	GEM 100 mg/m ² or 50 mg/m ²	62	45 Gy/1.8 Gy/25 Fx		3D-CRT	14	NR	22%
Murphy et al ³¹	2007	R	74	GEM 1,000 mg/m ²	64.5	20–42 Gy/1.3–2.8 Gy/15 Fx		NR	11.2	6.4	15%
Yamazaki et al ²⁹	2007	R	22	GEM 1,000 mg/m ²	66	50 Gy/2 Gy/25 Fx		3D-CRT	16		32%
Small Jr et al ²⁸	2008	P	41	GEM 1,000 mg/m ²	59.5	36 Gy/2.4 Gy/15 Fx		3D-CRT	NR	NR	5%
Cardenes et al ²⁴	2011	P	28	GEM 600 mg/m ²	65	50.4 Gy/1.8 Gy/28 Fx		3D-CRT	10.3	6	21%
Huang et al ²³	2011	R	55	GEM 1,000 mg/m ²	NR	22–42 Gy/2 Gy/11–21 Fx		3D-CRT	12.5	NR	NR
Loehrer Sr et al ⁴	2011	P	34	GEM 600 mg/m ²	66	50.4 Gy/1.8 Gy/28 Fx		3D-CRT	11.1	6	6%
Wang et al ²⁰	2012	R	35	GEM 1,000 mg/m ²	NR	50.4 Gy/1.8 Gy/28 Fx		3D-CRT	13	NR	74.30%
Mukherjee et al ¹⁷	2013	P	38	GEM 300 mg/m ²	66	50.4 Gy/1.8 Gy/28 Fx		NR	13.4	10	19%
Kim et al ²⁷	2009	P	25	S-1 40 mg/m ²	67.5	50.4 Gy/1.8 Gy/28 Fx		3D-CRT	12.9	6.5	24%
Jackson et al ²⁶	2010	R	30	CAP 500–600 mg/m ²	65	50.4 Gy/1.8 Gy/28 Fx		3D-CRT	9.7	8.8	17%
Kim et al ²⁵	2010	R	39	CAP 850 mg/m ²	61	44–54 Gy/1.8 Gy/24–30 Fx		3D-CRT	14.3	5.1	41.70%
Sudo et al ²²	2011	P	34	S-1 80 mg/m ²	63	50.4 Gy/1.8 Gy/28 Fx		3D-CRT	16.8	8.7	41%
Saif et al ³⁰	2007	P	20	CAP 1,600 mg/m ²	58	50.4 Gy/1.8 Gy/28 Fx		3D-CRT	12		20%
Shinchi et al ²¹	2012	P	50	S-1 80 mg/m ²	66	50 Gy/2 Gy/25 Fx		3D-CRT	14.3	6.7	30%
Ikeda et al ¹⁹	2013	P	60	S-1 80 mg/m ²	64	50.4 Gy/1.8 Gy/28 Fx		NR	16.2	9.7	27%
Kim et al ¹⁸	2013	R	52	CAP 800 mg/m ²	63	55.8 Gy/1.8 Gy/31 Fx		NR	12.5	NR	13.70%
Mukherjee et al ¹⁷	2013	P	36	CAP 830 mg/m ²	63.1	50.4 Gy/1.8 Gy/28 Fx		NR	15.2	12	23%

Abbreviations: OS, overall survival; PFS, progression-free survival; ORR, objective response rate; GEM, gemcitabine; CAP, capecitabine; NR, not reported; P, prospective; R, retrospective; 3D-CRT, three-dimensional conformal radiotherapy; Gy, gray; Fx, fraction.

Table 2 Baseline characteristics of concurrent radiotherapy with GEM versus oral FU

	GEM therapy	Oral FU therapy	P-value
Cohorts, n	14	9	N/A
Patients, n	497	346	N/A
Median age, years	64.7 (59–68.5)	63.1 (58–67.5)	0.69
Median PFS	6.4	8.7	0.22
Median OS	11.2	14.3	0.07
Median radiation dose, Gy	50.4	50.4	0.15

Abbreviations: GEM, gemcitabine; FU, fluoropyrimidines; PFS, progression-free survival; OS, overall survival; N/A, not available.

from the GITSG in 1981,⁶ chemoradiotherapy for inoperable adenocarcinoma of the pancreas has been a standard treatment in the US. According to the National Comprehensive Cancer Network (NCCN) guidelines version 2, 2014,³⁶ both 5-fluorouracil and GEM-based CRT are recommended for patients with non-metastatic LAPC, although several small RCTs^{9,10,37} and one meta-analysis¹¹ suggested that GEM-based CRT seemed better than 5-fluorouracil-based CRT. Recently, two novel oral FU drugs, capecitabine and S-1, have shown favorable antitumor activity when used in

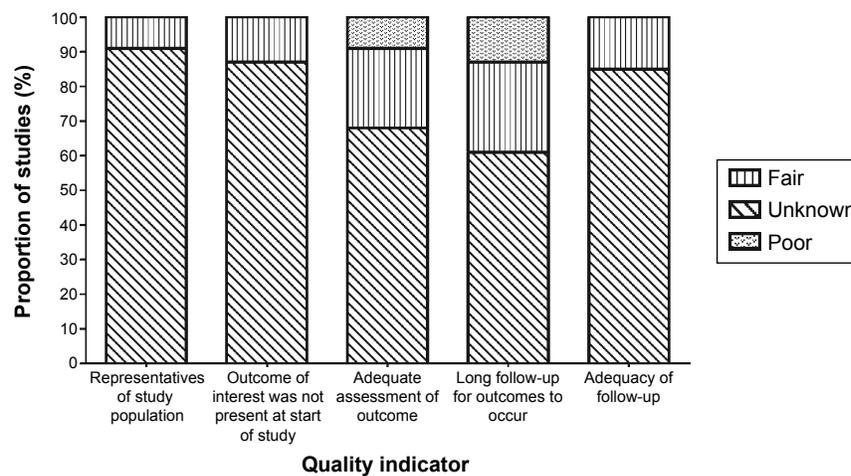


Figure 2 Selected methodological quality indicator.

combination with RT for treating LAPC in the concurrent setting; thus, both of these drugs are regarded as promising agents for the management of LAPC. However, to the best of our knowledge, there is lack of head-to-head comparison data available for oral FU versus GEM-based CRT in the treatment of LAPC, excepting one small RCT conducted by Mukherjee et al.¹⁷ In that trial, the authors concluded that capecitabine-based CRT might be preferable to GEM-based CRT for LAPC, but these findings should be interpreted with caution due to a non-significant difference between the two regimens and the relatively small sample size.¹⁷ As a result, we conducted the current systematic review and meta-analysis to evaluate the efficacy and toxicities of oral FU-based CRT compared with GEM-based CRT for the treatment of LAPC.

A total of 843 patients from 23 studies met the inclusion criteria and were used in the meta-analysis. Based on pooled results, we found that S-1-based CRT resulted in a statistically increased 1- and 2-year survival, but not for 1-year PFS and ORR, while comparable efficacy was found to be comparable between capecitabine-based CRT and GEM-based CRT in terms of OS, PFS, and ORR. Additionally, our results indicated that oral FU-based CRT is also advantageous in reducing treatment toxicity in LAPC when compared to GEM-based CRT. However, more evidence is still required before oral FU-based CRT can become the standard treatment for LAPC patients. We could not pool the results about quality of life (QoL) due to only one trial¹⁷ reporting QoL results, and a detailed QoL analysis is planned by the authors of the current review.

Table 3 Comparison of primary outcomes for oral FU versus GEM-based chemoradiotherapy

Groups	Cohorts, n	Patients, n	Incidence, n (95% CI)	I ²	Relative risk (95%)	P-value
ORR						
GEM	12	399	23.4 (14.5–25.6)	80.2	1	Ref
Capecitabine	5	177	22.7 (14.0–34.7)	60.9	0.97 (0.57–1.66)	0.45
S-1	4	169	30.5 (22.6–32.9)	0	1.30 (0.93–1.83)	0.06
1-year OS						
GEM	12	431	49.6 (40.8–58.5)	67.6	1	Ref
Capecitabine	5	177	57.1 (41.9–71.1)	72.7	1.15 (0.84–1.59)	0.19
S-1	4	169	63.4 (51.2–74.0)	56.8	1.27 (1.00–1.65)	0.03
2-year OS						
GEM	7	275	15.1 (11.2–19.9)	0	1	Ref
Capecitabine	2	91	11.0 (5.9–19.4)	0	0.73 (0.38–1.41)	0.17
S-1	3	144	26.5 (20–34.3)	0	1.75 (1.18–2.60)	0.002
1-year PFS						
GEM	5	206	27.5 (11.7–52.1)	87.3	1	
Capecitabine	2	66	36.3 (10.7–72.9)	89.0	1.32 (0.39–4.45)	0.33
S-1	3	135	31.5 (24.2–39.8)	0	1.15 (0.52–2.52)	0.37

Note: I² ≥ 50% suggests high heterogeneity across studies.

Abbreviations: GEM, gemcitabine; FU, fluoropyrimidine; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; CI, confidence interval; Ref, reference group.

Table 4 Comparison of \geq grade 3 acute toxic effect event rates for oral FU versus GEM-based chemoradiotherapy

	Studies included for analysis (n)	Events	Total	Events rate, % (95% CI)	I^2	RR (95% CI)	P-value
Hematologic toxicity							
Anemia							
GEM	12	23	407	8.5 (5.8–12.3)	36.3	1	
Oral FU	9	4	346	2.3 (1.1–4.7)	0	0.27 (0.12–0.61)	<0.001
Leukopenia							
GEM	12	83	407	19.7 (12.8–29.1)	72.3	1	
Oral FU	9	12	346	6.0 (3.6–9.7)	5.1	0.30 (0.16–0.58)	<0.001
Thrombocytopenia							
GEM	12	25	407	8.4 (5.8–12.1)	25.5	1	
Oral FU	9	2	346	1.8 (0.8–4.1)	0	0.21 (0.09–0.52)	<0.001
Non-hematologic toxicity							
Nausea							
GEM	10	44	342	13.8 (8.6–21.5)	58.3	1	
Oral FU	8	7	286	4.8 (2.5–9.0)	12.3	0.35 (0.18–0.66)	<0.001
Vomiting							
GEM	10	30	342	12.2 (8.7–17.0)	47.9	1	
Oral FU	8	2	286	2.1 (0.9–4.9)	0	0.17 (0.69–0.43)	<0.001
Diarrhea							
GEM	8	15	296	6.1 (3.8–9.7)	0	1	
Oral FU	8	3	286	3.1 (1.4–6.5)	0	0.51 (0.21–1.25)	0.07
Fatigue							
GEM	7	23	230	9.0 (4.0–19.0)	66.9	1	
Oral FU	6	5	212	3.5 (1.6–7.4)	0	0.39 (0.13–1.16)	0.05

Abbreviations: FU, fluoropyrimidine; GEM, gemcitabine; RR, relative risk; CI, confidence interval.

Several limitations exist in the present analysis. First and most importantly, the application of formal meta-analytic methods to observational studies has been controversial.³⁸ One of the most important reasons for this is that the designs and populations of reviewed studies are often diverse, and these differences may influence the pooled estimates. However, when only one small RCT is available, a meta-analysis of observational studies is one of the few methods available for assessing efficacy and toxicities.³⁹ Moreover, meta-analysis reduces the uncertainty surrounding the pooled estimates, and is a valuable method to inform the decision whether more evidence is needed, which is a timely discussion topic with regard to chemoradiotherapy in LAPC. However, potential bias may have occurred in the current review due to selection bias. Finally, the present meta-analysis only considers published literature, and lack of individual patient data prevented us from adjusting the treatment effect according to disease and patient variables.

Conclusion

Currently available clinical evidence for LAPC indicates that oral FU plus RT may be a safe and feasible regimen for patients with LAPC, with similar efficacy and low rate of toxicities compared with GEM plus RT. However, the overall quantity and quality of data regarding oral FU and GEM-based CRT are poor. The reported results do not allow

for definite conclusions. As a result, prospective randomized studies, definitively comparing the survival and treatment toxicity between oral FU and GEM-based CRT, are strongly encouraged to clearly set the role of oral FU-based CRT in the treatment of LAPC.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Newcastle–Ottawa quality assessment scale

Selection

1. Representativeness of the exposed cohort
 - a) Truly representative of the average CRC pancreatic cancer patients in the community (★)
 - b) Somewhat representative of the average CRC pancreatic cancer patients in the community (★)
 - c) Selected group of users (eg, nurses, volunteers)
 - d) No description of the derivation of the cohort
2. Selection of the non-exposed cohort
 - a) Drawn from the same community as the exposed cohort (★)
 - b) Drawn from a different source
 - c) No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure
 - a) Secure record (eg, surgical records) (★)
 - b) Structured interview (★)
 - c) Written self-report
 - d) No description
4. Demonstration that outcome of interest was not present at start of study
 - a) Yes (★)
 - b) No

Comparability

1. Comparability of cohorts on the basis of the design or analysis
 - a) Study controls for metastasis or micro-metastasis (★)
 - b) Study controls for any additional factor (★)

Outcome

1. Assessment of outcome
 - a) Independent blind assessment (★)
 - b) Record linkage (★)
 - c) Self-report
 - d) No description
2. Was follow-up long enough for outcomes to occur?
 - a) Yes (2 years) (★)
 - b) No
3. Adequacy of follow-up of cohorts
 - a) Complete follow-up – all subjects accounted for (★)
 - b) Subjects lost to follow-up unlikely to introduce bias – small number lost 25% follow-up, or description of those lost (★)
 - c) Follow-up rate <75% and no description of those lost
 - d) No statement

Notes: The star symbol signifies that study quality score; more stars means the study has higher quality.

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