pISSN 1598-2998, eISSN 2005-9256

https://doi.org/10.4143/crt.2022.329

Cancer Res Treat. 2022;54(4):953-969

Original Article

Role of Local Treatment for Oligometastasis: A Comparability-Based Meta-Analysis

Chai Hong Rim[1], **Won Kyung Cho**[2], **Jong Hoon Lee**[3], **Young Seok Kim**[4], **Yang-Gun Suh**[5], **Kyung Hwan Kim**[6], **Eui Kyu Chie**[7], **Yong Chan Ahn**[2], **The Oligometastasis Working Group, Korea Cancer Association**

[1]Department of Radiation Oncology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, [2]Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [3]Department of Radiation Oncology, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, [4]Department of Radiation Oncology, Asan Medical Center, Ulsan University College of Medicine, Seoul, [5]Proton Therapy Center, Research Institute and Hospital, National Cancer Center, Goyang, [6]Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, [7]Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Korea

Purpose We intend to investigate the oncological efficacy and feasibility of local consolidative therapy (LCT) through a meta-analysis method.

Materials and Methods Four databases including PubMed, MEDLINE, Embase, and Cochrane library were searched. Target studies are controlled trials comparing outcomes of LCT versus a control group. Primary endpoints are overall survival (OS) and progression-free survival (PFS).

Results A total of 54 studies involving 7,242 patients were included. Pooled analyses showed that the LCT arm could achieve improved OS with pooled odds ratio of 2.896 (95% confidence interval [CI], 2.377 to 3.528; p < 0.001). Regarding PFS, pooled analyses showed pooled odds ratio of 3.045 (95% CI, 2.356 to 3.937; p < 0.001) in favor of the LCT arm. In the subgroup analyses including the studies with reliable comparability (e.g. randomized studies or intentionally matched studies without significant favorable prognosticator in LCT arms), pooled odds ratio was 2.548 (95% CI, 1.808 to 3.591; p < 0.001) favoring the LCT arm regarding OS. Regarding PFS, pooled OR was 2.656 (95% CI, 1.713 to 4.120; p < 0.001) which also favored the LCT arm. Subgroup analyses limited to the randomized controlled trials (RCT) were also performed and pooled odds ratios on OS and PFS were 1.535 (95% CI, 1.082 to 2.177; p=0.016) and 1.668 (95% CI, 1.187 to 2.344; p=0.003). The rates of grade ≥ 3 complications related to LCT was mostly low (< 10%) and not significantly higher compared to the control arm.

Conclusion Pooled analyses results of all included studies, selected studies with reliable comparability, and RCT's demonstrated the survival benefit of LCT. These consistent results suggest that LCT was beneficial to the patients with oligometastasis.

Key words Oligometastasis, Local therapy, Radiotherapy, Surgery, Meta-analysis

Introduction

With the classic general oncologic concept, the role of aggressive local treatment in the patients with systemic metastatic lesions used to be limited in a few clinical situations. Nevertheless, the benefit of locally ablative therapy for metastatic lesion(s) and/or primary disease has recently been proposed in the patients with "oligometastasis", which has been defined as the disease status with only a few, but not disseminated, metastatic foci [1]. Resection of limited metastatic lesions involving the lung or liver, for example, enabled favorable long-term survival outcome in significant portion of the colorectal cancer patients [2,3]. Given the advances in radiation therapy (RT) techniques capable of high-dose delivery with precise targeting, the utilization of local consolidative therapy (LCT) in oligometastatic setting has become dramatically and increasingly popular over the recent past years [4,5].

Many recently published studies have shown that improved long-term survival outcomes were achieved, by applying LCT to oligometastasis, when compared to the historic controls. Majority of these studies, however, were single arm studies or small phase 2 comparative series [6-10]. Furthermore, there was no preclinical evidence on the role of local treatment in the process of tumors undergoing the events of metastatic cascade. Therefore, it is unclear whether the

Correspondence: Yong Chan Ahn
Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: 82-2-3410-2612 Fax: 82-2-6190-5882 E-mail: ahnyc@skku.edu

Co-correspondence: Eui Kyu Chie
Department of Radiation Oncology, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: 82-2-2072-3705 Fax: 82-2-742-2073 E-mail: ekchie93@snu.ac.kr

*Chai Hong Rim and Won Kyung Cho contributed equally to this work.

Received May 24, 2022 **Accepted** August 13, 2022
Published Online August 16, 2022

improved outcomes following LCT were by virtue of the provided local therapy per se, or the bias of selecting out more favorable patients' subgroup having better clinical conditions and indolent disease nature. In clinical practice, there is still insufficient consensus in regards to the role of additional LCT to systemic therapy or supportive care in oligometastatic setting.

In this meta-analysis, the oncologic benefit of LCT in oligometastic disease was investigated by analyzing the literatures that explored the role of LCT in terms of survival outcomes as the endpoints with their comparative groups. In particular, the clinical balancing between the LCT and control arms was taken into account in further detail.

Materials and Methods

1. Study design and eligibility criteria

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [11] were strictly observed. The population, intervention, comparison, and outcome (PICO) question of the hypothesis was as follows: "Did LCT confer an oncologic benefit (regarding overall survival [OS] and progression-free survival [PFS]) in managing the patients with oligometastasis?" The following inclusion criteria were used to include the eligible studies: (1) controlled trial involving the patients with oligometastasis that compared the outcomes of those who underwent LCT versus a control group; (2) 10 or more patients in each arm; (3) at least one primary endpoint provided; and (4) oligometastasis defined as five or fewer metastases or as the metastatic lesions that could definitely be encompassed and treated by the provided LCT.

2. Protocol registration

This study is registered in PROSPERO (protocol No. CRD42022316613).

3. Information sources and search strategy

Four databases including PubMed, MEDLINE, Embase, and Cochrane library were systematically searched, as recommended by Cochrane handbook [12], and the last date of the search was the 14th of March, 2022. Detailed searching strategy including the search terms are as shown in the Supplement Data 1. The conference abstracts and in-press studies were also searched and included if they met the inclusion criteria. No language limitation was applied. For the studies possibly having the overlapping patients' cohort, those with the larger number of patients or those published more recently, if the number of patients are similar between competing studies, were chosen. Searching process was performed independently by two investigators (CH Rim, WK Cho) and any disagreements were resolved by discussion or re-evaluation of the databases in question.

4. Data items and collection process

The primary endpoints were OS and PFS. The incidences and types of grade 3 or higher adverse events were collected and subjectively reviewed. A pre-designed data sheet included the followings.

(1) General information including the author, affiliation, year of publication, patient recruitment, type of study, target disease, and definition of oligometastasis.

(2) Clinical data including the number of patients in each arm (LCT arm vs. control arm), target sites for LCT (e.g., metastatic or primary site), number of oligometastasis, treatment modality employed, OS, PFS, and adverse events of grade 3 or higher.

The survival data were acquired from the descriptive graphs if the numerical data were not provided in the articles. Data collection processes were also performed by two independent investigators (CH Rim, WK Cho) and any disagreements were resolved by re-evaluation of the literature.

5. Risk of bias and subgroup analyses

Although the current study intended to investigate on the studies that had the control arms (LCT vs. control), only few were in randomized study design, whereas majority were in retrospective ones. Possible confounders were carefully analyzed following the guidelines provided by the Cochrane group [13]. Reliable comparability was defined as either randomized controlled trials (RCT) or the studies with clinical balancing effort (e.g., propensity score matching) without any major prognosticators skewed in favor of any arm. Major prognosticators include the number of metastases, patients' age, performance status, and TNM stage, respectively, which were common and important clinical factors across various cancer primaries. The studies were regarded as having non-reliable comparability, if any of the above prognosticators or disease-specific factors were regarded important at the authors' discretion (e.g., prostate specific antigen in prostate cancer and or α-fetoprotein in hepatocellular carcinoma, respectively) and had favorable slant toward the LCT arm (e.g., statistically significant or > 20% difference). After the pooled analyses of all included studies, subgroup analyses were serially performed for the studies with reliable comparability and RCT's, and RCT's only, respectively.

Since the included studies dealt with heterogenous primary sites, subgroup analyses per primary were also subsequently performed. Subgroup analyses were performed according to hierarchical comparability and study designs, as suggested by Shin and Rim [14].

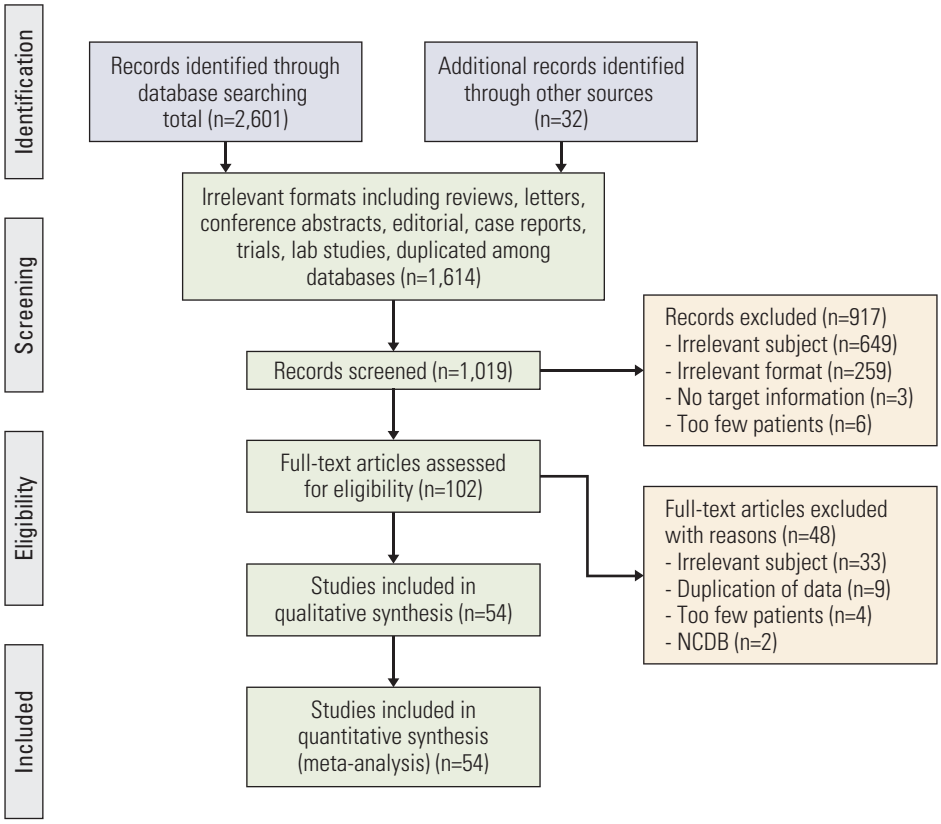


Fig. 1. Study inclusion plot. NCDB, National Cancer Database.

6. Quality assessment

Considering that most eligible studies were non-randomized, Newcastle-Ottawa scales of the included studies were used for the quantitative quality analyses [15]. The studies having quality scale of high (8 or 9 points) and moderate (6 or 7 points) were included in the pooled analysis, but not those with low score (5 or lower points) [13].

7. Statistics

The effect measures of primary endpoints (OS and PFS) were assessed as the odds ratio (OR) in comparison to percentile OS or PFS rates at 2-years between the LCT and control arms. 1- or 5-year rates were evaluated considering the natural courses of different primaries and histology (e.g., OS or PFS nearly nil at 2 years in small cell lung cancer [SCLC] studies; minimal OS or PFS changes within 2 years in prostate cancer studies). For pooled analyses of OR's, the random effects model was used based on the possible heterogeneity in clinical setting and study designs, referencing the Cochrane handbook [13]. In subgroup analyses that included RCT's only, fixed-effect model was applied if heterogeneity among the studies were regarded insignificant ($p < 0.1$ and $I^2 \leq 50\%$). In addition, pooled analyses of temporal OS percentile were performed according to the primary sites, using the random effects model.

In pooled analyses, heterogeneity was assessed using the Cochrane Q test [16] and I^2 statistics [17]. Studies with an I^2 statistic of 25%, 50%, and 75% were regarded to have low, moderate, and high heterogeneity, respectively. Publication bias was assessed in pooled analyses including 10 or more studies, using visual funnel plot evaluation and quantitative Egger's test [18]. If 2-tailed p-value was < 0.1 in Egger's test and asymmetry was noted in funnel plot, Duval and Tweedie's trim and fill methods were performed for the sensitivity analyses [19]. All the statistical analyses were performed using the Comprehensive Meta-Analysis ver. 3 (Biostat Inc., Englewood, NJ).

Results

1. Study selection and characteristics

The selection process is illustrated in Fig. 1. At the initial search across the databases, a total of 2,601 studies were identified. Thirty-two studies were added from the reference lists of the searched studies. After filtering of 1,614 studies

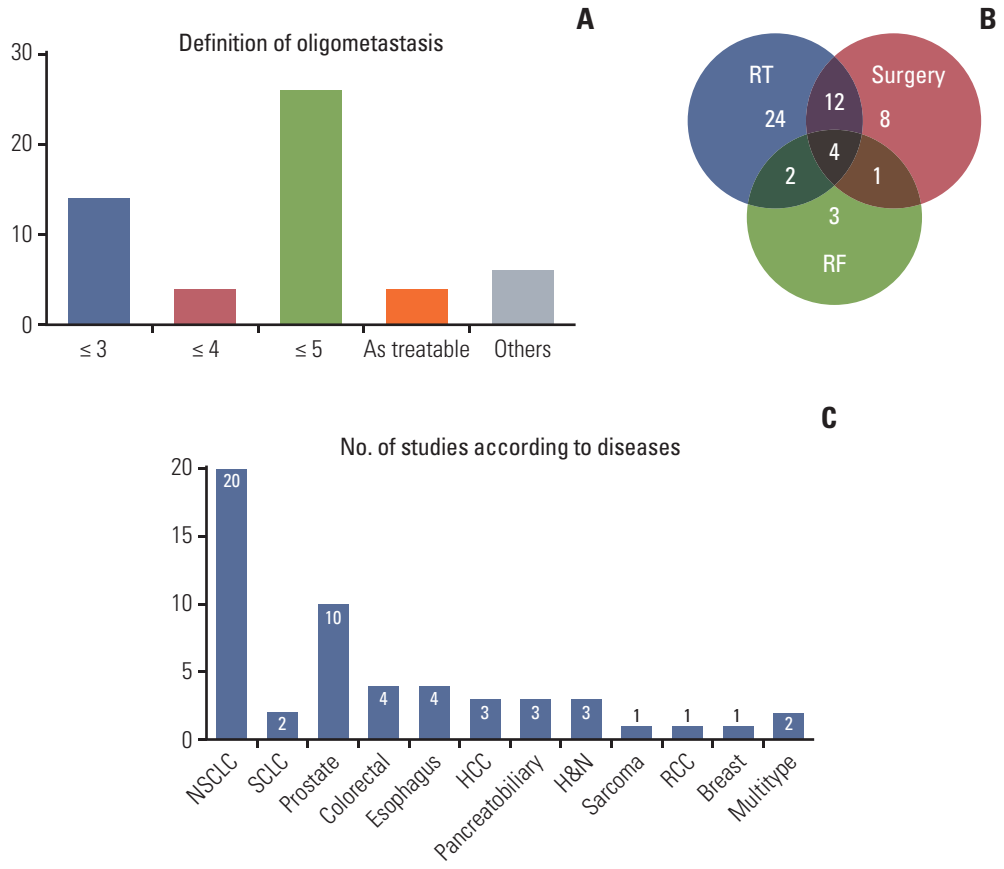


Fig. 2. Descriptive summary of definition of oligometastases among included studies (A), modality of local consolidative therapy used in included studies (B), and number of studies included according to site of origin (C). HCC, hepatocellular carcinoma; H&N, head and neck; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

with irrelevant format or duplicates among databases, abstracts of 1,019 studies were screened. Full-text evaluation was performed for 102 studies, and 54 studies finally fulfilled the inclusion criteria, which comprised as the final cohort of the current study [6,7,20-71].

Regarding the study design, eight studies were prospective RCTs, whereas the remainders were retrospective series. Fourteen studies did clinical balancing effort (e.g., propensity score matching) between the LCT and control arms. Among all 54 selected studies, 26 studies (48.1%) defined oligometastases as having metastatic foci of 5 or less, four studies (7.4%) as having 4 or less, and 14 studies (25.9%) as having 3 or less, respectively. Remaining studies used various individualized clinical definitions such as "resectable" "controllable with surgery", "within RT portal", or "confined to a single organ", respectively (Fig. 2A). Regarding the LCT modality, RT was performed in 42 studies (77.8%), surgery in 25 studies (46.3%), and radiofrequency ablation in 10 studies (18.5%), respectively (Fig. 2B). Twenty-two studies investigated oligometastasis of lung primary (40.7%, 20 on non–small cell lung cancer (NSCLC) plus 2 on SCLC, 10 of prostate primary (18.5%), four of colorectal primary, four of esophagus primary, three of liver primary, three of pancreatobiliary primary, and three of head and neck primary, respectively. There were three studies that focused only on single disease site: soft tissue sarcoma; renal cell carcinoma; and breast cancer, respectively. Two studies included various primaries (Fig. 2C). Further information on the included studies are summarized in S1 and S2 Tables.

2. Quality assessment

As for the selection category of Newcastle-Ottawa scale, all included studies acquired 4 points. All included studies had high representativeness as investigating a specific disease condition (oligometastases of cancers), adequate selection of non-exposed cohort (drawn from the same community), ascertainment of exposure (all studies acquired data from the secure medical records), and demonstrated the outcomes of interest (e.g., death or recurrence) not present at the initiation of study, respectively. Regarding the outcome category,

Table 1. Pooled analyses of studies

	No. of studies	No. of patients	Heterogeneity p-value	I^2 (%)	Heterogeneity	Pooled OR (95% CI)	p-value favoring LCT
Overall survival							
All studies	48	6,759	< 0.001	50.6	Moderate	2.896 (2.337-3.528)	< 0.001
Reliable comparability	15	2,690	0.007	53.4	Moderate	2.548 (1.808-3.591)	< 0.001
RCTs only	5	1,172	0.346	10.5	Low	1.535 (1.082-2.177)	0.016
NSCLC	17	1,525	0.06	37.5	Low to moderate	2.928 (2.151-3.985)	< 0.001
SCLC	2	130	0.184	43.2	Moderate	1.043 (0.336-3.240)	0.942
Prostate	6	2,055	0.2	31.4	Low to moderate	1.941 (1.282-2.938)	0.002
Colorectal	4	914	0.016	70.9	Moderate to high	4.453 (2.103-9.429)	< 0.001
HCC	3	218	0.541	~0	Very low	4.436 (2.439-8.069)	< 0.001
Esophagus	4	777	0.556	~0	Very low	2.092 (1.485-2.947)	< 0.001
Progression-free survival							
All studies	39	5,021	< 0.001	62.1	Moderate to high	3.045 (2.356-3.937)	< 0.001
Reliable comparability	16	2,109	0.001	60.3	Moderate to high	2.656 (1.713-4.120)	< 0.001
RCTs only	8	1,317	0.282	18.0	Low	1.668 (1.187-2.344)	0.003
NSCLC	13	1,277	0.049	43.0	Moderate	3.993 (2.262-5.087)	< 0.001
SCLC	2	130	0.276	15.8	Low	1.654 (0.544-5.034)	0.376
Prostate	10	1,726	0.003	63.6	Moderate to high	2.278 (1.463-3.546)	< 0.001
Colorectal	3	684	0.031	71.3	Moderate to high	4.911 (2.212-10.903)	< 0.001
HCC	2	126	0.854	~0	Very low	7.974 (2.081-30.547)	0.002
Esophagus	2	675	0.016	82.8	High	2.895 (0.524-15.984)	0.223

CI, confidence interval; HCC, hepatocellular carcinoma; LCT, local consolidative therapy; NSCLC, non–small cell lung cancer; OR, odds ratio; RCT, randomized controlled trial; SCLC, small cell lung cancer.

majority of studies acquired 3 points as they acquired data based on the medical records and few or negligible proportion of follow-up loss. Several studies, however, were regarded as having 2 points if the duration of follow-up was less than one year. Since RCTs and studies with matched control compared at least two known clinical prognosticators, they acquired 2 points in comparability category, whereas others acquired 0 points. The resulting quality points of the selected studies were at least 6 (S3 Table), which met the pre-defined cut-off value, and all were included in the pooled analyses.

3. Synthesized results

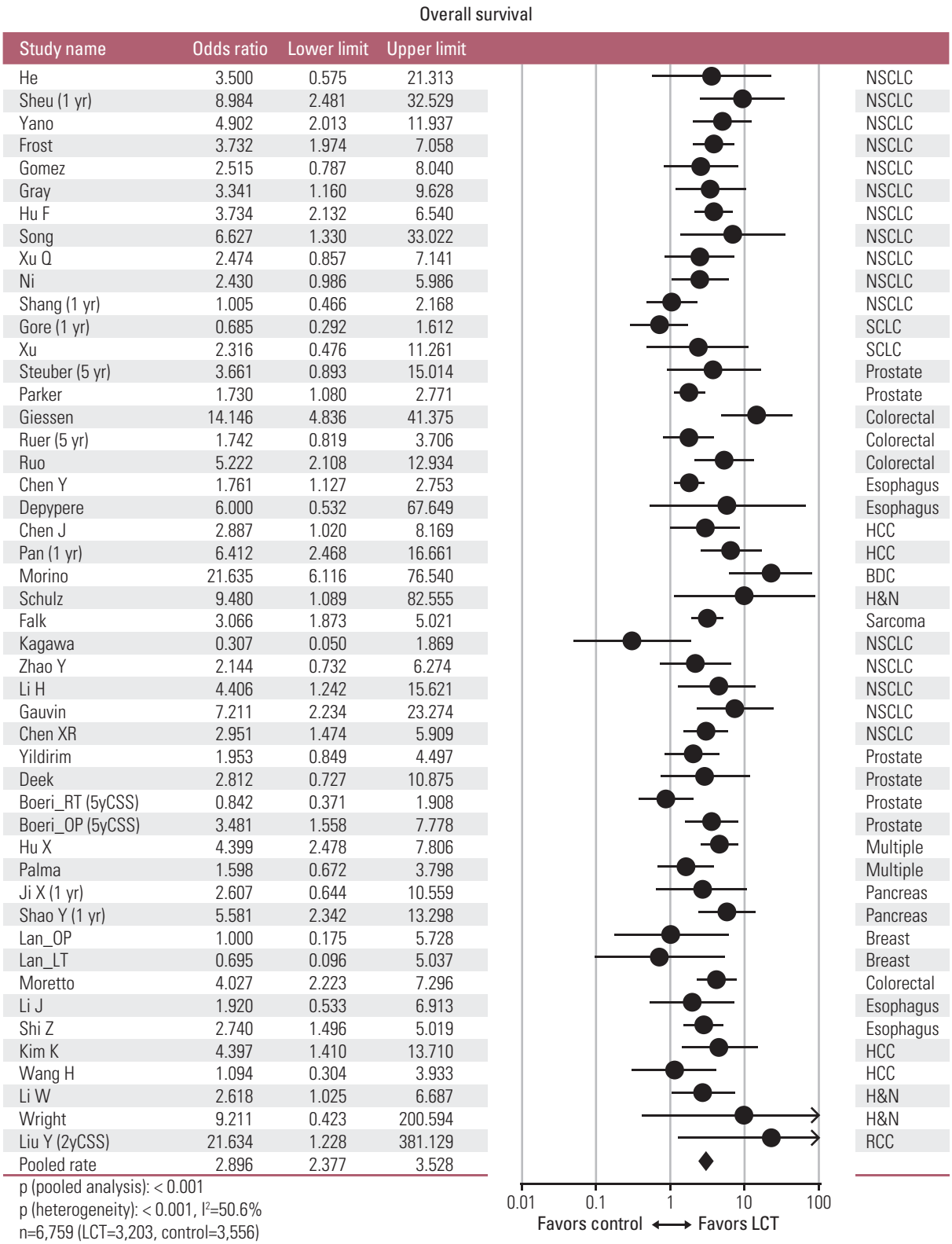
Pooled analyses of all included studies showed that the patients in the LCT arm could achieve improved OS with pooled OR of 2.896 (95% confidence interval [CI], 2.377 to 3.528; $p < 0.001$), with moderate heterogeneity ($p < 0.001$, I^2=50.6%) (Table 1, Fig. 3A). Regarding PFS, pooled analyses showed pooled OR of 3.045 (95% CI, 2.356 to 3.937; $p < 0.001$), with moderate heterogeneity ($p < 0.001$, I^2=62.1%) in favor of the LCT arm (Table 1, Fig. 4A).

In the subgroup analyses including the studies with reliable comparability (RCTs and intentional matched studies without known favorable prognosticator in the LCT arms), pooled OR was 2.548 (95% CI, 1.808 to 3.591; $p < 0.001$) favoring the LCT arm regarding OS, with moderate heterogeneity (p=0.007, I^2=53.4%) (Table 1, Fig. 3B). Regarding PFS, pooled OR was 2.656 (95% CI, 1.713 to 4.120; $p < 0.001$) which also favored the LCT arm, with moderate to high heterogeneity among studies (p=0.001, I^2=60.3%) (Table 1, Fig. 4B). Subgroup analyses limited to the RCT's only were also performed and all favored the LCT arm: pooled ORs on OS and PFS were 1.535 (95% CI, 1.082 to 2.177; p=0.016) with low heterogeneity (p=0.346, I^2=10.5%) (Fig. 3C) and 1.668 (95% CI, 1.187 to 2.344; p=0.003) with low heterogeneity (p=0.282, I^2=18.0%) (Table 1, Fig. 4C), respectively.

4. Pooled survival according to the primary site

Subgroup pooled analyses were performed according to the primary sites (Table 1). Pooled OR's for OS in NSCLC, SCLC, prostate cancer, colorectal cancer, liver cancer, and esophageal cancer were 2.928 (95% CI, 2.151 to 3.985; $p < 0.001$), 1.043 (95% CI, 0.336 to 3.240; p=0.942), 1.941 (95% CI, 1.282 to 2.938; p=0.002), 4.453 (95% CI, 2.103 to 9.429; $p < 0.001$), 4.436 (95% CI, 2.439 to 8.069; $p < 0.001$), and 2.092 (95% CI, 1.485 to 2.947; $p < 0.001$), respectively. Improved OS was achievable in the LCT arm in all disease sites except in SCLC. For PFS, pooled OR's for NSCLC, SCLC, prostate cancer, colorectal cancer, liver cancer, and esophageal can-

A



p (pooled analysis): < 0.001
p (heterogeneity): < 0.001, I^2=50.6%
n=6,759 (LCT=3,203, control=3,556)

Fig. 3. Forest plots of pooled analyses regarding overall survival, including all studies (A), studies with reliable comparability (B), and randomized controlled trials (C) [7,8,21-31,34,35,37-45,47-53,55-66,68-71,73]. BDC, biliary duct cancer; HCC, hepatocellular carcinoma; H&N, head and neck; LCT, local consolidative therapy; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; 2yCSS, 2-year cancer-specific survival; 5yCSS, 5-year cancer-specific survival. *(Continued to the next page)*

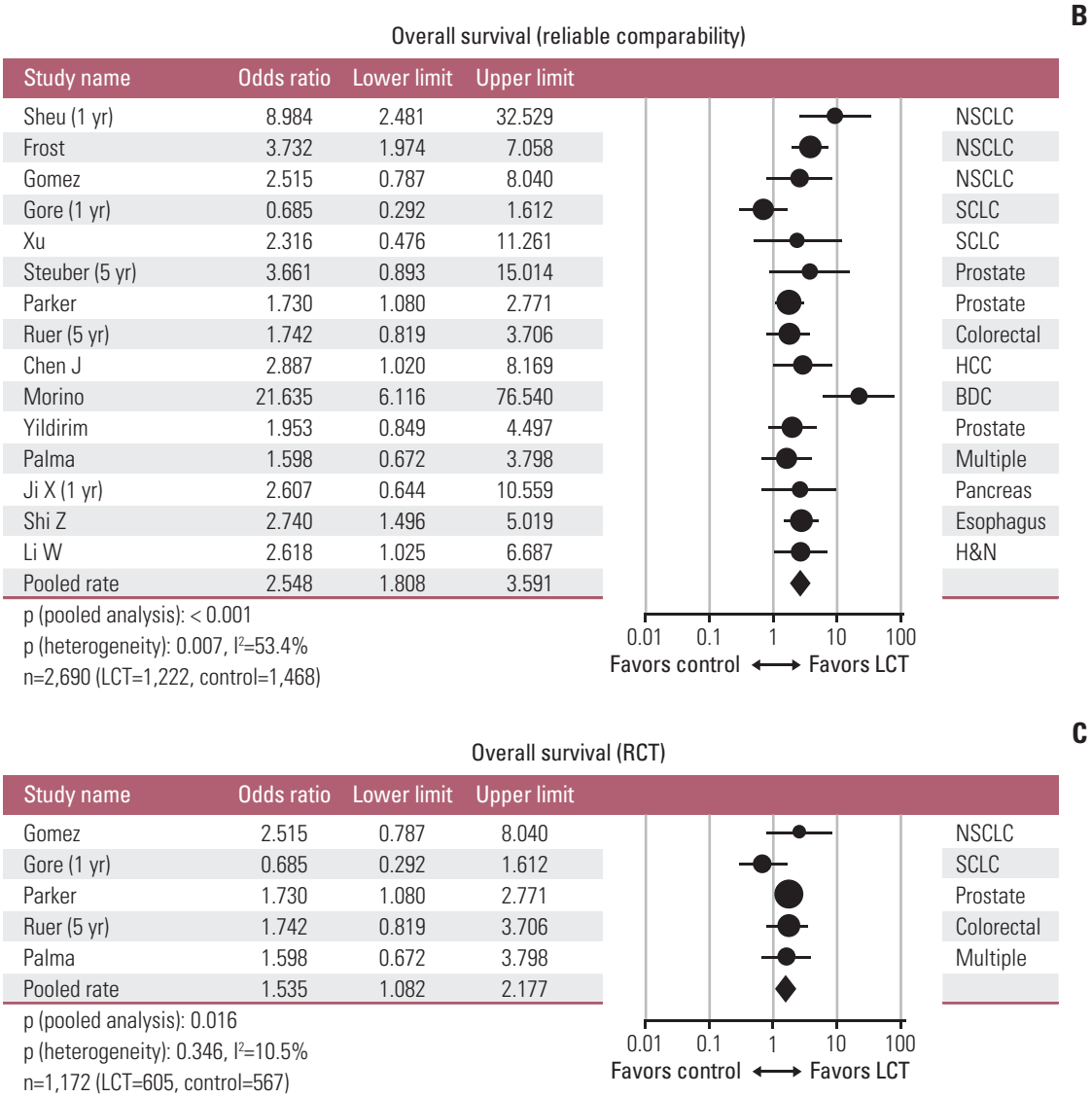


Fig. 3. *(Continued from the previous page)*

cer were 3.993 (95% CI, 2.262 to 5.087; p < 0.001), 1.654 (95% CI, 0.554 to 5.034; p=0.376), 2.278 (95% CI, 1.463 to 3.546; p < 0.001), 4.911 (95% CI, 2.212 to 10.903), 7.974 (95% CI, 2.081 to 30.547; p=0.002), and 2.895 (95% CI, 0.524 to 15.984; p=0.223), respectively. Again, improved PFS was achievable in the LCT arm in all disease sites except SCLC. The percentile rates of OS and PFS by pooled analyses according to the primary sites are illustrated and summarized in Table 2 and Fig. 5.

5. Publication bias

Regarding OS, no significant publication bias was noted (Egger's p=0.234). However, publication bias was highly suggested in the pooled analysis regarding PFS (Egger's p < 0.001). The trimmed OR using Duval and Tweedie's method was 2.278 (95% CI, 1.753 to 2.961). Funnel plots and results of quantitative Egger's test are shown in S4 Fig.

6. Adverse events

Twenty studies (seven on lung cancer; five on prostate cancer; two on pancreas cancer; two on esophageal cancer; one on colorectal cancer; one on liver cancer; and two on various cancers, respectively) involving 2,963 patients (1,487 in the LCT arm, 1,476 in the control arm) provided comparative information on the incidences and grade of adverse events. Regarding lung cancer studies, LCT-related adverse events were relatively more frequent when compared to other primaries, with grade 3 or higher rates ranging from 8% to 28.6%. Three studies reported the possibility of excessive

A

Progression-free survival

Study name	Odds ratio	Lower limit	Upper limit	
Iyengar (1 yr)	3.619	0.570	22.979	NSCLC
Sheu (1 yr)	3.938	0.924	16.775	NSCLC
Frost	11.178	4.849	25.768	NSCLC
Gomez	2.722	0.612	12.101	NSCLC
Hu F	1.887	0.853	4.175	NSCLC
Xu Q (1 yr)	2.636	0.919	7.562	NSCLC
Ni (1 yr)	4.679	1.435	15.261	NSCLC
Shang (1 yr)	1.630	0.781	3.404	NSCLC
Gore (1 yr)	1.218	0.440	3.375	SCLC
Xu	4.743	0.514	43.809	SCLC
Bouman-Wammes (1 yr)	8.850	2.556	30.640	Prostate
Lan	2.731	1.194	6.245	Prostate
Ost	1.729	0.615	4.857	Prostate
Parker	1.169	0.864	1.583	Prostate
Tsumura	2.917	0.538	15.828	Prostate
Giessen	10.615	4.347	25.923	Colorectal
Ruer	2.114	0.925	4.833	Colorectal
Chen Y (1 yr)	1.359	0.886	2.085	Esophagus
Chen J (1 yr)	10.211	0.528	197.396	HCC
Hsu KH	8.376	2.173	32.279	NSCLC
Zhao Y (1 yr)	5.127	1.515	17.354	NSCLC
Li H	2.796	0.564	13.854	NSCLC
Gauvin	6.544	1.509	28.374	NSCLC
Wang	1.693	0.865	3.317	NSCLC
Yildirim	1.332	0.312	5.679	Prostate
Phillips (1 yr)	2.672	0.835	8.543	Prostate
Deek	1.629	0.487	5.449	Prostate
Boeri_RT (5ySSFS)	1.715	0.870	3.378	Prostate
Boeri_OP (5ySSFS)	4.220	2.393	7.443	Prostate
Palma	3.920	1.244	12.353	Multiple
Ji X (6 mo)	1.605	0.416	6.199	Pancreas
Lan_OP	7.429	1.778	31.040	Breast
Lan_LT	1.714	0.301	9.773	Breast
Moretto	5.375	3.174	9.101	Colorectal
Shi Z	7.911	2.016	31.043	Esophagus
Kim K	7.479	1.657	33.754	HCC
Li W	2.070	0.630	6.794	H&N
Wright (1 yr)	58.586	4.253	806.971	H&N
Liu Y	2.108	0.901	4.931	RCC
Pooled rate	3.045	2.356	3.937	

p (pooled analysis): < 0.001
p (heterogeneity): < 0.001, I^2=62.1%
n=5,021 (LCT=2,454, control=2,567)

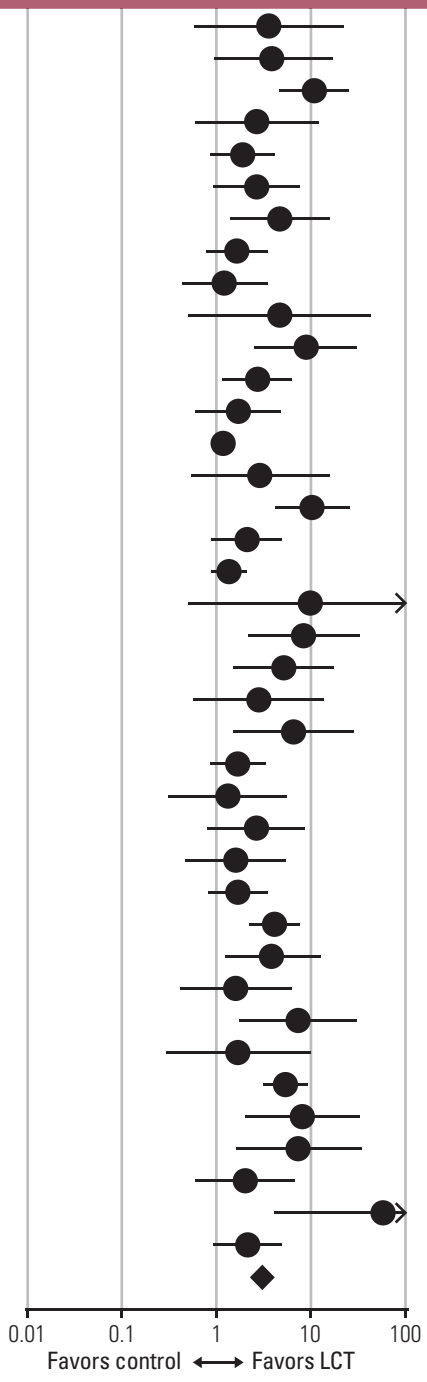


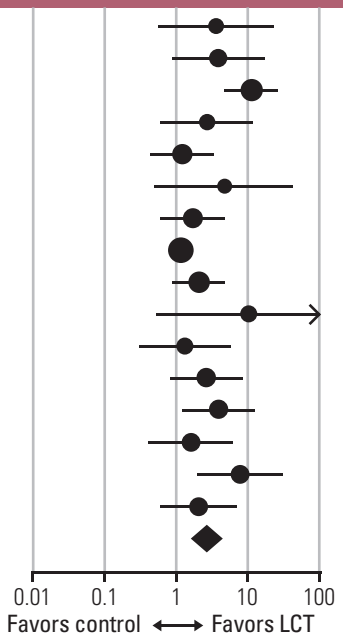
Fig. 4. Forest plots of pooled analyses regarding progression-free survival, including all studies (A), studies with reliable comparability (B), and randomized controlled trials (C) [6-8,20-22,25-28,31-33,35,36,38,39,42,43,46-48,50,52-54,56,58-60,62-64,66,67,69-71,73]. HCC, hepatocellular carcinoma; H&N, head and neck; LCT, local consolidative therapy; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; SCLC, small cell lung cancer; 5ySSFS, 5-year second-line systemic therapy free survival. *(Continued to the next page)*

B

Progression-free survival (reliable comparability)

Study name	Odds ratio	Lower limit	Upper limit	
Iyengar (1 yr)	3.619	0.570	22.929	NSCLC
Sheu (1 yr)	3.938	0.924	16.775	NSCLC
Frost	11.178	4.849	25.768	NSCLC
Gomez	2.722	0.612	12.101	NSCLC
Gore (1 yr)	1.218	0.440	3.375	SCLC
Xu	4.743	0.514	43.809	SCLC
Ost	1.729	0.615	4.857	Prostate
Parker	1.169	0.864	1.583	Prostate
Ruer	2.114	0.925	4.833	Colorectal
Chen J (1 yr)	10.211	0.528	197.396	HCC
Yildirim	1.332	0.312	5.679	Prostate
Phillips (1 yr)	2.672	0.835	8.543	Prostate
Palma	3.920	1.244	12.353	Multiple
Ji X (6 mo)	1.605	0.416	6.199	Pancreas
Shi Z	7.911	2.016	31.043	Esophagus
Li W	2.070	0.630	6.794	H&N
Pooled rate	2.656	1.713	4.120	

p (pooled analysis): < 0.001
p (heterogeneity): 0.001, I^2=60.3%
n=2,109 (LCT=1,105, control=1,004)



C

Progression-free survival (RCT only)

Study name	Odds ratio	Lower limit	Upper limit	
Iyengar (1 yr)	3.619	0.570	22.979	NSCLC
Gomez	2.722	0.612	12.101	NSCLC
Gore (1 yr)	1.218	0.440	3.375	SCLC
Ost	1.729	0.615	4.857	Prostate
Parker	1.169	0.864	1.583	Prostate
Ruer	2.114	0.925	4.833	Colorectal
Philips (1 yr)	2.672	0.835	8.543	Prostate
Palma	3.920	1.244	12.353	Multiple
Pooled rate	1.668	1.187	2.344	

p (pooled analysis): 0.003
p (heterogeneity): 0.288, I^2=18.0%
n=1,317 (LCT=686, control=631)

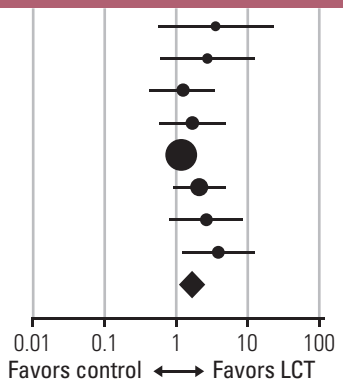


Fig. 4. *(Continued from the previous page)*

grade 3 or higher adverse events related to LCT [28,35,67]. Grade 5 adverse event, potentially related to the LCT, occurred in three cases among seven lung cancer studies (3 of 281, 1.07%). Regarding prostate cancer studies, grade 3 or higher adverse events related to the LCT was quite rare, and no studies reported significantly excessive adverse events related to the LCT, and grade 5 case, however, was also not reported. Palma et al. [7] reported three grade 5 adverse events among 66 patients (4.5%) following stereotactic body radiotherapy (SBRT) (radiation pneumonitis, pulmonary abscess, gastric ulcer). Ruo et al. [40] reported two out of 127 patients (1.6%) with postoperative death, and significant postoperative morbidity incidence of 20.5%. The types and rates of adverse events varied in other studies. The rates of grade 3 or higher adverse events related to LCT was mostly low (< 10%) and not significantly excessive when compared to the control arm (Table 3).

Table 2. Pooled survival rates according to disease

	No. of studies	No. of patients	LCT	Control	p-value
Overall survival					
NSCLC					
1-Year OS	17	1,539	84.1 (77.0-89.3)	66.0 (54.0-76.2)	0.004
2-Year OS	16	1,387	60.5 (52.5-68.0)	35.1 (26.3-45.0)	< 0.001
SCLC					
1-Year OS	2	130	60.7 (38.1-79.4)	42.8 (14.7-76.4)	0.411
Prostate					
3-Year OS	6	1,980	86.6 (65.0-95.7)	77.3 (44.6-93.5)	0.512
Colorectal					
1-Year OS	4	914	92.3 (67.9-98.6)	73.2 (48.1-89.0)	0.157
2-Year OS	4	914	72.5 (33.7-93.2)	40.5 (19.3-65.9)	0.173
Esophagus					
1-Year OS	4	777	72.8 (68.0-77.2)	59.0 (46.6-70.3)	0.026
2-Year OS	4	777	31.5 (22.6-42.0)	18.0 (14.6-22.0)	0.005
Pancreas					
1-Year OS	2	146	30.6 (21.1-42.1)	6.9 (8-40.2)	0.122
HCC					
1-Year OS	3	218	72.1 (51.8-86.1)	36.7 (16.0-63.8)	0.039
2-Year OS	3	218	38.8 (13.1-72.7)	18.4 (6.3-43.2)	0.282
H&N					
1-Year OS	3	145	83.7 (58.9-94.8)	67.3 (20.4-94.3)	0.463
2-Year OS	3	145	61.9 (41.1-79.1)	40.8 (13.8-74.9)	0.321
Progression-free survival					
NSCLC					
1-Year PFS	13	1,291	60.3 (51.0-68.9)	34.7 (26.2-44.3)	< 0.001
2-Year PFS	10	1,036	32.1 (22.2-43.9)	10.6 (5.7-19.0)	0.001
SCLC					
1-Year PFS	2	130	30.9 (17.2-49.2)	16.6 (8.0-31.3)	0.159
Prostate					
1-Year PFS	8	1,324	71.7 (51.4-85.9)	56.5 (30.7-79.2)	0.344
2-Year PFS	7	1,270	46.8 (26.0-68.7)	30.3 (13.4-54.9)	0.316
Colorectal					
1-Year PFS	3	684	68.1 (52.3-80.6)	34.6 (19.7-53.3)	0.007
2-Year PFS	3	684	41.8 (31.5-53.0)	12.2 (5.7-24.4)	0.001
Esophagus					
1-Year PFS	2	675	33.7 (22.0-47.8)	23.2 (19.2-27.8)	0.108
2-Year PFS	2	675	8.9 (2.6-26.4)	1.4 (0.6-3.6)	0.021
H&N					
1-Year PFS	2	98	69.6 (50.6-83.6)	25.4 (3.1-78.1)	0.133
2-Year PFS	2	98	37.5 (14.4-68.1)	12.4 (5.6-25.5)	0.068

HCC, hepatocellular carcinoma; H&N, head and neck; LCT, local consolidative therapy; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer.

Discussion

There is little disagreement that the patients with a lower metastatic burden have a far better prognosis, when compared to those with higher metastatic burden. There exist controversies, however, whether aggressive local treatment directed to oligometastasis may derive oncological benefits either by delaying disease progression or hindering metastatic cascade [5,72,73]. In addition to the several previous prospective studies which reported their conclusive results, the current analysis could provide a support on the role of LCT in managing the patients with oligometastatic disease.

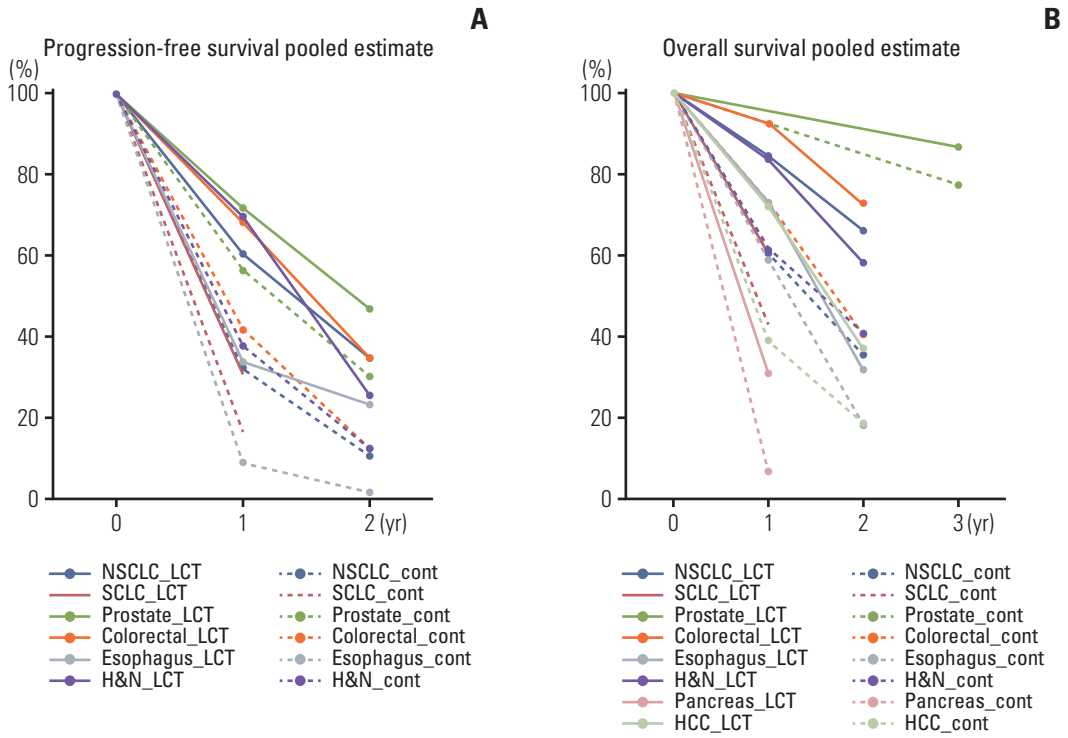


Fig. 5. Pooled survival percentile of overall survival (A) and progression-free survival (B) according to site of origin. HCC, hepatocellular carcinoma; H&N, head and neck; LCT, local consolidative therapy; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer.

In the present study, application of LCT resulted in significant benefit in terms of OS or PFS through the analyses for all included studies. In a subsequent subgroup analysis confined to the studies with reliable comparability, the effect size and the degree of hetererogeneity were similar to those from all studies. Finally, in an analysis limited to randomized controlled studies, the benefit of LCT remained significant in favor of the LCT, and the heterogeneity between studies was small. In another subgroup analyses on the various primary sites, the effect sizes related to the benefit of LCT varied and the degree of heterogeneity generally tended to decrease, when compared to those on all studies. As the benefit of LCT was consistently significant across all the analyses, we would speculate that the current study results strongly support the role of LCT in oligometastatic disease. The benefit of LCT in subgroup of RCTs with low heterogeneity suggested significant clinical advantages of LCT in oligometastatic patients. In addition, the effect size was different for primary sites, which suggests the needs for disease-specific approach.

The key question that remains is whether LCT can alter the biologic course of the oligometastatic patients. Several researchers recently suggested their hypotheses based on their own observations. Gomez et al. [8,27] investigated the role of LCT in the oligoprogression following the first-line chemotherapy for NSCLC, and reported that PFS benefit from LCT might have led to long-term OS benefit. Moreover, they also suggested that LCT could have removed the treatment-resistant cancer clones, or at least, could have slowed down the progression of metastatic spread by reduction of residual disease burden [27]. In another recent study, Phillips et al. [6] reported that total ablation of disease detectable by prostate-specific membrane antigen positron emission tomography–computed tomography using SBRT could reduce the development of new metastases. Based on these results, they suggested that the application of SBRT to metastatic lesions would not only delay the time for reemergence of detectable metastases, but also could prevent the progression of remaining micrometastases. Although the initial report by Palma et al. [7], with follow-up of approximately 2 years, failed to demonstrate the survival benefit following LCT, they later proved significant OS benefit in favor of LCT arm in the latest update with 51-months' follow-up (median OS difference of 22 months). As such, majority of clinical studies suggested the oncologic benefit by LCT and relevant hypotheses. However, preclinical studies are insufficient to provide biologic rationale and underlying mechanism. Phillips et al. [6] found that the circulating tumor DNA (ctDNA) was lower in the oligometastatic patients, when compared to

Table 3. Complication assessment

Author, target disease	Modality of LCT	No.	Control	No.	Grade ≥ 3 toxicity
Gomez, NSCLC [8]	RT or surgery & standard maintenance	25	Standard maintenance	24	2 cases G3 esophagitis in LCT; 1 G3 fatigue and 1 G3 anemia cases in control
Ni, NSCLC [35]	TKI & MWA	34	TKI	52	4 (9.3%) of MWA group needed chest tube drainage No G ≥ 3 toxicity related to TKI
Shang, NSCLC [42] (postop)	RT or RFA and/or CTx	105	CTx or BSC	47	Overall: 24.8% vs. 21.2% (LCT vs. control) (most common complication was myelosuppression) 1 case (0.9%) G5 infection in LCT arm
Wang, NSCLC [67]	RT (one site only) & ICI	59	ICI	93	9 of 59 (15%); mostly pneumonia or BM toxicity; 1 G5 mortality case due to severe pneumonia in LCT arm
Iyengar, NSCLC [32]	SBRT & CTx	14	CTx	15	Total 4 (28.6%) and 3 (20%) cases at LCT and control; no G5 toxicity
Wang, NSCLC [68]	^{125}I brachy	25	CTx	28	≥ G3 complication is lower in LCT arm (8%, pneumothorax vs. 25%, hematologic & nausea/vomiting)
Gore, SCLC [28]	PCI and cRT (45 Gy/15 F)	44	PCI	42	Overall: 25% vs. 9.5% 1 case of G5 pneumonitis in LCT arm
Bouman-Wammes, prostate [20]	SBRT (mostly 30 Gy/3 F or 35 Gy/7 F)	43	Active surveillance	20	No SBRT related toxicity
Ost, prostate [36]	SBRT (81%) or resection	31	Active surveillance	31	No grade 2 or higher toxicity in LCT arm
Parker, prostate [38]	RT and ADT	410	ADT	409	No data in low metastatic burden subgroup; 4% vs. 1% for whole population
Tsumura, prostate [46]	RT to metastases, prostate brachy & HTx	22	Prostate brachy & HTx	18	No difference in grade ≥ 2 toxicity
Phillips, prostate [6]	SBRT 24-48 Gy/3-5 F	36	Observation (allow CTx or ADT after 6 mo)	18	No G3 or higher adverse event in both arms
Ruo, colorectal [40]	Bowel surgery and CTx	127	CTx (83.5%)	103	Grade 5 cases (2 postoperative cases, 1.6%) postop OP morbidity (20.5%)
Ji, pancreas [56]	SBRT (m 41 Gy/5-7 F)+CTx	23	CTx	23	1 case of G3 duodenal bleeding in LCT arm
Shao, pancreas [65]	Liver and pancreas surgery+CTx	50	Palliative surgery + CTx	50	Longer hospital stay (21 vs. 13 days, $p < 0.001$), more transfusion and OP time in LCT arm
Chen, esophagus [22]	CCRT (IMRT, 50 Gy/25 F to primary; 45 Gy/15 F to metastases; cisplatin/paclitaxel)	196	CTx	265	No significant difference in both arms
Li J, esophagus [61]	IMRT (60 Gy) and/or CTx	55	CTx (90%), BSC (10%)	27	G3 complication: 7.3% (LCT) vs. 11.1% (control) No G4 or 5 toxicity in both arms
Kim K, HCC [58]	Surgery, RT and/or CTx	36	CTx	22	1 case of G3 pneumonitis after surgery
Palma, multiple [7]	SBRT and/or standard CTx	66	CTx	33	More in LCT (10.6% vs. 3%) grade 5 cases due to SBRT

(Continued to the next page)

Table 3. Continued

Author, target disease	Modality of LCT	No.	Control	No.	Grade ≥ 3 toxicity
Hu, multiple [55]	RT (SBRT, WBRT) & CTx or HTx	86	CTx or HTx	156	G3 pneumonia 3 cases (3.5%) and G3 leukopenia 1 case (1.2%) in LCT arm

ADT, androgen deprivation therapy; BM, bone marrow; BSC, best supportive care; CCRT, concurrent chemoradiation; cRT, chest radiotherapy; CTx, chemotherapy; HCC, hepatocellular carcinoma; HTx, hormone therapy; ICI, immune-checkpoint inhibitor; IMRT, intensity modulated radiation therapy; LCT, local consolidation therapy; MWA, microwave ablation; NSCLC, non-small cell lung cancer; OP, operation; PCI, prophylactic cranial irradiation; RFA, radiofrequency ablation; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.

that in polymetastaic patients, but failed to elucidate the relationship between ctDNA and oncologic outcomes [6]. Ongoing studies by Palma et al. [7], namely SABR-COMET 3 and SABR-COMET 10, intend to elucidate the biologic characteristics of oligometastasis by collecting ctDNA and circulating tumor cells, whose results are highly awaited.

Current study is not free from a few limitations. Relative significance of meta-analysis including the observational studies could be debated, because the uncontrolled confounders and possible heterogeneity could have affected pooled analyses [13]. However, the clinical decisions in oncology field could not be based solely on the level-1 evidence drawn from multiple well-designed prospective randomized clinical trials [74]. Furthermore, with the increasing evidence in favor of the role of LCT, it might be quite difficult to initiate a large-scale prospective trials in this clinical setting. On the other hand, there are suggestions that well-designed observational studies may provide high level of evidence similar to those from the prospective randomized trials [75]. In addition, our study comprehensively analyzed various cancer types, which is a rather unfamiliar method in oncology studies. Such approach can yield the heterogeneity of the pooled analysis. However, because the existence of oligometastic status having potential benefit of local treatment is still controversial, an integrated study is needed for overall clinical decisions [76]. To overcome the heterogeneity of pooled analysis, we performed hierarchical analysis, disease-specific subgroup analyses, and quantitative heterogeneity analyses. However, through the comprehensive analysis, the authors' could demonstrate, more or less, consistent and reliable results in favor of LCT based on various primaries, which may be shared in the clinical setting of the intermediate metastatic cascade called oligometsatasis. Another weakness of the current study included the fact that the innate mechanism of LCT could not be verified, as the speculations of the current study are based on external integration of the published clinical series. Based on these perspectives, we would strongly believe that the current analyses would be fruitful in our routine clinical practice, through our comparability-based formal meta-analyses, to support the necessity of applying LCT to the oligometastatic patients, and also in promoting the relevant basic biologic researches on oncologic mechanism of LCT, respectively.

The result of the current analyses suggested that LCT application be beneficial to the oligometastatic patients, based on the consistent findings by pooled analyses among (1) all included studies, (2) selected studies with reliable comparability, and (3) RCT's, respectively. LCTs might have different magnitude of oncologic benefits according to the primary sites, since the pooled survival percentiles varied among different primaries. Additional adverse events relat-

ed to LCT, however, need to be considered in the treatment decision process, especially for optimizing the potency of LCT when treating the lesions adjacent to the critical organs at risk.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Contributions

Conceived and designed the analysis: Ahn YC, Chie EK, Lee JH, Kim YS, Suh YG, Kim KH, Rim CH, Cho WK.
Collected the data: Rim CH, Cho WK.
Contributed data or analysis tools: Ahn YC, Chie EK, Lee JH, Kim YS, Suh YG, Kim KH, Rim CH, Cho WK.
Performed the analysis: Rim CH
Wrote the paper: Rim CH, Cho WK, Ahn YC, Chie EK.

ORCID iDs

Chai Hong Rim : https://orcid.org/0000-0001-7431-4588
Won Kyung Cho : https://orcid.org/0000-0002-4736-8270
Eui Kyu Chie : https://orcid.org/0000-0003-2027-7472
Yong Chan Ahn : https://orcid.org/0000-0002-1971-8472

Conflicts of Interest

Yong Chan Ahn, the editor-in-chief of the Cancer Research and Treatment, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Acknowledgments

This work has been approved and assisted by the board of directors of Korean Cancer Association.

References

1. Barney JD, Churchill EJ. Adenocarcinoma of the kidney with metastasis to the lung: cured by nephrectomy and lobectomy. J Urol. 1939;42:269-76.
2. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver: a prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer. 1996;77:1254-62.
3. Pastorino U, Buyse M, Friedel G, Ginsberg RJ, Girard P, Goldstraw P, et al. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg. 1997;113:37-49.
4. Chalkidou A, Macmillan T, Grzeda MT, Peacock J, Summers J, Eddy S, et al. Stereotactic ablative body radiotherapy in patients with oligometastatic cancers: a prospective, registry-based, single-arm, observational, evaluation study. Lancet Oncol. 2021;22:98-106.
5. Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. Radiother Oncol. 2020;148:157-66.
6. Phillips R, Shi WY, Deek M, Radwan N, Lim SJ, Antonarakis ES, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: the ORIOLE phase 2 randomized clinical trial. JAMA Oncol. 2020;6:650-9.
7. Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. J Clin Oncol. 2020;38:2830-8.
8. Gomez DR, Blumenschein GR Jr, Lee JJ, Hernandez M, Ye R, Camidge DR, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study. Lancet Oncol. 2016;17:1672-82.
9. Lehrer EJ, Singh R, Wang M, Chinchilli VM, Trifiletti DM, Ost P, et al. Safety and survival rates associated with ablative stereotactic radiotherapy for patients with oligometastatic cancer: a systematic review and meta-analysis. JAMA Oncol. 2021;7:92-106.
10. Jingu K, Matsushita H, Yamamoto T, Umezawa R, Ishikawa Y, Takahashi N, et al. Stereotactic radiotherapy for pulmonary oligometastases from colorectal cancer: a systematic review and meta-analysis. Technol Cancer Res Treat. 2018;17:1533033818794936.
11. Moher D, Altman DG, Liberati A, Tetzlaff J. PRISMA statement. Epidemiology. 2011;22:128.
12. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester: John Wiley & Sons; 2019.
13. Reeves BC, Deeks JJ, Higgins JP, Shea B, Tugwell P, Wells GA, et al. Including non-randomized studies on intervention effects. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester: John Wiley & Sons; 2019. p. 595-620.
14. Shin IS, Rim CH. Stepwise-hierarchical pooled analysis for synergistic interpretation of meta-analyses involving randomized and observational studies: methodology develop-

ment. J Med Internet Res. 2021;23:e29642.
15. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Ottawa: Ottawa Hospital Research Institute; 2011 [cited 2022 May 24]. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
16. Cochran WG. The combination of estimates from different experiments. Biometrics. 1954;10:101-29.
17. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21:1539-58.
18. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629-34.
19. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000;56:455-63.
20. Bouman-Wammes EW, van Dodewaard-De Jong JM, Dahele M, Cysouw MCF, Hoekstra OS, van Moorselaar RJA, et al. Benefits of using stereotactic body radiotherapy in patients with metachronous oligometastases of hormone-sensitive prostate cancer detected by [18F]fluoromethylcholine PET/CT. Clin Genitourin Cancer. 2017;15:e773-82.
21. Chen J, Lu S, Zhang Y, Xu L, Chen J, Wang J, et al. Sorafenib monotherapy versus sorafenib combined with regional therapies for hepatocellular carcinoma patients with pulmonary oligometastases: a propensity score-matched analysis. J Cancer. 2018;9:1745-53.
22. Chen Y, Cheng X, Song H, Wu AJ, Ku GY, Lee P, et al. Outcomes of concurrent chemoradiotherapy versus chemotherapy alone for esophageal squamous cell cancer patients presenting with oligometastases. J Thorac Dis. 2019;11:1536-45.
23. Depypere LP, Moons J, Lerut TE, Coosemans W, Van Veer H, Nafteux PR. Palliative esophagectomy in unexpected metastatic disease: sense or nonsense? Asian Cardiovasc Thorac Ann. 2018;26:552-7.
24. Falk AT, Moureau-Zabotto L, Ouali M, Penel N, Italiano A, Bay JO, et al. Effect on survival of local ablative treatment of metastases from sarcomas: a study of the French sarcoma group. Clin Oncol (R Coll Radiol). 2015;27:48-55.
25. Frost N, Tessmer A, Schmittel A, van Laak V, Raspe M, Ruwwe-Glosenkamp C, et al. Local ablative treatment for synchronous single organ oligometastatic lung cancer: a propensity score analysis of 180 patients. Lung Cancer. 2018;125:164-73.
26. Giessen C, Fischer von Weikersthal L, Laubender RP, Stintzing S, Modest DP, Schalhorn A, et al. Evaluation of prognostic factors in liver-limited metastatic colorectal cancer: a preplanned analysis of the FIRE-1 trial. Br J Cancer. 2013;109:1428-36.
27. Gomez DR, Tang C, Zhang J, Blumenschein GR Jr, Hernandez M, Lee JJ, et al. Local consolidative therapy Vs. maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer: long-term results of a multi-institutional, phase II, randomized study. J Clin Oncol. 2019;37:1558-65.
28. Gore EM, Hu C, Sun AY, Grimm DF, Ramalingam SS, Dunlap NE, et al. Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive-disease small cell lung cancer (ED SCLC): NRG Oncology RTOG 0937. J Thorac Oncol. 2017;12:1561-70.
29. Gray PJ, Mak RH, Yeap BY, Cryer SK, Pinnell NE, Christianson LW, et al. Aggressive therapy for patients with non-small cell lung carcinoma and synchronous brain-only oligometastatic disease is associated with long-term survival. Lung Cancer. 2014;85:239-44.
30. He J, Li Y, An J, Hu L, Zhang J. Surgical treatment in non-small cell lung cancer with pulmonary oligometastasis. World J Surg Oncol. 2017;15:36.
31. Hu F, Xu J, Zhang B, Li C, Nie W, Gu P, et al. Efficacy of local consolidative therapy for oligometastatic lung adenocarcinoma patients harboring epidermal growth factor receptor mutations. Clin Lung Cancer. 2019;20:e81-90.
32. Iyengar P, Wardak Z, Gerber DE, Tumati V, Ahn C, Hughes RS, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: a phase 2 randomized clinical trial. JAMA Oncol. 2018;4:e173501.
33. Lan T, Chen Y, Su Q, Ye J. Oncological outcome of cytoreductive radical prostatectomy in prostate cancer patients with bone oligometastases. Urology. 2019;131:166-75.
34. Morino K, Seo S, Yoh T, Fukumitsu K, Ishii T, Taura K, et al. Proposed definition for oligometastatic recurrence in biliary tract cancer based on results of locoregional treatment: a propensity-score-stratified analysis. Ann Surg Oncol. 2020;27: 1908-17.
35. Ni Y, Ye X, Yang X, Huang G, Li W, Wang J, et al. Microwave ablation as local consolidative therapy for patients with extracranial oligometastatic EGFR-mutant non-small cell lung cancer without progression after first-line EGFR-TKIs treatment. J Cancer Res Clin Oncol. 2020;146:197-203.
36. Ost P, Reynders D, Decaestecker K, Fonteyne V, Lumen N, De Bruycker A, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: a prospective, randomized, multicenter phase II trial. J Clin Oncol. 2018;36: 446-53.
37. Pan T, Xie QK, Lv N, Li XS, Mu LW, Wu PH, et al. Percutaneous CT-guided radiofrequency ablation for lymph node oligometastases from hepatocellular carcinoma: a propensity score-matching analysis. Radiology. 2017;282:259-70.
38. Parker CC, James ND, Brawley CD, Clarke NW, Hoyle AP, Ali A, et al. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. Lancet. 2018;392:2353-66.
39. Ruers T, Van Coevorden F, Punt CJ, Pierie JE, Borel-Rinkes I, Ledermann JA, et al. Local treatment of unresectable colorectal liver metastases: results of a randomized phase II trial. J Natl Cancer Inst. 2017;109:djx015.
40. Ruo L, Gougoutas C, Paty PB, Guillem JG, Cohen AM, Wong WD. Elective bowel resection for incurable stage IV colorectal cancer: prognostic variables for asymptomatic patients. J Am Coll Surg. 2003;196:722-8.
41. Schulz D, Wirth M, Piontek G, Knopf A, Straube C, Pigorsch S, et al. Improved overall survival in head and neck cancer

patients after specific therapy of distant metastases. Eur Arch Otorhinolaryngol. 2018;275:1239-47.
42. Shang S, Wang L, Su Y, Li B, Guo M, Zhu Z, et al. Local therapy combined with chemotherapy versus chemotherapy for postoperative oligometastatic non-small-cell lung cancer. Future Oncol. 2019;15:1593-603.
43. Sheu T, Heymach JV, Swisher SG, Rao G, Weinberg JS, Mehran R, et al. Propensity score-matched analysis of comprehensive local therapy for oligometastatic non-small cell lung cancer that did not progress after front-line chemotherapy. Int J Radiat Oncol Biol Phys. 2014;90:850-7.
44. Song YQ, Wang N, Qiao Y, He L, Li X, Zhang XF, et al. Treatment patterns and survival after 18F-fluorodeoxyglucose positron emission tomography/computed tomography-guided local consolidation therapy for oligometastatic non-small cell lung cancer: a two-center propensity score-matched analysis. J Cancer Res Clin Oncol. 2020;146:1021-31.
45. Steuber T, Jilg C, Tennstedt P, De Bruycker A, Tilki D, Decaestecker K, et al. Standard of care versus metastases-directed therapy for PET-detected nodal oligorecurrent prostate cancer following multimodality treatment: a multi-institutional case-control study. Eur Urol Focus. 2019;5:1007-13.
46. Tsumura H, Ishiyama H, Tabata KI, Sekiguchi A, Kawakami S, Satoh T, et al. Long-term outcomes of combining prostate brachytherapy and metastasis-directed radiotherapy in newly diagnosed oligometastatic prostate cancer: a retrospective cohort study. Prostate. 2019;79:506-14.
47. Xu LM, Cheng C, Kang M, Luo J, Gong LL, Pang QS, et al. Thoracic radiotherapy (TRT) improved survival in both oligo- and polymetastatic extensive stage small cell lung cancer. Sci Rep. 2017;7:9255.
48. Xu Q, Zhou F, Liu H, Jiang T, Li X, Xu Y, et al. Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs. J Thorac Oncol. 2018;13:1383-92.
49. Yano T, Haro A, Yoshida T, Morodomi Y, Ito K, Shikada Y, et al. Prognostic impact of local treatment against postoperative oligometastases in non-small cell lung cancer. J Surg Oncol. 2010;102:852-5.
50. Boeri L, Sharma V, Kwon E, Stish BJ, Davis BJ, Karnes RJ. Oligorecurrent prostate cancer treated with metastases-directed therapy or standard of care: a single-center experience. Prostate Cancer Prostatic Dis. 2021;24:514-23.
51. Chen XR, Hou X, Li DL, Sai K, Dinglin XX, Chen J, et al. Management of non-small-cell lung cancer patients initially diagnosed with 1 to 3 synchronous brain-only metastases: a retrospective study. Clin Lung Cancer. 2021;22:e25-34.
52. Deek MP, Taparra K, Phillips R, Velho PI, Gao RW, Deville C, et al. Metastasis-directed therapy prolongs efficacy of systemic therapy and improves clinical outcomes in oligoprogressive castration-resistant prostate cancer. Eur Urol Oncol. 2021;4:447-55.
53. Gauvin C, Krishnan V, Kaci I, Tran-Thanh D, Bedard K, Albadine R, et al. Survival impact of aggressive treatment and PD-L1 expression in oligometastatic NSCLC. Curr Oncol. 2021;28:593-605.
54. Hsu KH, Huang JW, Tseng JS, Chen KW, Weng YC, Yu SL, et al. Primary tumor radiotherapy during EGFR-TKI disease control improves survival of treatment naive advanced EGFR-mutant lung adenocarcinoma patients. Onco Targets Ther. 2021;14:2139-48.
55. Hu X, Li H, Kang X, Wang X, Pang H, Liu C, et al. Efficacy and safety of local radiotherapy to all oligometastatic sites in elderly patients with metachronous oligometastatic cancers after initial teatment for the primary tumor. Cancer Manag Res. 2021;13:9247-59.
56. Ji X, Zhao Y, He C, Han S, Zhu X, Shen Z, et al. Clinical effects of stereotactic body radiation therapy targeting the primary tumor of liver-only oligometastatic pancreatic cancer. Front Oncol. 2021;11:659987.
57. Kagawa Y, Furuta H, Uemura T, Watanabe N, Shimizu J, Horio Y, et al. Efficacy of local therapy for oligoprogressive disease after programmed cell death 1 blockade in advanced non-small cell lung cancer. Cancer Sci. 2020;111:4442-52.
58. Kim K, Kim TH, Kim TH, Seong J. Efficacy of local rherapy for oligometastatic hepatocellular carcinoma: a propensity score matched analysis. J Hepatocell Carcinoma. 2021;8:35-44.
59. Lan B, Abudureheiyimu N, Zhang J, Wang C, Jiang S, Wang J, et al. Clinical features and prognostic factors for extracranial oligometastatic breast cancer in China. Int J Cancer. 2020;147:3199-205.
60. Li H, Duan Z, Zhao C, Fang W, Jia Y, Li X, et al. Combination of brachytherapy with iodine-125 seeds and systemic chemotherapy versus systemic chemotherapy alone for synchronous extracranial oligometastatic non-small cell lung cancer. Cancer Manag Res. 2020;12:8209-20.
61. Li J, Wen Y, Xiang Z, Du H, Geng L, Yang X, et al. Radical radiotherapy for metachronous oligometastasis after initial treatment of esophageal cancer. Radiother Oncol. 2021;154:201-6.
62. Li W, Bai Y, Wu M, Shen L, Shi F, Sun X, et al. Combined CT-guided radiofrequency ablation with systemic chemotherapy improves the survival for nasopharyngeal carcinoma with oligometastasis in liver: propensity score matching analysis. Oncotarget. 2016;8:52132-41.
63. Liu Y, Long W, Zhang Z, Zhang Z, Mai L, Huang S, et al. Metastasis-directed stereotactic body radiotherapy for oligometastatic renal cell carcinoma: extent of tumor burden eradicated by radiotherapy. World J Urol. 2021;39:4183-90.
64. Moretto R, Rossini D, Zucchelli G, Lonardi S, Bergamo F, Santini D, et al. Oligometastatic colorectal cancer: prognosis, role of locoregional treatments and impact of first-line chemotherapy-a pooled analysis of TRIBE and TRIBE2 studies by Gruppo Oncologico del Nord Ovest. Eur J Cancer. 2020;139:81-9.
65. Shao Y, Feng J, Hu Z, Wu J, Zhang M, Shen Y, et al. Feasibility of pancreaticoduodenectomy with synchronous liver metastasectomy for oligometastatic pancreatic ductal adenocarcinoma: a case-control study. Ann Med Surg (Lond). 2021;62:490-4.
66. Shi Z, Zhu X, Ke S, Qiu H, Cai G, Zhangcai Y, et al. Survival impact of concurrent chemoradiotherapy for elderly patients with synchronous oligometastatic esophageal squamous cell

carcinoma: A propensity score matching and landmark analyses. Radiother Oncol. 2021;164:236-44.
67. Wang P, Yin T, Zhao K, Yu J, Teng F. Efficacy of single-site radiotherapy plus PD-1 inhibitors vs PD-1 inhibitors for oligometastatic non-small cell lung cancer. J Cancer Res Clin Oncol. 2022;148:1253-61.
68. Wang H, Lu J, Zheng XT, Zha JH, Jing WD, Wang Y, et al. Oligorecurrence non-small cell lung cancer after failure of first-line chemotherapy: computed tomography-guided (125)I seed implantation vs. second-line chemotherapy. Front Oncol. 2020;10:470.
69. Wright CM, Lee DY, Shimunov D, Carmona R, Barsky AR, Sun L, et al. Definitive tumor directed therapy confers a survival advantage for metachronous oligometastatic HPV-associated oropharyngeal cancer following trans-oral robotic surgery. Oral Oncol. 2021;121:105509.
70. Yildirim BA, Onal C, Kose F, Oymak E, Sedef AM, Besen AA, et al. Outcome of loco-regional radiotherapy in metastatic castration-resistant prostate cancer patients treated with abiraterone acetate. Strahlenther Onkol. 2019;195:872-81.
71. Zhao Y, Zhang X, Zhao H, Gong T, Li J, Tsauo J, et al. Systemic therapy plus thermal ablation versus systemic therapy alone for oligometastatic liver metastases from non-small cell lung cancer. Cardiovasc Intervent Radiol. 2020;43:1285-93.
72. Correa RJ, Salama JK, Milano MT, Palma DA. Stereotactic body radiotherapy for oligometastasis: opportunities for biology to guide clinical management. Cancer J. 2016;22:247-56.
73. Palma DA, Salama JK, Lo SS, Senan S, Treasure T, Govindan R, et al. The oligometastatic state: separating truth from wishful thinking. Nat Rev Clin Oncol. 2014;11:549-57.
74. Shin IS, Rim CH. Updating perspectives on meta-analyses in the field of radiation oncology. Medicina (Kaunas). 2021;57:117.
75. Shrier I, Boivin JF, Steele RJ, Platt RW, Furlan A, Kakuma R, et al. Should meta-analyses of interventions include observational studies in addition to randomized controlled trials? A critical examination of underlying principles. Am J Epidemiol. 2007;166:1203-9.
76. Beckham TH, Yang TJ, Gomez D, Tsai CJ. Metastasis-directed therapy for oligometastasis and beyond. Br J Cancer. 2021;124:136-41.