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Effects of chemoradiotherapy and chemotherapy on survival of patients with locally advanced pancreatic cancer

A meta-analysis of randomized controlled trials

Cuiying Wang, MD, Xiaohua Liu, BD*, Xiaohua Wang, BD, Yanlei Wang, BD, Na Cha, BD

Abstract

To comparatively evaluate chemoradiotherapy (CRT) and chemotherapy (CT) for the treatment of locally advanced pancreatic cancer (LAPC) by meta-analysis.

A literature search was performed until August 2016 to identify comparative studies assessing survival rates and complications. Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were determined with the fixed or random effects model.

Five randomized controlled trials (RCTs) met the defined inclusion criteria. A total of 593 patients were included, with 295 and 298 treated with CRT and CT, respectively. Overall survival showed no statistically significant difference in patients treated with CRT and CT at 6, 12, 18, and 24 months (respectively: OR = 1.13, 95% CI: 0.60–2.17; OR = 1.15, 95% CI: 0.53–2.52; OR = 1.13, 95% CI: 0.43–2.95; OR = 1.07, 95% CI: 0.67–1.72). Meanwhile, CRT had higher rates of grade 3 to 4 adverse events (nausea and vomiting, OR = 2.74, 95% CI: 1.36–5.52; diarrhea, OR = 4.28, 95% CI: 1.16–15.71).

The data are not sufficient to change from CT to CRT in the treatment of patients with LAPC and thus clinical discretion is required until more data is accumulated.

Abbreviation: 5-FU = 5-fluorouracil, 95% = CI 95% confidence intervals, CNKI = China National Knowledge Internet, CRT = chemoradiotherapy, CT = chemotherapy, FOLFIRINOX = 5-FU, leucovorin, irinotecan and oxaliplatin, GEMOX = Gemcitabine, oxaliplatin, IMRT = intensity-modulated radiotherapy, LAPC = locally advanced pancreatic cancer, OR = odds ratios, PC = pancreatic cancer, RCT = randomized controlled trial, RRS = robotic radiosurgery, SBRT = stereotactic body radiotherapy.

Keywords: chemoradiotherapy, chemotherapy, local advanced pancreatic cancer, meta-analysis

1. Introduction

Pancreatic cancer (PC) is the 4th leading cause of cancer-related death in the United States, and is expected to become 2nd by 2030. The American Cancer Society estimated that 53,070 (27,670 men and 25,400 women) individuals would be diagnosed with pancreatic cancer in 2016, with 41,780 (21,450 men and 20,330 women) succumbing to the disease.[1] Epidemiological data in Europe reveal that PC is the 6th most prevalent cancer and the 5th leading cause of cancer related death, with yearly 70,000 estimated deaths. PC incidence has increased in recent decades, possibly due to elevated prevalence of obesity, aging, and unknown factors.[2] At initial diagnosis, 50% of patients present with metastatic disease while 30% have locally advanced tumors; therefore, only 20% of cases are resectable.[3]

The management of locally advanced pancreas cancer (LAPC) is fraught with difficulties because of the tantalizing goal shared by patients and clinicians that conversion to a resectable cancer can be achieved with favorable response to intensive induction treatment. Surgeons cannot remove tumors that encase the aorta, obliterate the superior mesenteric vein, or involve more than 180° of the superior mesenteric artery or celiac vessels, achieving negative tumor margins. In this context, surgery is not advised due to the associated morbidity and improbability of cure. In unusual circumstances, intensive treatment with chemotherapy (CT) and/or radiation therapy has the potential to convert unresectable to resectable lesions. This possibility, albeit remote, and the categorization of some tumors as borderline resectable motivate the search for strategies to achieve pronounced responses to chemotherapy or radiation therapy necessary to make surgery feasible.[4]

The role of radiation therapy in the management of LAPC remains controversial. In the early 1980s, fluorouracil-based concomitant chemoradiotherapy (CRT) was shown to be better compared with radiotherapy alone.[5] In the late 1990s, gemcitabine was adopted as the preferred treatment strategy, replacing CRT, in patients with LAPC. In addition, 7 randomized trials of LAPC patients comparing CRT with CT yielded contradictory data.[6–12]

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Department of Medical Oncology, Affiliated Hospital of Chifeng College, Chifeng, Inner Mongolia Autonomous Region, China.

** Correspondence: Xiaohua Liu, Department of Medical Oncology, Affiliated Hospital of Chifeng College, Chifeng 024000, Inner Mongolia Autonomous Region, China (e-mail: lxh201101@126.com).*

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The purpose of this study was to comparatively evaluate the effects of CRT and CT in patients with LAPC.

2. Methods

2.1. Literature review

A systematic review of the MEDLINE, Embase, Cochrane center, China National Knowledge Internet (CNKI), and WanFang databases was performed from inception to August 2016, using the following keywords and combinations: ["PC (MeSH) or PC (Text word)"] and ["antineoplastic agents (Text word) or chemotherapy (MeSH) or chemotherapy (Text word) or chemoradiotherapy (Text word)"] and "clinical trials (Text word)." In addition, reference lists of the selected trials were screened for other relevant studies. Only English and Chinese languages were included. In addition to full-text publications, we also screened relevant reviews and meta-analyses of CRT in PC.

2.2. Data extraction and quality assessment

Data were extracted by 3 independent investigators using standardized forms. The recorded data included the number of patients, overall survival rates and complications. The quality of the selected articles was evaluated based on the nonrandomized controlled clinical trial quality evaluation standard.

2.3. Study selection criteria

Inclusion criteria for this study were: assessment of patients with a diagnosis of LAPC; prospective randomized controlled trial (RCT); both blinded and nonblinded studies were included; treatment with CT or CRT therapy.

2.4. Exclusion criteria

Abstracts, letters, editorials and expert opinions, reviews without original data, case reports, and studies lacking control groups were excluded. The following studies were also excluded: nonrandomized trials; inclusion of patients with metastatic disease or after resection surgery; trials with 2 separate cancer types, which did not report pancreatic data separately; no available survival data; treatment with radiation therapy alone.

2.5. Statistical analysis

The current meta-analysis was performed with the RevMan 5.3.0 software package. Odds ratios (ORs) or mean differences with 95% confidence intervals (95%CIs) were calculated for dichotomous and continuous outcomes, respectively. Random- and fixed-effects models were used with the "intention-to-treat" analysis. If results were similar between the 2 models, the random-effects model was reported, as it is commonly used for indirect comparisons. If results differed between the 2 models, both results were reported. Heterogeneity was explored by χ^2 and I^2. $I^2 < 25\%$ and $I^2 > 50\%$ reflected small and large inconsistencies, respectively. $P < .05$ was considered statistically significant.

2.6. Publication bias

A funnel plot was used to explore bias. Asymmetry in the funnel plot of trial size against the treatment effect was used to assess the risk of bias.

2.7. Ethics

Since this article is based on meta-analysis of literature search, it does not involve ethics.

3. Results

3.1. Description of studies

A total of 7 studies meeting the inclusion criteria were identified.[6–12] However, there is currently no clear definition of LAPC, and some eligible gastric carcinoma patients had liver metastases in Hazel's report;[6] therefore, we believed there may be metastatic PC cases, and decided to exclude this article. According to the AJCC cancer staging manual, stage IV cases have distant metastasis; hence we also excluded Lin's study.[11] Eventually, 5 RCTs[7–10,12] were included in the meta-analysis. Of 593 patients assessed in 5 studies, 295 and 298 were allocated to the CRT and CT groups, respectively, to evaluate their therapeutic effects on LAPC. Patient characteristics and evaluation indices are shown in Tables 1–3.

3.2. Overall survival rates

Six-month survival rates: A meta-analysis of 4 trials reporting these data showed that there was no significant difference between the 2 groups [OR = 1.13, 95% CI: 0.60–2.17; $P = .71$], and no evidence of significant heterogeneity (Table 4).

Twelve-month survival rates: A meta-analysis of 4 trials reporting these data showed that there was no statistically significant difference between the 2 groups [OR = 1.15, 95%CI: 0.53–2.52; $P = .73$], with certain heterogeneity.

Eighteen-month survival rates: A meta-analysis of 4 trials reporting these data showed that there was no statistically significant difference between the 2 groups [OR = 1.13, 95%CI: 0.43–2.95; $P = .87$], with certain heterogeneity.

Twenty four-month survival rates: A meta-analysis of 5 trials reporting these data showed that there was no statistically significant difference between the 2 groups [OR = 1.07, 95%CI: 0.67–1.72; $P = .77$], with no evidence of heterogeneity (Fig. 1).

3.3. Grade 3 to 4 adverse events

Nausea and vomiting: A meta-analysis of 4 trials reporting these data showed that CRT resulted in significantly higher rates than the control CT [OR = 2.74, 95%CI: 1.36–5.52; $P = .005$], with certain heterogeneity.

Diarrhea: A meta-analysis of 4 trials reporting these data showed that the experimental (CRT) group had a significantly higher rate than the control (CT) group [OR = 4.28, 95%CI: 1.16–15.71; $P = .03$], with no evidence of heterogeneity.

3.4. Stratified analysis

We conducted a stratified analysis by sample size and chemotherapy included gemcitabine.

Chemotherapy included gemcitabine: A meta-analysis of 3 trials reporting overall survival rates showed that there was no statistically significant difference between the 2 groups at 12 and 24 months (respectively: OR = 0.91, 95% CI: 0.42–1.98; OR = 1.03, 95% CI: 0.62–1.70), with no evidence of heterogeneity. The experimental (CRT) group had a significantly higher nausea rates than the control (CT) group (OR = 3.37, 95%CI: 1.50–7.56; $P = .003$), with no evidence of heterogeneity.

Due to heterogeneity in sample size, sensitivity analyses were conducted using the 4 small trials. The subgroup analysis showed

Table 1

Eligible patient criterion of the included articles.

	Eligible patient criterion
Klassen DJ, 1985	Histologically confirmed, locally unresectable pancreatic carcinoma without evidence of distant metastases. All patients had a WBC count >4,000 cells/AtL a platelet count >100,000/AL, and adequate hepatic and renal function. The patients were at least 20 days postsurgery requiring resection and 14 days postsurgery requiring only laparotomy and biopsy. The patients were not eligible if therapy was delayed more than 6 weeks after surgery, or if they were previously treated with radiation or chemotherapy. An ECOG performance status of 2 or better was required, and patients were to have an expected survival time of at least 2 months. Patients with acute intercurrent infections and postsurgical complications were excluded as were patients with active secondary tumors other than basal-cell cancers of the skin.
Gastrointestinal Tumor Study Group, 1988	Surgically staged and pathology-confirmed adenocarcinoma of the pancreas of ductal, acinar, or undifferentiated histology, confirmed by referee pathologists. Patients with surgically staged, locally unresectable cancer entirely confined to the pancreas and contiguous organs, to regional lymph nodes, or to the peritoneum overlying the pancreas and confined within an area of $<400\,cm^2$ on anterior and posterior projections were all evaluated by a radiation therapist before randomization 2 to 6 weeks following surgery. An oral food intake of 1500 kcal/day had been maintained for 3 consecutive days; ambulatory for more than one-half of the day; were free of infection, and had satisfactory test results (leukocyte count $>4000/mm^3$, platelet count $>150,000/mm^3$, hemoglobin >10 g/dL, total bilirubin <3.0 mg/dL, and creatinine clearance >70 mL/min).
Chauffert B, 2008	Histologically proven ductal adenocarcinoma of the pancreas, no distant metastases at computed tomography (CT) scan, and 0 to 2 World Health Organization (WHO) performance status (PS). Tumors were judged as nonresectable due to extension to regional lymph nodes and/or vascular structures such as the superior mesenteric artery or the celiac trunk or the existence of a portal or superior mesenteric–portal venous confluent thrombosis. Adequate organ function was required (absolute granulocyte count>1500/mm^3, platelet count>100,000/mm^3, serum bilirubin<50 mM/L, if indicated after biliary drainage; serum creatinine<130 mM/L; prothrombin rate >80%).
Loehrer PJ, 2011	Cytologic or histologic evidence of locally unresectable adenocarcinoma of the pancreas, not amenable for complete surgical resection based on clinical or radiographic evaluation. Patients with small-cell carcinoma, mucinouscyst adenocarcinoma, or islet cell or papillary cystic neoplasm were not eligible. Patients must also have been at least 18 years of age, had an ECOG performance score of 0 to 2, and received no prior chemotherapy or radiotherapy. Eligible patients had an absolute granulocyte count of 2.0×10^9/L or greater, platelet count >100,000/L, total bilirubin of <3 mg/dL, AST <5 upper limit of normal, albumin >2.5 g/dL, and serum creatinine 1.5 or less than upper limit of normal. Patients were not eligible if they had a history of active collagen vascular disease or signs of recent peptic or duodenal ulcer. Other contradictions included serious concomitant systemic disorders or active infections.
Hammel P, 2016	At least 18 years of age; had histologically or cytologically confirmed stage III locally advanced pancreatic cancer according to the International Union Against Cancer staging system; had measurable or evaluable disease as assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) criteria, the World Health Organization (WHO) performance status score of 2 or less (0 indicates fully active, 1 indicates ability only to carry out light work, and 2 indicates capacity for self-care but inability to carry out work); had adequate biological hematologic, hepatic, and renal parameters; and had no prior chemotherapy or radiation therapy,

that there was no statistically significant difference between the 2 groups at 24 months (OR = 1.08, 95%CI: 0.46–2.54; $P = .86$), with no evidence of heterogeneity. There was no statistically significant difference between the 2 groups at 12 months (OR = 1.34, 95%CI: 0.35–5.11; $P = .66$), with no evidence of heterogeneity. The experimental (CRT) group had a significantly higher nausea rates than the control (CT) group (OR = 2.20, 95% CI: 1.05–4.62; $P = .04$), with no evidence of heterogeneity.

3.5. Sensitivity analysis and publication bias

Publication bias may exist when no significant findings remain unpublished, thus artificially inflating the apparent magnitude of an effect.

Complications and overall survival rates following CRT or CT for LAPC treatment were determined by the random-effects models.

Funnel plot of the study results is shown in Figure 2. The funnel plot for 24-month overall survival rate following CRT or CT for LAPC treatment showed asymmetry, which suggested some publication bias.

4. Discussion

As shown in our current meta-analysis: the CRT group was not superior to the CT group in 6-, 12-, 18-, 24-month survival rates; the CRT group had significantly more grade 3 to 4 treatment-related adverse events than the CT group. At the same time, the results of further stratification analysis are similar.

Many centers currently consider locally advanced tumors as cancers with no distant metastasis, the absence of blood flow through the SMV and/or portal vein lumen, or venous involvement not amenable to reconstruction, involvement of the common hepatic artery or superior mesenteric artery over >180° of the vessel circumference, any celiac abutment or aortic or inferior vena cava invasion or encasement. However, there is not standardized definition of LAPC in early stage.[13] LAPC has been diagnosed by laparotomy for 3 decades. However, current diagnosis mainly depends on the imaging technology. Meanwhile, with advances in surgical techniques, the definition of LAPC is also changing.

As shown in early clinical practice, conventional radiotherapy for LAPC often cannot improve treatment efficacy. Three-dimensional conformal radiotherapy, intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and robotic radiosurgery (RRS) improve the therapeutic effectiveness. IMRT splits a typical radiation treatment field into smaller "beamlets." It is implemented as dynamic IMRT (collimating leaves move in and out of the radiation beam path during treatment) or "step and shoot" IMRT (leaves change the field

Table 2

Treatment of the included articles.

	Opening treatment time	Treatment programs
Klassen DJ, 1985	20 days postsurgery requiring resection and 14 days postsurgery requiring only laparotomy and biopsy and within 6 weeks after surgery	Chemotherapy: 5-FU 600 mg/m^2 weekly Chemoradiotherapy: 40 Gy over 4 weeks plus 5-FU 600 mg/m^2 on the first 3 days of therapy and then 5-FU 600 mg/m^2 starting day of completion of radiation
Gastrointestinal Tumor Study Group, 1988	Within 1 week of randomization and within 6 weeks of surgery.	Chemotherapy: 5-FU 600 mg/m^2 on days 1, 8, 29, and 36; streptozocin 1 g/m^2 every 8 weeks; and mitomycin 10 mg/m^2 8 weeks. Chemoradiotherapy: Rad 54 Gy (1.8 Gy×5 days every week for 6 weeks and 5-FU 350 mg/m^2 iv daily on first 3 days and last 3 days of radiotherapy. SMF: begin on day 64; 5-FU 600 mg/m^2 on days 1, 8, 29, and 36; streptozocin 1 g/m^2 every 8 weeks; and mitomycin 5 mg/m^2 first dose (day 64) then 10 mg/m^2 day 120 and every 8 weeks.
Chauffert B, 2008	Unstated	Chemotherapy: gemcitabine 1000 mg/m^2 weekly for 7 weeks and then 1000 mg/m^2 3 weeks every 4 weeks. Chemoradiotherapy: 60 Gy (2.0 Gy × 5 days every week for 6 weeks), concomitant 5-FU 300 mg/m^2/day days 1 to 5 each week during radiation and cisplatin 20 mg/m^2 day from days 1 to 5 only during weeks 1 and 5.
Loehrer PJ, 2011	Unstated	Chemotherapy: gemcitabine 1000 mg/m^2 weekly for 6 weeks 1 week off then 1000 mg/m^2 weekly for 3 weeks Chemoradiotherapy: 50.4 Gy (1.8 Gy × 5 days every week for 5.5 weeks) with gemcitabine 600 mg/m^2 beginning the first day of radiation and then weekly while getting radiation, followed by gemcitabine 1000 mg/m^2 weekly 3 weeks on and 1 week off × 5 cycles.
Hammel P, 2016	After 4 months of induction chemotherapy	Chemotherapy: gemcitabine 1000 mg/m^2 infusion weekly for 3 weeks, followed by a 1-week rest (1 cycle), for 2 cycle; with or without erlotinib 150 mg/day for a total of 2 months. Chemoradiotherapy: 54 Gy (1.8 Gy × 5 days every week for 6 weeks), capecitabine was given at a dose of 800 mg/m^2 twice daily on days of radiation therapy. gemcitabine 1000 mg/m^2 infusion weekly for 3 weeks, followed by a 1-week rest (1 cycle), for 2 cycle; with or without erlotinib 150 mg/day for a total of 2 months.

shape while the machine is off). The cumulative effect is that the prescription dose conforms around the delineated target volumes, significantly reducing the doses reaching adjacent normal tissues.[14,15] SBRT can employ many of the same strategies, and is coupled with a high degree of anatomic targeting accuracy and reproducibility with high doses of ionizing radiation. This maximizes the cell-killing effect on the target while minimizing injury to adjacent normal tissues.[16,17] RRS is a particular SBRT technique. It is based on the delivery of a single large radiation fraction using a robotic linear accelerator. The reduced volume of irradiated normal tissue achieved by improving the treatment precision allows the delivery of a single radiation fraction (with RRS), which can potentially ablate all tissues in the treated area.[18]

The chemotherapy types and dosages administered concurrently with radiation therapy were also different in these trials. The standard of chemotherapy has also changed in the last few years in the treatment of LAPC. The nucleoside analogs

Table 3

Characteristics of included articles.

	No. of patients		Age, median (IQR), y		Sex (Male/Female)		Tumor location (head/ body or tail)		WHO performance status score (0+1/2)	
	CRT	CT	CRT	CT	CRT	CT	CRT	CT	CRT	CT
Klassen DJ, 1985	47	44	—	—	22/25	31/13	—	—	35/12	37/7
Gastrointestinal Tumor Study Group, 1988	22	21	61	60	14/8	13/8	19/3	18/3	20/2	18/3
Chauffert B, 2008	59	60	60	62	31/28	34/26	46/13	40/20	54/5	46/14
Loehrer PJ, 2011	34	37	66 (46.9–83.5)	69 (49.7–83.7)	19/15	18/19	20/9	25/5	34/0	37/0
Hammel P, 2016	133	136	62.0 (55.0–70.0)	63.0 (57.0–70.0)	58/765	76/60	88/44	93/43	124/7	124/8

CRT = chemoradiotherapy, CT = chemotherapy.

Table 4

Summary of the results between CRT and CT in the management of LAPC and subgroup analysis.

Variables	No. of studies furnishing data	Results		RR (95%CI)	*P*-value	I^2
		CRT	CT			
Overall survival						
6 months	4 [8–10,12]	90.73%	89.37%	1.13 [0.60–2.17]	.71	0%
12 months	4 [8–10,12]	54.03%	54.72%	1.15 [0.53–2.52]	.73	72%
18 months	4 [8–10,12]	28.23%	31.50%	1.13 [0.43–2.95]	.87	70%
24 months	5 [7–10,12]	14.92%	13.76%	1.07 [0.67–1.72]	.77	0%
Grade 3 to 4 adverse events						
Nausea, vomiting	4 [8–10,12]	11.69%	4.72%	2.74 [1.36–5.52]	.005	45%
Diarrhea	4 [8–10,12]	4.84%	0.79%	4.28 [1.16–15.71]	.03	0%
Chemotherapy included gemcitabine						
12 months	3 [9,10,12]	54.87%	57.94%	0.91 [0.42–1.98]	.80	72%
24 months	3 [9,10,12]	16.81%	16.31%	1.03 [0.62–1.70]	.91	0%
Nausea, vomiting	3 [9,10,12]	12.39%	3.86%	3.37 [1.50–7.56]	.003	0%
Small sample size						
12 months	3 [8–10]	40.87%	41.53%	1.34 [0.35–5.11]	.66	81%
24 months	3 [8–10]	11.11%	10.49%	1.08 [0.46–2.54]	.86	16%
Nausea, vomiting	3 [8–10]	20%	10.17%	2.20 [1.05–4.62]	.04	51%

CRT = chemoradiotherapy, CT = chemotherapy, LAPC = locally advanced pancreatic cancer.

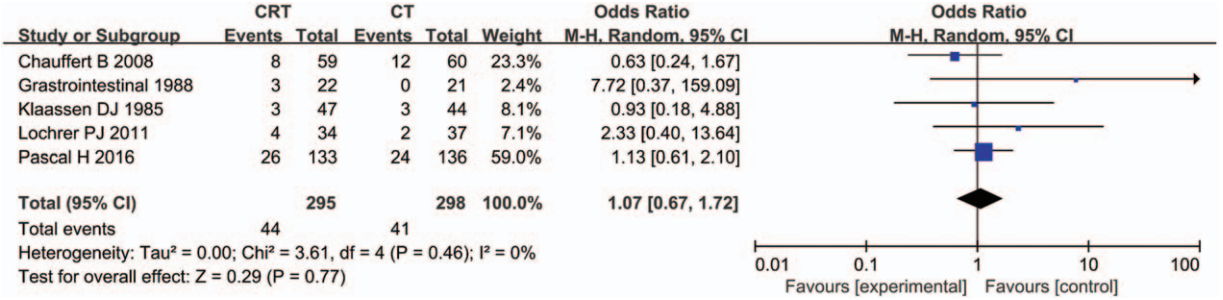

Figure 1. 24-months overall survival rates by CRT versus CT for the treatment of LAPC.

5-fluorouracil (5-FU) and gemcitabine are potent radiosensitizers, and combined use of radiotherapy with 5-FU and gemcitabine has been shown to improve the survival of patients with locally advanced pancreatic cancer compared with radiotherapy alone. Gemcitabine and the oral fluoropyrimidine S-1 with IMRT for patients with LAPC is feasible and reduces toxicity, particularly nausea and vomiting.[19] Gemcitabine, oxaliplatin (GEMOX) and radiotherapy is feasible, and results in a high percentage of R0 resection, with encouraging outcome given the majority of patients with borderline resectable disease.[20] A capecitabine-based regimen is preferable to a gemcitabine-based counterpart in the context of consolidation CRT after a course of induction CT for LAPC.[21] With the introduction of active modern chemotherapeutic regimens, such as FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin),[22] mFOLFIRINOX (no bolus 5-FU and a lower dose of irinotecan)[23] and gemcitabine plus nab-paclitaxel,[24] there has been a resurging interest in the concept of converting unresectable or borderline resectable tumors to resectable ones.

The conclusions of this meta-analysis were limited by various factors. First, there was heterogeneity between study design, sample size, and the years covered. This may lead to false positives or false negatives, that is, risk of random errors. Secondly, the randomization procedure was unclear or inadequate in the assessed trials.[25] Funnel plots can be suggestive of publication bias with lack of negative small RCTs. However, a firm conclusion about bias was difficult to reach as the asymmetry of the funnel plot was minimal. In addition, funnel plots can show asymmetry for reasons other than publication bias. Therefore, the above pooled OR might be an overestimate of the true effect. Due to data constraints, this meta-analysis could not analyze the quality of life and progression-free survival rates, and was unable to carry out stratified analyses of other possible confounding factors. If the method is to be more effective, larger samples and randomized controlled studies with longer follow-up are required.

Furthermore, the included reports had different patient eligibility standards, evaluation times, initial treatment times, treatment programs, pathological types and progression-free survival criteria.

Advances in imaging have improved the diagnosis and staging of patients with pancreatic cancer, and neoadjuvant therapy has demonstrated promising early results; however, the prognosis of patients with LAPC remains poor. The following aspects may need further investigation. Additional imagining modalities are required to evaluate true response to treatment, to provide more

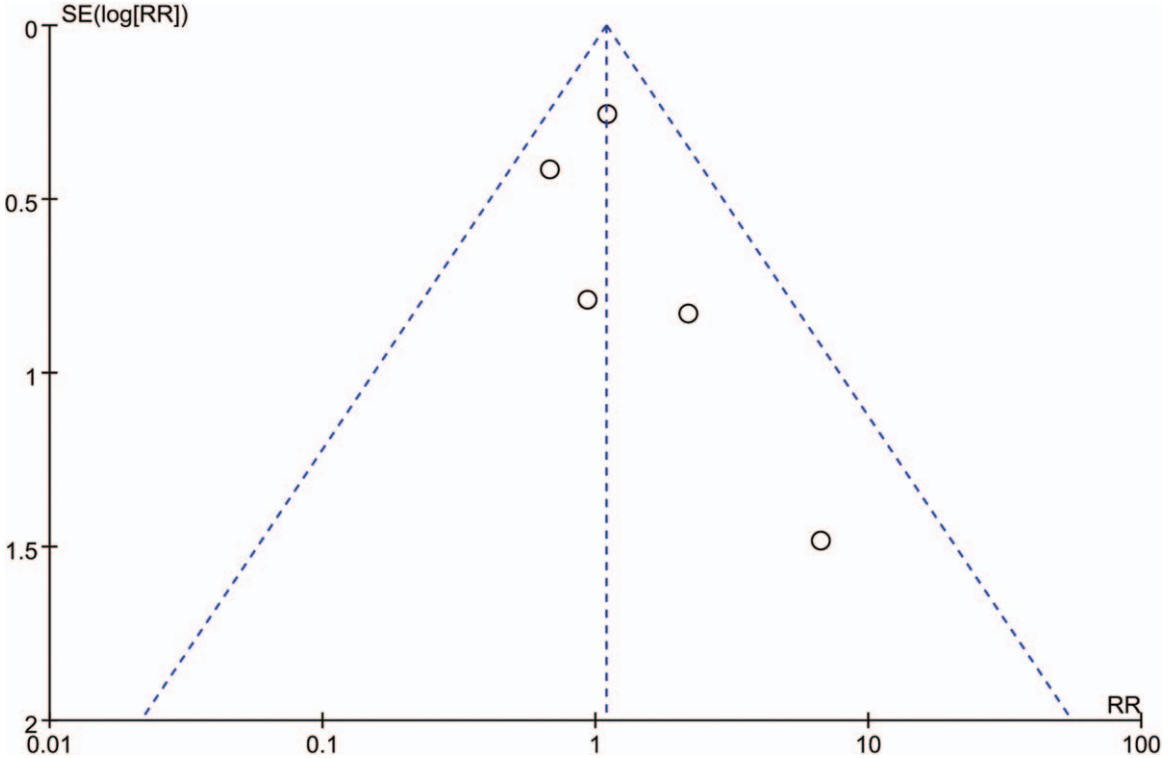

Figure 2. Funnel plot of the outcome of 24-months overall survival rates.

accurate prognostic information and to guide optimal treatment. Novel tumor markers or other prognostic factors might also better guide therapeutic options, including assessing who might best benefit from surgical resection. Uniform inspection and judgment standards are also important. The resection rates should be a result of judgment indicators. Another important point is that treatment of LAPC requires a multidisciplinary team (radiologists, oncologists, surgeons, dietitians, and pathologists).

5. Conclusions

CRT was not superior to CT in the treatment of patients with LAPC, but had more complications. Further RCTs are warranted to clarify the exact values of CRT and CT for LAPC treatment.

Author contributions

Conceptualization: Cuiying Wang, Xiaohua Liu.
Data curation: Cuiying Wang, Xiaohua Wang, Yanlei Wang, Na Cha.
Formal analysis: Cuiying Wang, Xiaohua Liu, Xiaohua Wang, Yanlei Wang, Na Cha.
Project administration: Xiaohua Liu.
Writing – original draft: Cuiying Wang.
Writing – review & editing: Xiaohua Liu, Xiaohua Wang, Yanlei Wang, Na Cha.

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