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Survival outcome after stereotactic body radiotherapy for locally advanced and borderline resectable pancreatic cancer: A systematic review and meta-analysis

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ABSTRACT

Background: Some studies reported stereotactic body radiotherapy (SBRT) has demonstrated superior therapeutic results than conventional radiotherapy. Nevertheless, this statement is controversial and the trial attempting to prove this is underway. We conducted this systemic review and meta-analysis aiming to combine the latest and most complete information about the survival outcomes and toxicities following SBRT for locally advanced pancreatic cancer (LAPC) and borderline resectable pancreatic cancer (BRPC).

Methods: Items involving SBRT and pancreatic cancer were searched in PubMed, EMBASE, Cochrane Library, SCOPUS and Web of Science. Median overall survival (OS), 1/2/3-year OS, median progression-free survival (PFS), 1/2/3-year PFS and incidence of grade 3–5 toxicities were the endpoints of interest in this meta-analysis. These endpoint proportions were pooled and analyzed using R.

Results: For the LAPC series, the median OS was 14.1 months; pooled 1/2/3-year OS rates were 57%, 19% and 10%, respectively; the median PFS was 10 months; pooled 1/2/3-year PFS rates were 36%, 12% and 4%; pooled incidence rates of acute gastrointestinal (GI), acute hematologic and late GI toxicity (grade \geq 3) were 2%, 4% and 8%. For the BRPC series, the median OS was 17.5 months; pooled 1/2-year OS rates were 75% and 29%; the median PFS was 12.2 months; pooled 1/2-year PFS rates were 48% and 18%; the incidence rates of toxicity (grade \geq 3) were all 0%.

Conclusions: Our meta-analysis based on published results of OS, PFS and incidence rates of toxicity demonstrated that SBRT does not show desirable therapeutic result than the standard therapies for LAPC and BRPC.

Introduction

Pancreatic cancer (PC) is one of the most aggressive cancers with a 5-year OS rate of 6% [1] and a median OS of up to 13.6 months [2]. Unfortunately, treatment for patients with LAPC and BRPC is largely ineffective and controversial and combined chemoradiotherapy or integrative chemotherapy is a common choice. Nevertheless, these treatments are often accompanied by severe toxicities (grade \geq 3) [3].

In recent years, a new radiation technique, SBRT, emerged and has been used in the treatment of solid tumors such as NSCLC, prostate

cancer, hepatic cancer and PC [4]. SBRT can deliver higher doses of radiation to the tumor in only a few treatment fractions. Furthermore, SBRT can be combined with chemotherapy more conveniently than conventional radiotherapy due to fewer radiation fractions. Some studies reported SBRT has demonstrated superior therapeutic results with less acute and late toxicity than conventional radiotherapy because of improved dosimetry accuracy and normal tissue sparing [5–7]. Nevertheless, this statement is controversial and the trial attempting to prove this is underway [8].

Many studies on SBRT for PC have been published and various survival outcome data based on meta-analyses have been reported, espe-

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cially in the last 5 years. For example, Buwenge et al. focused on the pain relief effect of SBRT for PC [9], Zaorsky et al. reported the relationship between SBRT dose and therapeutic effect for PC [10], and Petrelli et al. reviewed SBRT for PC based on data prior to 2016 [11]. This inspired us to conduct this systemic review and meta-analysis aiming to combine the latest and most complete information about the survival outcomes and toxicities following SBRT for LAPC and BRPC. We expected these information will helpful to evaluate the therapeutic effect and safety of SBRT for LAPC and BRPC.

Materials and methods

Search strategy

Items involving SBRT and PC were searched in PubMed, EMBASE, Cochrane Library, SCOPUS and Web of Science through November 25, 2019. Searching terms were (pancreatic OR pancreas) AND (cancer OR carcinoma OR adenocarcinoma OR neoplasm) AND (SBRT OR stereotactic body radiotherapy OR stereotactic body radiation therapy OR stereotactic body radiotherapy OR stereotactic radiosurgery OR radiosurgery). Two authors retrieved papers independently and disagreements were resolved by the remaining co-authors.

Study selection

The inclusion criteria for papers in this meta-analysis were (1) published in English; (2) reported LAPC or BRPC or unresectable pancreatic cancer patients treated with SBRT and SBRT as a part of the initial treatment plan; (3) prospective or retrospective studies or clinical trials including at least 10 PC patients; (4) reported OS or PFS data. Studies involved metastatic or re-irradiation cases; studies with populations selected from the national database, studies with patients selected for being non-progressors, studies with patients treated with elective nodal irradiation and without motion management, phase I trials, mechanistic researches, cell experiments, animal studies, reviews, letters, commentaries, conference abstracts, book chapters and duplicated articles were excluded. Two independent authors selected all of the papers by examining titles and abstracts. Furthermore, full text reviewing was conducted with the above criteria. Disagreements were resolved by the remaining co-authors.

Data extraction

The following data was extracted from selected papers: last name of the first author, publication year, study design, study country, age and sex of patients, study period, the number of patients, disease stage, lymph node stage, follow-up period, SBRT dose (we consider it to be SBRT if the irradiation dose per fraction is more than 5 Gy and fractions no more than 5.), number of SBRT fractions, chemotherapy regimens, endpoints of interest, median OS, OS (1, 2 and 3-year), median PFS, PFS (1, 2 and 3-year), and incidence of grade 3–5 toxicities (acute GI, acute hematologic, late GI and late hematologic toxicities). When numerical data of OS and PFS was not reported, they were extracted from the Kaplan-Meier (K-M) curves using Engauge Digitizer V12.1. Two authors extracted data independently and disagreements were resolved by the remaining co-authors.

Quality assessment

Two independent authors used the Newcastle-Ottawa scale (NOS) to evaluate the quality of selected studies. High quality reports scored 7 to 9 and medium quality studies scored 4 to 6 points.

Statistical analysis

Median OS, OS (1, 2 and 3-year), median PFS, PFS (1, 2 and 3-year) and incidence of grade 3–5 toxicities (acute and late) were the

endpoints of interest in this meta-analysis. These endpoint proportions were pooled and analyzed using the 'metaprop' function in R (both fixed and random effect methods). The heterogeneity among the studies was evaluated by the I^2 value. $I^2 > 50\%$ was considered an existing heterogeneity ($I^2 > 75\%$ considered significant heterogeneity) and a random-effect result was utilized, with an otherwise fixed-effect result. Potential reasons for heterogeneity were investigated by subgroup analysis, meta-regression and sensitivity analysis. For the subgroup analysis, all studies were categorized into subgroups according to publication year, study design, patient race (studies on American, Australian and Italian patients are categorized into Caucasian subgroup, studies on Chinese and Korean into the Asian subgroup) and study country. We tested all potential parameters, and the variables of patient age, numbers of patients, follow-up period and SBRT dose were meaningful and employed in the meta-regression analysis. The result of each analysis was demonstrated in a forest plot. Publication biases were assessed using funnel plots and an Egger's test. All statistical analyses were conducted with R using 'meta' package. A $P < 0.05$ value was considered statistically significant.

Results

Search results and study characteristics

A total of 69 papers were selected from 1929 potentially relevant reports. Nineteen studies [12–30] were included in this meta-analysis based on inclusion criteria (Fig. 1). These included studies involving 800 patients published from 2010 to 2019 (Table 1). Fifteen studies based on LAPC patients [14–20]: [23–30], 1 based on BRPC patients [12] and 3 based on both [13,21,22]. In these studies, 8 were prospective studies [14,15,17,18,24,26,27,30], including 4 phase II clinical trials [15,18,26,27], and 11 were retrospective series [12,13,16,19–23,25,28,29]. The number of patients ranged from 10^{14} to $11,021$ and the median age ranged from $62^{28,29}$ to $74^{17,25}$. The median follow-up period ranged from 7.8^{13} to 24^{19} months. SBRT doses ranged from $25^{12,20,26,27}$ to 45^{29} Gy and the fractions ranged from $1^{26,27}$ to 8^{29} . The survival outcome was tabulated from the diagnosis of PC in most of these studies and from the start of SBRT treatment in the others. The quality of included studies was good with a medium score over 7.

Pooled analysis of OS

The effects of SBRT on OS were shown in Fig. 2. For the LAPC series, the median OS (range: 10.6–20 months, median: 14.1 months) was available for all studies except one [23]. One-year OS was available for all studies except one [22], 2-year for 14 studies [14–21,23,24,26–29] and 3-year for 7 studies [15,16,21,23,27–29]. Furthermore, three 1-year OS [18–20], four 2-year OS [16,18–20] and five 3-year OS [15,16,23,28,29] were extracted from the K-M curves. The OS rates for 1-year, 2-year and 3-year ranged from 39.1 to 82.1%, 0 to 35.7% and 2 to 20.5%, respectively. Pooled OS rates for 1-year, 2-year and 3-year by a random effects model were 57% (95% confidence interval [CI]: 51–64%), 19% (95% CI: 12–27%) and 10% (95% CI: 5–16%), respectively. For the BRPC series, the median OS (range: 14.4–20 months, median: 17.5 months) was available for all studies. One-year OS was available for 3 studies [12,13,21], 2-year for 2 studies [12,21] and 3-year for 1 study [21]. Furthermore, one 2-year OS [12] was extracted from the K-M curve. Pooled OS rates for 1-year and 2-year by a random effects model were 75% (95% CI: 60–93%) and 29% (95% CI: 21–41%), respectively.

Pooled analysis of PFS

The effects of SBRT on PFS were shown in Fig. 3. For the LAPC series, the median PFS (range: 6–15 months, median: 10 months) was available for 13 studies [13–16,19–21,24–29]. PFS of 1-year was available for

Table 1
Characteristics of the included studies.

Study/Subgroup	Publication year	Study design	Country	Median age (range), y	Sex	Study period	Total patients	Stage	N stage	Median follow-up (range), mo	SBRT dose, Gy	Fractions
Chuong et al	2012	R	United States	64 (44–77)	M/F	2009–2011	30	BRPC, T3=29 T4=1	N0=12 N1=18	15.6 (6.3–26.1)	25 (25–30)	5
Chuong et al. group1	2013	R	United States	64 (38–87)	M/F	2009–2011	16	LAPC	N0=29 N1=44	11 (2.2–21)	35 (25–50)	5
Chuong et al. group2							57	BRPC	7.8 (3.4–25.9)			
Gurka et al	2013	P	United States	62.5 (50–79)	M/F	2009–2011	10	LAPC	N0=4 N1=6	N/A	25	5
Herman et al	2015	Phase II	United States	67 (35–87)	M/F	2010–2012	49	LAPC	N/A	13.9 (3.9–45.2)	33	5
Jung et al	2019	R	Korea	64 (38–84)	M/F	2011–2016	95	LAPC	N0=72 N1=23	15 (2–49)	28 (24–36)	4
Kim et al	2019	P	Australia	74 (56–92)	M/F	2015–2017	27	LAPC, IB (n = 2) II (n = 13) III (n = 11)	N/A	9 (3–32.7)	29 (25–42)	3 or 5
Lin et al	2019	Phase II	United States	65 (45–79)	M/F	2013–2016	11	LAPC, T1=2 T2=2 T3=3 T4=4	N0=5 N1=6	13	40	5
Mahadevan et al	2010	R	United States	65 (43–88)	M/F	2005–2007	36	LAPC	N/A	24 (12–33)	29 (24–36)	3
Mahadevan et al	2011	R	United States	67 (44–88)	M/F	2007–2010	47	LAPC	N/A	21 (6–36)	25 (24–30)	3
Mellon et al. group1	2015	R	United States	67.2 (47–85)	M/F	2009–2014	49	LAPC	N0=20 N1=29	14 (4–46)	40 (28–50)	5
Mellon et al. group2							110	BRPC	N0=48 N1=62	40 (20–50)		
Moningi et al. group1	2015	R	United States	67.2 (35–87)	M/F	2010–2014	74	LAPC	N/A	14.5	25–33	5
Moningi et al. group2							14	BRPC	10.3			
Park et al	2017	R	United States	68.3 (45–90)	M/F	2008–2016	44	LAPC, I/II (n = 14) III (n = 30)	N/A	12.9 (1.7–107.6)	30–33	5
Polistina et al	2010	P	Italy	68 (44–75)	M/F	2004–2007	23	LAPC	N0=9 N1=14	9 (6–20)	30	3
Ryan et al	2018	R	United States	74 (68–79)	M/F	2010–2016	29	LAPC	N/A	15 (4–18)	28 (25–33)	5
Schellenberg et al	2008	Phase II	United States	69 (39–87)	M/F	2004–2006	16	LAPC	N/A	22.3	25	1
Schellenberg et al	2011	Phase II	United States	63 (45–85)	M/F	2006–2007	20	LAPC, T4=20	N0=16 N1=4	N/A	25	1
Shen et al	2019	R	China	62 (38–84)	M/F	2010–2016	56	LAPC	N0=36 N1=20	17 (3–43)	40 (30–50)	5
Song et al	2015	R	China	62 (28–86)	M/F	2006–2014	59	LAPC	N/A	10.9 (3.2–48.7)	45 (35–50)	3–8
Zhang et al	2018	P	China	64 (44–80)	M/F	2015–2017	41	LAPC	N/A	12.4 (2.8–24)	30–36	5 or 6

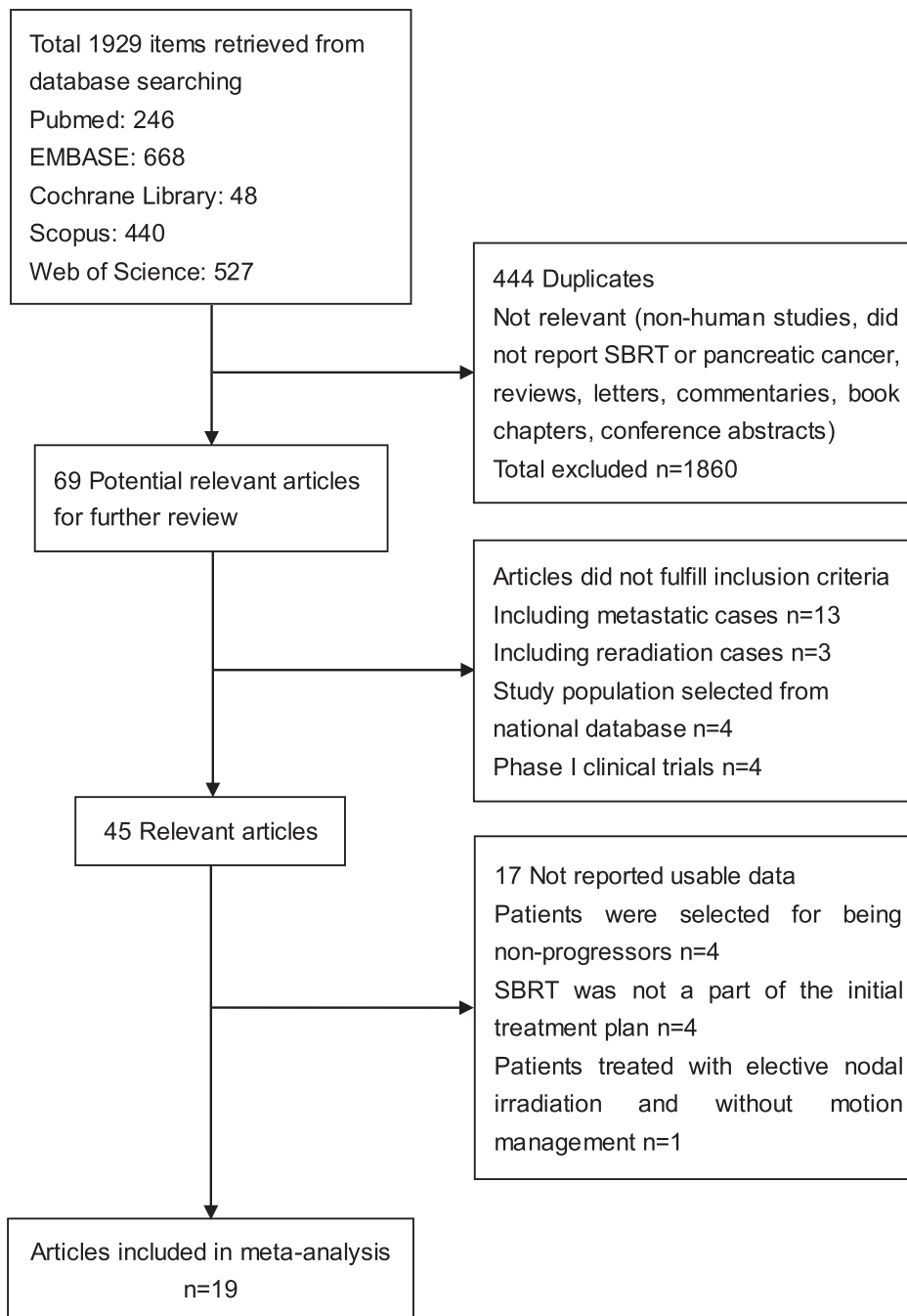
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Table 1
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N	Outcome of interest	Median OS, mo	1-year OS (%)	2-year OS (%)	3-year OS (%)	Median PFS, mo	1-year PFS (%)	2-year PFS (%)	3-year PFS (%)	Acute GI toxicity (G ≥ 3)	Acute hematologic toxicity (G ≥ 3)	Late GI toxicity (G ≥ 3)
GTX	OS/PFS	20	90.00	36.67	N/A	14.9	60.00	23.33	N/A	0	0	0
GTX	OS/PFS	15	68.10	N/A	N/A	9.8	41.00	N/A	N/A	0	0	4
		16.4	72.20	N/A	N/A	9.7	42.80	N/A	N/A	0	0	0
GE	OS/PFS	12.2	50.00	0.00	N/A	6.8	20.00	N/A	N/A	0	0	0
GE	OS/PFS	13.9	59.18	18.37	6.12	7.8	32.65	10.20	N/A	8	6	6
	OS/PFS/LPFS											
GE/ FOLFIRINOX/ FOLFIRI	LPFS/OS/PFS	16.7	67.37	20.00	5.26	10.2	43.16	7.37	2.11	3	0	3
GE	OS	11.6	40.74	14.81	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
CIT	OS	13	54.55	18.18	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GE	OS/PFS	14.3	50.00	25.00	N/A	9.6	33.33	13.89	N/A	2	1	2
GE	OS/PFS	20	68.09	31.91	N/A	15	55.32	25.53	N/A	0	0	3
FOLFIRINOX/ GE-based/ GTX	OS/PFS	15	46.94	14.29	2.04	13.2	34.69	8.16	2.04	N/A	N/A	N/A
GTX/GE- based/ FOLFIRINOX		19.2	63.64	25.46	8.18	11.9	43.64	15.45	5.45	N/A	N/A	N/A
GE/GE-based/ FOLFIRINOX- based	OS/LPFS/PFS	18.4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GE-based/ FOLFIRINOX- based/FOLFOX	OS	14.4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
GE	OS	N/A	56.20	25.70	20.45	N/A	N/A	N/A	N/A	0	2	N/A
GE/GE-based/ FOLFIRINOX	OS/PFS/LPFS	10.6	39.13	0.00	N/A	7.3	N/A	N/A	N/A	0	0	0
GE	OS/PFS	13	51.72	N/A	N/A	6	17.24	N/A	N/A	3	0	1
GE	OS/PFS	11.4	50.00	18.75	N/A	9	18.75	6.25	N/A	1	0	2
GE	OS/PFS	11.8	50.00	20.00	7.00	9.2	35.00	15.00	N/A	0	0	1
	OS/LPFS/PFS											
GE+CA	OS/PFS	19	82.14	35.71	16.07	12	48.21	14.29	7.14	6	13	5
No data	LPFS/OS	12.5	53.90	35.10	20.34	13.90	N/A	N/A	N/A	0	0	1
N/A	OS	11.7	46.34	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

BRPC: borderline resectable pancreatic cancer; CA: Capecitabine; CIT: Gemcitabine+Leucovorin+Fluorouracil+Oregovoma; GE: Gemcitabine; GI: gastrointestinal; GTX: Gemcitabine+Docetaxel+Capecitabine; LAPC: locally advanced pancreatic cancer; OS: overall survival; P: prospective study; PFS: progression-free survival; Phase II: phase II clinical trial; R: retrospective study.

Fig. 1. Flow diagram of study selecting process.



11 studies [13-16,19-21,25-28], 2-year for 8 studies [15,16,19-21,26-28] and 3-year for 3 studies [16,21,28]. Furthermore, four 1-year PFS [19,20,26,27], five 2-year PFS [16,19,20] and two 3-year PFS [16,28] were extracted from the K-M curves. The PFS rates of 1-year, 2-year and 3-year ranged from 17.2 to 60%, 6.3 to 25.5% and 2 to 7.1%, respectively. Pooled PFS rates of 1-year, 2-year and 3-year by the random effects model were 36% (95% CI: 30–44%), 12% (95% CI: 8–16%) and 4% (95% CI: 2–10%), respectively. For the BRPC series, the median PFS (range: 9.7–14.9 months, median: 12.2 months) was available for 3 studies [12,13,21]. PFS of 1-year was available for 3 studies [12,13,21] and 2-year for 2 studies [12,21]. Furthermore, one 2-year PFS [12] was extracted from the K-M curve. Pooled PFS rates of 1-year and 2-year by the random effects model were 48% (95% CI: 39–59%) and 18% (95% CI: 12–26%), respectively.

Toxicity

The proportions of acute GI, acute hematologic, late GI and late hematologic toxicities after SBRT were shown in Fig. 4. For the LAPC series, the proportions of acute GI and hematologic toxicity were available for 13 studies [12-16,19,20,23-29] and late GI and hematologic toxicity for 12 studies [12-16,19,20,24-29]. The incidence rates of acute GI, acute hematologic and late GI toxicities (grade \geq 3) ranged from 0 to 16%, 0 to 23% and 0 to 25%, respectively. The incidence rate of late hematologic toxicity (grade \geq 3) was 0%. The pooled incidence rates of acute GI, acute hematologic and late GI toxicities (grade \geq 3) by the random effects model were 2% (95% CI: 0–6%), 4% (95% CI: 2–9%) and 8% (95% CI: 5–12%), respectively. For the BRPC series, the proportion of acute GI, acute hematologic and late GI toxicities were available for 2

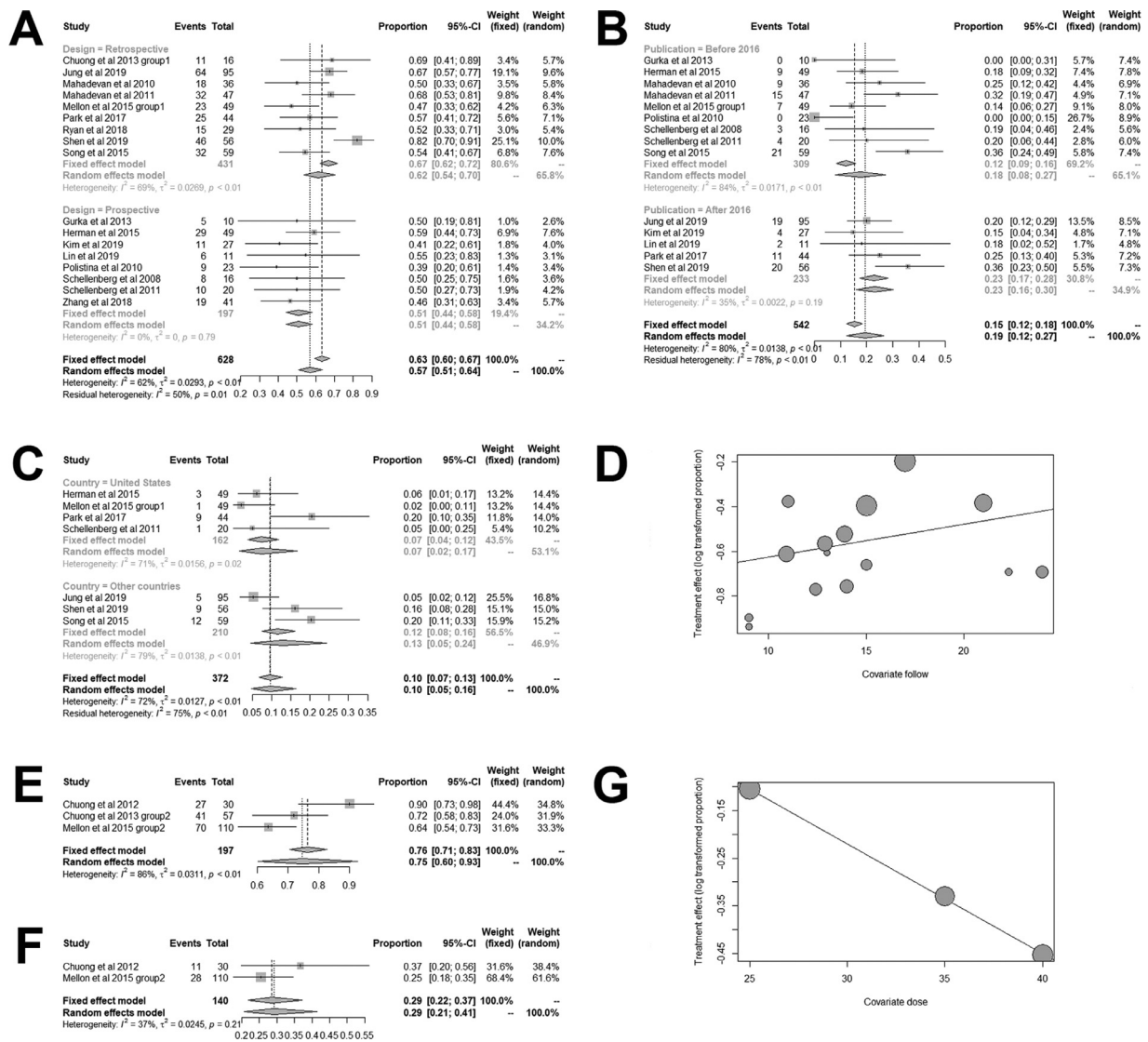


Fig. 2. Forest plot of pooled OS rates. LAPC series, (a) Pooled 1-year OS rate categorized by study design; (b) Pooled 2-year OS rate categorized by publication year; (c) Pooled 3-year OS rate categorized by study country; (d) Meta-regression demonstrates follow-up has a statistical correlation with 1-year OS. BRPC series, (e) Pooled 1-year OS rate; (f) Pooled 2-year OS rate; (g) Meta-regression demonstrates SBRT dose has a statistical correlation with 1-year OS.

studies. The incidence rates of acute GI, acute hematologic, late GI and late hematologic toxicities (grade \geq 3) were all 0%.

Heterogeneity analysis

For the LAPC series, 1-year, 2-year and 3-year OS rates, 1-year PFS rate, the incidence rates of acute GI and hematologic toxicities (grade \geq 3) demonstrated significant or borderline significant heterogeneities among the studies. For subgroup analysis, 1-year, 2-year and 3-year OS rates, 1 and 2-year PFS rates, the incidence rates of acute GI, acute hematologic and late GI toxicities (grade \geq 3) were categorized by publication year, study design, patient race and study country; the variables of patient age, number of patients, follow-up period and SBRT dose were employed in the meta-regression analysis, shown in Table 2. For sensitive analysis, the combined OS rates of 1-year, 2-year and 3-year ranged from 55.6 to 57.9%, 18.1 to 21.4% and 8.2 to 11.5% (I^2 were 20.9–64.2%, 57.5–81.9% and 66.9–76.3%, respectively) after any single study was omitted; the combined PFS rates of 1-year and 2-year ranged from 34.6 to 39% and 9.8 to 13.3% (I^2 were 33–54.8% and 0–38.2%, respectively) after any single study was omitted; the combined incidence rates of acute GI, acute hematologic and late GI toxicities (grade \geq 3)

ranged from 1.6 to 3%, 0.6 to 1.9% and 4.3 to 5.7% (I^2 were 44.7–64.1%, 39.8–76.1% and 9.6–39.8%, respectively) after any single study was omitted, these did not significantly affect the pooled results.

For the BRPC series, 1-year OS rate demonstrated significant heterogeneity among the studies. For meta-regression, numbers of patients and SBRT dose demonstrated a statistical correlation with 1-year OS ($P = 0.0021$ and $P = 0.0002$), shown in Table 2. For sensitive analysis, the combined OS rates of 1-year ranged from 67.2 to 81% (I^2 was 19.8–92.6%) after any single study was omitted, which did not significantly affect the pooled results.

Publication bias

For the LAPC series, the funnel plot and Egger’s test did not show any publication bias in pooled analysis of 1-year OS ($p = 0.08498$), 2-year OS ($p = 0.1107$), 1-year PFS ($p = 0.102$), acute GI toxicity (grade \geq 3) ($p = 0.8912$), acute hematologic toxicity (grade \geq 3) ($p = 0.8951$) and late GI toxicity (grade \geq 3) ($p = 0.374$). The Egger’s test and funnel plot were not conducted because limited studies were included in the other interest endpoint analyses.

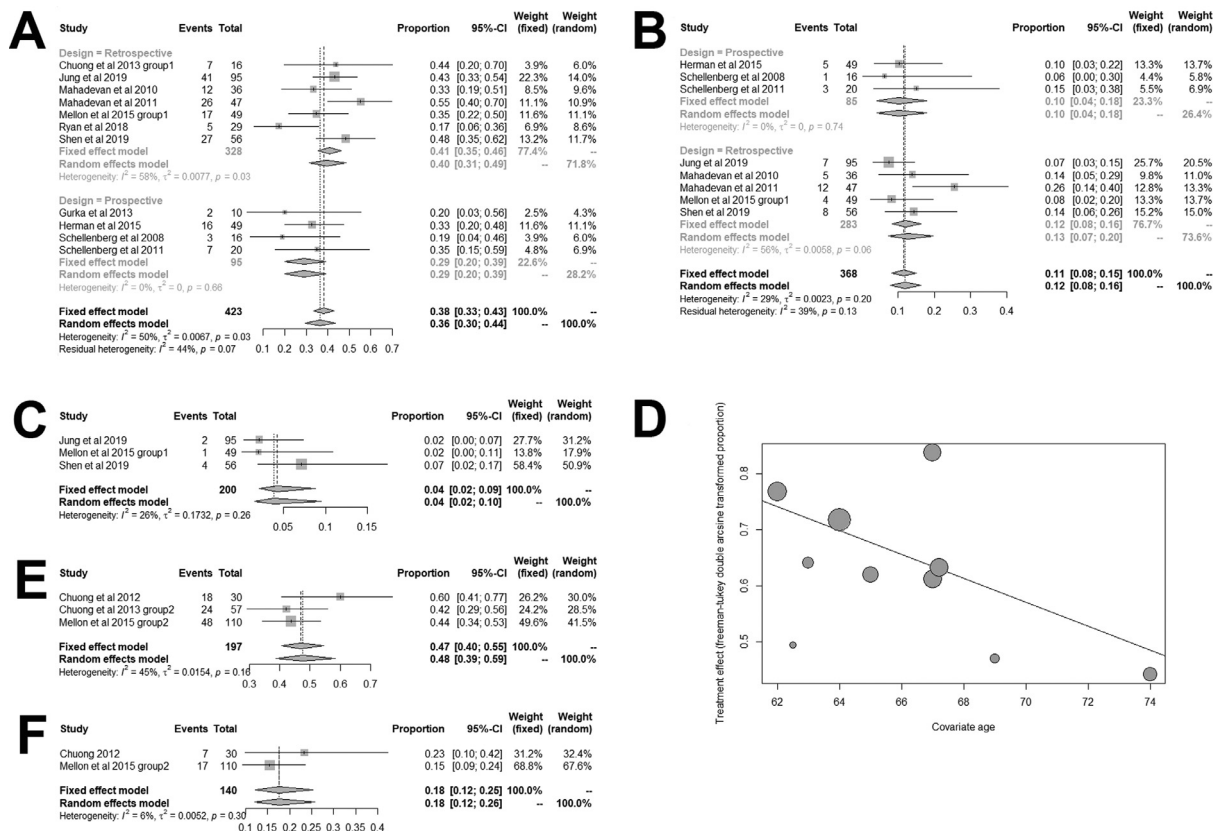


Fig. 3. Forest plot of pooled PFS rates. LAPC series, (a) Pooled 1-year PFS rate categorized by study design; (b) Pooled 2-year PFS rate categorized by study design; (c) Pooled 3-year PFS rate; (d) Meta-regression demonstrates patient age has a statistical correlation with 1-year PFS. BRPC series, (e) Pooled 1-year PFS rate; (f) Pooled 2-year PFS rate.

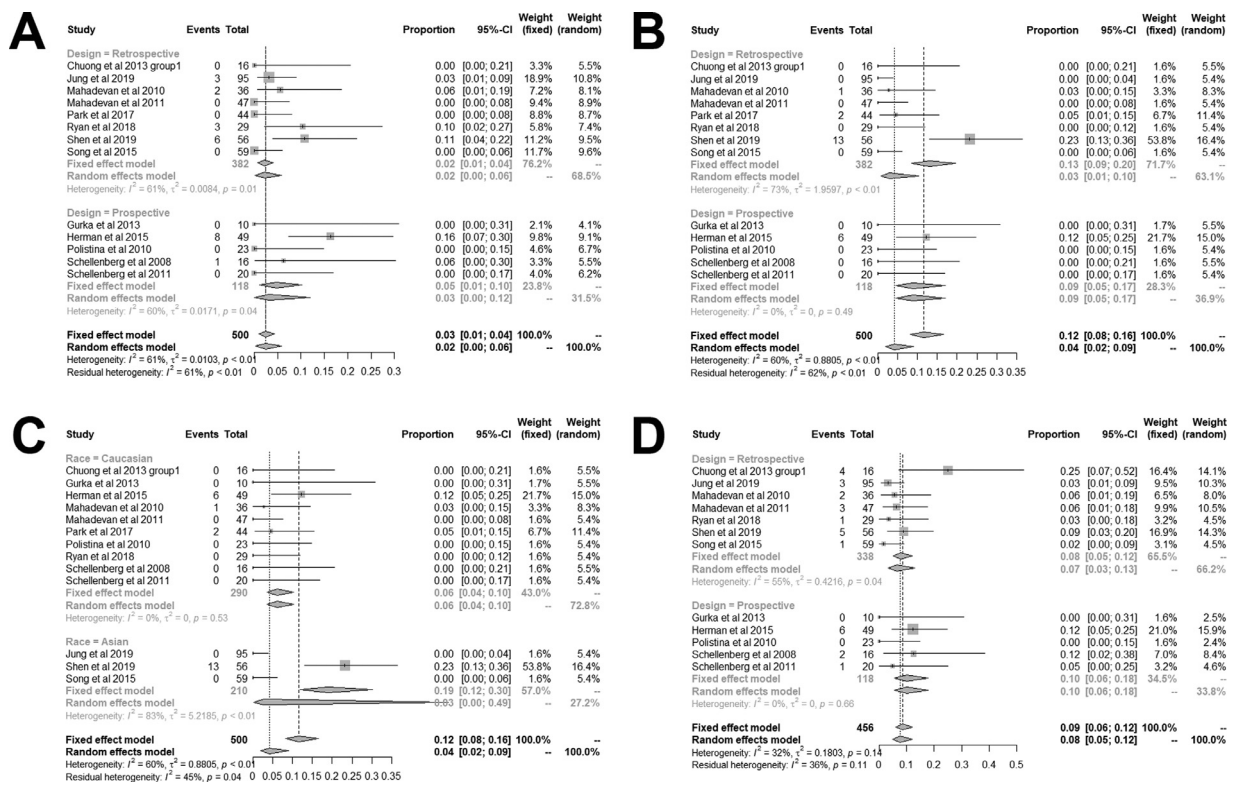


Fig. 4. Forest plot of pooled toxicity (grade ≥ 3) incidence rates of LAPC series. (a) Pooled acute GI toxicity (grade ≥ 3) incidence rate categorized by study design; (b) Pooled acute hematologic toxicity (grade ≥ 3) incidence rate categorized by study design; (c) Pooled acute hematologic toxicity (grade ≥ 3) incidence rate categorized by study race; (d) Pooled late GI toxicity (grade ≥ 3) incidence rate categorized by study design.

Table 2
Details of subgroup analysis and meta-regression.

Value	Category	1-year OS	2-year OS	3-year OS	1-year PFS	2-year PFS	3-year PFS	Acute GI toxicity	Acute hematologic toxicity	Late GI toxicity	
I²(%)	Before 2016	8	84	76	34	25	N/A	61	11	30	
	After 2016	75	35	77	78	45	N/A	68	79	18	
	Prospective	0	53	N/A	0	0	N/A	60	0	0	
	Retrospective	69	65	N/A	58	56	N/A	61	73	55	
	Caucasian	0	75	71	48	25	N/A	58	0	15	
	Asian	83	70	79	0	45	N/A	78	83	45	
	United States	0	47	71	48	25	N/A	61	0	13	
	Other country	82	92	79	0	45	N/A	69	79	26	
	P	Patient age		0.3637	0.5238	0.0254	0.9489	0.3392	0.4223	0.5906	0.8827
		Total patients	0.0486XX0.2125 ^a	0.0878	0.9051	0.1016	0.2254	0.5519	0.9131	0.8719	0.3041
Follow-up period		0.1053XX0.0021 ^a	0.1393	0.5118	0.9590	0.0851	0.1669	0.3769	0.8074	0.4445	
SBRT dose		0.0001XX0.6974 ^a	0.2123	0.1472	0.5151	0.4938	0.4194	0.9725	0.2817	0.9553	
		0.8462XX0.0002 ^a									

OS: overall survival; PFS: progression-free survival.

^a Data of BRPC series.

Discussion

A total of 19 studies involving 800 patients were included in this meta-analysis. For the LAPC series, the median OS was 14.1 months; pooled OS rates of 1-year, 2-year and 3-year were 57%, 19% and 10%, respectively; the median PFS was 10 months; pooled PFS rates of 1-year, 2-year and 3-year were 36%, 12% and 4%, respectively; pooled incidence rates of acute GI, acute hematologic and late GI toxicity (grade \geq 3) were 2%, 4% and 8%, respectively. For the BRPC series, the median OS was 17.5 months; pooled OS rates of 1-year and 2-year were 75% and 29%, respectively; the median PFS was 12.2 months; pooled PFS rates of 1-year and 2-year were 48% and 18%, respectively; the incidence rates of toxicity (grade \geq 3) were all 0%. Petrelli's meta-analysis [11] of SBRT and LAPC reported a pooled 1-year OS rate of 51.6%, which is lower than 57% in our study. Nevertheless, Petrelli reported a median OS of 17 months, which is superior to 14.1 months in the present study. Actually, the Petrelli study focused on local region control of SBRT for LAPC and the technical details of SBRT. Petrelli's paper was based on data obtained before 2016 and our study reviewed literature before 2020. Furthermore, some papers included in Petrelli's study were included in the present study and the other papers were excluded because of the different inclusion/exclusion criteria. Therefore, we believe the different inclusion/exclusion criteria and the publication bias contributed to this difference. A National Cancer Data Base based review of SBRT and unresectable PC [31] reported a median OS of 13.9 months which is similar to our study (14.1 months). Rombouts's paper [32] reviewed literature of many ablative therapies including high intensity focused ultrasound, iodine-125, iodine-125-cryosurgery, irreversible electroporation, microwave ablation, photodynamic therapy, radiofrequency ablation and SBRT for LAPC before 2014. Furthermore, in the Rombouts paper, only one small section discussed SBRT for LAPC and reported a median OS ranged from 6.2 to 24 months. We estimated this median OS may be similar to ours. However, Petrelli et al. [11] reported late toxicity rates (0–11%) and Buwenge's meta-analysis [9] concluded acute and late toxicity (grade \geq 3) rates of 3.3%–18.0% and 6.0–8.2% which were different from this study (acute GI, acute hematologic and late GI toxicity [grade \geq 3] ranged from 0 to 16%, 0 to 23% and 0 to 25%, respectively). These discrepancies may be due to the acute and late toxicity (Grade \geq 3) is only generically and cumulatively reported in the two studies mentioned. Furthermore, Buwenge's literature inclusion standard is derived from its goal of SBRT and PC pain relief. FOLFIRINOX is a standard chemotherapy for LAPC supported by high level evidence. The median OS and PFS for LAPC treated with standard FOLFIRINOX are 24.2 months and 15 months from the start of chemotherapy [33]. In the present meta-analysis, the median OS and PFS of SBRT for LAPC are both worse than this standard chemotherapy. Presently, SBRT is a non-standard treatment and unsupported by high level evidence and unproven in a large randomized trial. We would rather suggest that the role of SBRT may be put in further doubt for BRPC by the results of an ongoing phase II [34], and a large Phase II for LAPC with an OS better than 24 months would be required before moving to a Phase III. These information suggest that SBRT is failed to demonstrate encouraging therapeutic outcome than the standard treatment for LAPC and BRPC.

Subgroup analyses were conducted to locate the source of heterogeneities. In the LAPC series, 1-year OS, 2-year OS, 3-year OS, 1 year PFS, 2-year PFS, acute GI, acute hematologic and late GI toxicity (grade \geq 3) rates were categorized by publication year, study design, patient race and study country. The results suggested that study design, study country, patient race and publication year contributed to the heterogeneities to some extent. Furthermore, most prospective study subgroups had much lower heterogeneities than their counterparts. For instance, I^2 was 0% in prospective studies and 69%, 58%, 56%, 73% and 55% in retrospective studies when the 1-year OS, 1-year PFS, 2-year PFS, acute hematologic and late GI toxicity (grade \geq 3) rates were categorized

by study design. We suspected that the scientific research methods and criteria used in these prospective studies could explain these results.

Meta-regression was used to determine if the endpoints of interest were related to patient age, number of patients, follow-up period and SBRT dosage. For the LAPC series: patient age and the follow-up period demonstrated statistical correlations with 1-year OS rates ($P = 0.0486$ and $P = 0.0001$). As the median age of the patient increased, 1-year OS rates showed a clear downward trend. Obviously, a higher 1-year OS rate signifies an extended follow-up period. Patient age manifested a statistical correlation with 1-year PFS rates ($P = 0.0254$). Similarly, as the median age of the patient increased, 1-year PFS rates tended to decrease. For the BRPC series: the number of patients and SBRT dose demonstrated statistical correlations with 1-year OS rates ($P = 0.0021$ and $P = 0.0002$). As the number of patients and SBRT dose increased, 1-year OS rates showed a trend of decrease. However, there were only 3 studies included in each of these two pooled analyses; therefore, we need additional large clinical trials to support our results.

In this work, sensitive analysis was performed to find heterogeneity changes in the pooled endpoints of interest after any single study was omitted. In the LAPC series: the heterogeneities were significant or borderline-significant in pooled 2-year OS, 3-year OS and acute GI toxicity (grade \geq 3) rates after any single study was excluded. The heterogeneity changed from significant to moderate (from 62% to 20.9%) in the pooled 1-year OS rate after the Shen et al. study was omitted. Nevertheless, we included this study in the final result because it did not affect the combined 1-year OS rate significantly (from 56.9% to 56.5%). The heterogeneity changed from 76.1% to 39.8% in the pooled acute hematologic toxicity (grade \geq 3) rate after the Shen et al. study was omitted. However, we did not omit this study from the pooled result because the combined acute hematologic toxicity (grade \geq 3) rate only changed slightly (from 1.5% to 0.6%). The study by Shen et al. on prognostic factors of SBRT combined with gemcitabine plus capecitabine for LAPC played a significant role in the heterogeneity analysis. We considered the chemotherapy regimen of gemcitabine plus capecitabine as the main resource of heterogeneity since, among all studies, this regimen was only shown in the Shen et al. study and it will affect the survival outcomes to a certain extent.

Admittedly, this meta-analysis has some limitations: (1) Less than half of the included studies (8/19) [14,15,17,18,24,26,27,30] were prospectively designed, including 4 phase II randomized clinical trials (RCT). Furthermore, most of these RCTs were single center studies based on small patient populations. More multicenter RCTs are needed to assess the efficacy of SBRT for LAPC and BRPC. As with any small size and single center study, there is a greater statistical bias. (2) Some studies included local recurrent or local lymph node metastatic cases. Obviously, these cases showed a poorer prognosis and shorter survival period, which could compromise the accuracy of the overall survival outcomes. (3) Different doses, fractionation schemes, delivery systems and image guidance techniques were used in these studies, which could influence the survival and toxicity results. (4) Diverse percentages of patients who underwent different chemotherapy regimens were included in these studies, which could affect the efficacy of combined chemoradiotherapy treatments. (5) The toxicity assessment criteria and methods were inconsistent among the selected studies. (6) For some studies, numerical data were extracted from the K-M curves because they could not be obtained from the original sources. (7) Some critical information, such as study period or follow-up period of several included studies was unavailable.

Conclusions

In this work, we have conducted a systematic review of the application of SBRT for the treatment of LAPC and BRPC. Our meta-analysis based on published results of OS, PFS and incidence rates of toxicity demonstrated that SBRT does not show desirable therapeutic result than the standard therapies for LAPC and BRPC. Furthermore, more large

phase II RCTs with an OS better than 24 months would be required before moving to a Phase III, since most of these studies are retrospective or small patient-population based single center studies.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics approval

Not applicable to the present study.

Declaration of Competing Interest

We declare that we have no competing interests.

CRedit authorship contribution statement

Shi Liu: Conceptualization, Methodology, Software, Investigation, Writing- original draft. **Ying Liu:** Investigation, Writing- original draft. **Jian Yang:** Methodology, Investigation. **Troy Dos Santos:** Software. **Lili Yang:** Investigation. **Min Li:** Investigation. **Qingfeng Jiang:** Investigation.

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