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Role of local ablative treatment in oligometastatic non-small cell lung cancer: a meta-analysis

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Short title: local treatment for oligometastatic NSCLC

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Footnote

Trial registration

The protocol of present study is registered in PROSPERO (CRD42022383410).

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Ethical Statement

Ethical approval was not required because this study retrieved and synthesized data from previously published studies.

Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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Author contributions

Conceived and designed the analysis: Rim CH, Cho WK, Park SM

Collected the data: Rim CH, Cho WK, Park SM

Contributed data or analysis tools: Rim CH, Cho WK, Park SM

Performed the analysis: Rim CH

Wrote the paper: Rim CH

Supervision and editing: Rim CH, WS Yoon, DS Yang

Data Sharing Statement

All data generated or analysed during this study are included in this article [and/or] its supplementary material files. Further enquiries can be directed to the corresponding author.

Highlights

- The role of local treatment for metastatic cancer in classical tumor treatment principles is limited.
- Recent studies have reported the effectiveness of local ablative treatment, including surgery or radiotherapy.
- This meta-analysis analyzed all comparative clinical series related to non-small cell lung cancer oligometastasis and reported the effectiveness of local ablative treatment (odds ratio for overall- and progression free survival: 3.492 and 3.743)
- The oligoprogression/recurrence disease could have less benefit from local ablative treatment than synchronous or oligopersistent disease.

Data availability statement: All data generated or analysed during this study are included in this article [and/or] its supplementary material files. Further enquiries can be directed to the corresponding author.

Role of local ablative treatment in oligometastatic non-small cell lung cancer: a meta-analysis

Running title: local treatment for oligometastatic NSCLC

Abstract

Introduction

This meta-analysis analyzed the oncologic role of local ablative treatment (LAT) in oligometastatic non-small cell lung cancer (NSCLC).

Method

Pubmed, MEDLINE, Embase, and Cochrane library were searched until October, 2022. Studies comparing LAT with standard care (control) were included. Sensitivity analyses were performed including randomized controlled studies (RCTs). Subgroup analyses were performed according to specific categories and metastatic burden. The primary endpoints were overall survival (OS) and (PFS). Considering the median OS and PFS from landmark studies, 2-year OS and 1-year PFS rates were used to calculate pooled odds ratios (ORs).

Results

A total of 20 studies (four RCTs) encompassing 1750 patients were included. Surgery and radiotherapy (60% and 90% of studies) were mainly used as LATs. Pooled ORs of overall survival (OS) and progression free-survival (PFS) were 3.492 (95% confidence interval [CI]:2.612-4.699, p<0.001) and 3.743 (95% CI:2.586-5.419, p<0.001), favoring LAT, respectively. Sensitivity analyses including RCTs showed OR of 4.111 (p<0.001) and 4.959 (p=0.001) regarding OS and PFS, favoring LCT, respectively. Pooled 1- and 2-year OS rates were 83.8% and 58.4% in LAT arms, whereas 64.4% and 31% in control arms; pooled 1- and 2-year PFS rates were 64.6% and 32.8% in LAT arms, and 36.1% and 10% in control arms. In subgroup analyses, pooled ORs were 3.981 (p<0.001), 3.355 (p<0.001), and 1.726 (p=0.373) in synchronous, oligopersistence, and oligoprogression/recurrence subgroups, respectively. Regarding PFS comparison, pooled ORs were 5.631 (p<0.001), 3.484 (p<0.001), and 1.777 (p=0.07), respectively. According to metastatic burden categories, pooled ORs favored LAT arms in both analyses including low-metastatic and high-metastatic burden subgroups.

Conclusion

The present study supports the role of LAT in treating NSCLC oligometastasis. The oligoprogression/recurrence disease could have less LAT benefit than synchronous or

oligopersistent disease.

Keywords: oligometastasis, lung cancer, NSCLC, radiotherapy, stereotactic body radiotherapy

Introduction

Metastatic non-small cell lung cancer (NSCLC) has been considered incurable with a life expectancy of less than a year, with supportive care or conventional chemotherapy [1]. However, several studies reported that long-term survival could be achieved by performing local treatments, such as surgery, for metastatic cancer with a limited burden [2, 3]. In a recent study using the Surveillance, Epidemiology, and End Results database, the median survival of metastatic NSCLC patients who underwent resection for primary and metastatic tumors was 29.4 months, which was higher than that of the non-surgical control group (11.1 months) [4]. Nonetheless, majority of the patients experienced a metastatic cascade after active treatment. Therefore, in treating metastatic lesions, a noninvasive modality with a low therapeutic burden is necessary. The development of radiotherapy techniques, including computerized CT planning, has made it possible to treat metastatic foci with an ablative aim [5]. Stereotactic body radiotherapy (SBRT), which aims to treat a precise target within a short period of time, has been widely used recently, and the number of treatment attempts and related studies on oligometastasis has greatly increased [5]. Furthermore, recent randomized studies reported oncologic benefit of application of SBRT for oligometastatic NSCLC [6-9].

Since oligometastasis encompasses a range of diseases, the European Society for Radiotherapy and Oncology (ESTRO) and the European Organization for Research and Treatment of Cancer (EORTC) recently classified oligometastasis into nine specific categories [10]. Several researchers have reported that the prognosis of oligometastasis may vary depending on the specific category; although it was not statistically significant, it has been suggested that oligorecurrence or oligoprogression could have a poorer prognosis than de novo disease [11-13]. Oligomestasis is mostly defined as having fewer than three or five metastatic foci, but the definition varies from researcher to researcher. Therefore,

oligometastasis encompasses different metastatic burdens, and differences in the benefits of local treatment might be present [5].

The prognosis of advanced non-small cell lung cancer (NSCLC) has greatly improved owing to recent therapeutic developments [14]. Local ablative treatments (LAT), including surgery and conformal or stereotactic radiotherapy, for recurrent or metastatic of NSCLC is actively conducted in clinical practice and is the most actively researched field of oligometastasis. Through this meta-analysis, we intended to clarify the role of LAT in NSCLC oligometastasis and understand the clinical significance of specific categories and metastatic burden through subgroup analyses.

Method

Study design and eligibility criteria

The present study has been reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), Supplemental Digital Content 1, http://links.lww.com/JS9/A139; Supplemental Digital Content 2, http://links.lww.com/JS9/A140 and AMSTAR (Assessing the methodological quality of systematic reviews) Supplemental Digital Content 3, http://links.lww.com/JS9/A141 Guidelines [15, 16]. Our hypothetical PICO (population, intervention, comparison, and outcome) question is: “Does LAT yield an additional oncologic benefit (in comparison to the previous standard of care) in treating oligometastatic NSCLC patients?” Eligible studies for the present systematic review fulfilled the following criteria: 1) a study comparing the LAT arm and the standard of care arm (control arm); 2) more than 10 patients with NSCLC oligometastases were included in each arm; and 3) one primary endpoint, either overall

survival (OS) or progression-free survival (PFS), was provided. Oligometastasis is defined as a disease with ≤3 or ≤5 metastatic lesions, or disease with a metastatic burden that could be targeted with local therapies such as surgery or radiotherapy. LAT refers to local treatment that includes both metastatic and/or primary disease, while local treatment includes radiotherapy, surgery, and RFA. Treatments intentionally targeting only the partial disease burden are not considered LAT. The standard of care is systemic treatment and/or supportive care based on the physician's discretion. Studies regarding oligometastases of small cell lung cancer or lung metastases from other organs were not included.

Protocol registration

The protocol of present study is registered in PROSPERO (CRD42022383410).

Information source, search strategy, and data collection

Four databases, PubMed, MEDLINE, Embase, and the Cochrane Library, were searched until October 13, 2022. The search terms and detailed strategy are provided in Supplement Data 1, Supplemental Digital Content 4, http://links.lww.com/JS9/A142. Conference abstracts were also included as they fulfilled the inclusion criteria. No language restrictions were included. For studies with overlapping cohorts, those with a larger number of cohorts or more recent studies were included if they had a similar number of patients cohorts. Reference lists of included studies were also searched. The primary endpoints were OS and PFS. Grade ≥3 complications related to LAT were subjectively investigated. We used pre-standardized sheets to collect data, including: 1) general information including the name of the author, affiliation, publication year, study design, number of patients, the definition of oligometastasis, a

specific category of oligometastasis, LAT modality, and conflict of interest; 2) clinical outcomes including number of metastatic foci, location of metastases, 1- and 2-year percentiles and median values of OS and PFS, and description of grade ≥3 complications. The survival data were acquired from descriptive graphs in the absence of numerical data. Data collection and searches were performed by three independent investigators. Any disagreement regarding study inclusion and data acquisition was resolved via mutual discussion and re-evaluation of the literature.

Risk of bias and subgroup analyses

Since the majority of the target studies were non-randomized, the possible risk of bias was discussed as advised by the Cochrane group [17]. We performed sensitivity analyses including randomized studies only, as well as pooled analyses including all studies that met the inclusion criteria. For the integrated interpretation of the pooled results of the overall and sensitivity analyses, we referred to the stepwise hierarchical pooled analysis for synergistic interpretation by Shin and Rim [18] (i.e., the ascending pattern of effect size, statistical significance, and validity of subgroups strengthens the hypothesis, whereas the descending pattern weakens). Oligometastasis includes various diseases in terms of disease specificity and definition. Therefore, we performed subgroup analyses according to disease specificity with reference to the ESTRO-EORTC oligometastasis classification [10]. Oligometastasis is most commonly defined by the number of metastatic foci, and mostly defined to have three or fewer, or five or fewer metastases [10]. Therefore, studies that defined oligometastasis as having three or fewer metastases or those in which patients with a single metastasis accounted for more than 80% of the cohort were classified as a low-metastatic burden subgroup and analyzed.

Quality assessment

Since eligible studies encompassed several non-randomized studies, the Newcastle-Ottawa scale was used to quantitatively assess the quality of the included studies [19]. Studies scoring 8–9 were considered high-quality studies, and those scoring 6–7 were considered moderate-quality studies. Studies with a score of ≤5 were evaluated as low-quality studies. Since only the observational studies with moderate or low risk of bias are recommended to be included in pooled analyses, referencing the Cochrane handbook [20], low quality studies were excluded from formal pooled analyses with the consent of the authors.

Statistics

The primary endpoints of this study were OS and PFS. The effect measures of primary endpoints were assessed as odds ratios (OR) comparing the OS and PFS percentiles between the LAT and control arms. Considering the median OS and PFS from landmark studies [6-9], pooled ORs of the primary endpoints were calculated from the 2-year OS and 1-year PFS. Pooled rates of the OS and PFS percentiles were also calculated for clinical reference. A random effects model was used for pooled analyses of both ORs and percentiles of primary endpoints, considering the confounding variables unavoidable in non-randomized studies, the diversity of clinical situations among institutions where the studies were conducted, and that the random effects model is recommended by the Cochrane group as a default for analyzing non-randomized studies [17]. For subgroup analyses including only randomized studies, the fixed effects model was used if heterogeneity among studies was not significant ($I^2 \leq 50\%$ and $p > 0.1$).

For all pooled analyses performed, heterogeneity was assessed using the Cochran Q test [21] and I^2 statistics [22], and studies with I^2 statistics of 25%, 50%, and 75% were regarded as low, moderate, and high, respectively. Publication bias assessment was performed for pooled analyses, including ≥10 studies, using visual funnel plot analysis and Egger's test [23]. If the 2-tailed p-value of Egger's test was <0.1 with visual asymmetry noted in the funnel plots, Duval and Tweedie's trim-and-fill method was performed, yielding estimates correcting possible publication bias. Statistical analyses were performed using the Comprehensive Meta-Analysis version 4 (Biostat Inc., Englewood, NJ, USA).

Results

Study selection and characteristics

During the initial search, 3,022 studies were identified, and 32 studies from suggested references were also investigated. After filtering studies with irrelevant formats and duplicate records, 1,350 studies underwent abstract screening. The full-text screening was performed for 114 studies that remained after the abstract screening, and 20 studies that fulfilled all inclusion criteria were included in the present systematic review [6-9, 24-39]. The study inclusion process is summarized in Figure 1.

Among the 20 studies finally included, four studies were randomized, three used propensity-score matching methods, nine studies performed statistical comparisons between LAT and control groups, and the remaining studies had no statistical comparison information. Radiotherapy was the modality of LAT in 18 of 20 (90%) studies (including two brachytherapy studies), and surgery was performed in 12 studies (60%). RFA was the modality used for LAT in a study by Ni et al. [31]. Ten studies defined oligometastasis as

having five or fewer metastatic foci, and six studies defined oligometastasis as having three or fewer metastatic foci. Other definitions included four or fewer foci, controllable with local treatment, and six or fewer foci. Table 1 summarizes the general characteristics of the included studies. Regarding oligometastasis classification, because the information contained in the studies was insufficient to classify in detail all nine ESTRO-EORTC classifications [10], we classified them more simply: seven studies studied oligopersistence, six studies synchronous disease, three studies oligoprogression, and three studies oligorecurrence. One study had no relevant data. The general information of the included studies is summarized in Table 1. Detailed clinical information is provided in Supplement Table 1, Supplemental Digital Content 5, http://links.lww.com/JS9/A143.

Quality assessment

The studies included in this systematic review investigated a narrow range of diseases called oligometastasis of NSCLC and were conducted by tertiary hospitals or their associations. No study reported follow-up losses, which could induce a significant bias. All studies were scored except for queries related to comparability and the follow-up period. Referencing the Newcastle-Ottawa scoring manual, RCTs or propensity matching studies corrected for two or more clinical factors were fully scored for comparability, and studies that made only statistical comparisons or did not have information about comparisons were not scored. Considering the expected survival of patients with oligometastases of NSCLC, studies with a median follow-up period of <1 year or without follow-up information did not score the query regarding enough follow-up duration. The included studies scored from 7 to 9, and none were evaluated as low-quality studies. Therefore, all 20 studies were included in the pooled analysis. A detailed scoring sheet is provided in Supplementary Data 2, Supplemental Digital

Content 4, http://links.lww.com/JS9/A142.

Clinical results

Among 20 studies, the median OS ranged from 12.6 to 74 months (median: 33.6 months) in LAT arms, whereas it ranged from 5 to 30.8 months (median: 16.9 months) in control arms. Regarding PFS, the median value ranged from 9.7 to 25.1 months (median: 15 months) in LAT arms and 2.1 to 14.3 months (median: 7.6 months) in control arms. Among the 14 studies that provided statistical OS comparison, 12 of 14 (85.7%) 4 reported a significant benefit of LAT; regarding PFS, all 13 studies that provided statistical PFS comparison reported the benefit of LAT (Table 1).

The pooled OR of the OS comparison was 3.492 (95% confidence interval [CI]: 2.612–4.669, $p < 0.001$), with low heterogeneity ($p = 0.210$, $I^2 = 21.9\%$). No significant publication bias was noted (Egger's *p*: 0.8214). In the sensitivity analysis including RCTs, the pooled OR was 4.111 (95% CI: 2.159–7.829, $p < 0.001$), and the heterogeneity was very low ($p = 0.319$, $I^2 =$ ~0%). The pooled OR of the PFS comparison was 3.743 (95% CI: 2.586–5.419, $p < 0.001$), with low to moderate heterogeneity among the studies ($p = 0.071$, $I^2 = 39.5\%$). There was no possible publication bias noted (Egger's *p*: 0.2405). The sensitivity analysis including RCTs showed an OR of 4.959 (95% CI: 1.989–12.363, $p = 0.001$) with low to moderate heterogeneity among studies ($p = 0.119$, $I^2 = 48.7\%$). Figure 2 summarizes the OR of the synthesized results using forest plots. The pooled 1- and 2-year OS percentiles were 83.8% (95% CI: 76.4–89.2) and 58.4% (95% CI: 50.9–65.5) in the LAT arms, and 64.4% (95% CI: 52.0–75.1) and 31.0% (95% CI: 23.0–40.0) in the control arms, respectively. The pooled 1- and 2-year PFS percentiles were 64.6% (95% CI: 53.1–74.5) and 32.8% (95% CI: 23.1–44.3) in the LAT arms, and 36.1% (95% CI: 27.2–26.0) and 10.0% (95% CI: 6.3–15.7) in the

control arms, respectively (Figure 3).

Subgroup analyses

Subgroup analyses were performed according to the oligometastasis category and metastatic burden. We categorized oligometastatic disease into synchronous, oligopersistence, oligoprogression, and oligorecurrence. Oligoprogression and oligorecurrence were regarded as a single category, considering the biological rationale, limited number of studies, and suboptimal clinical information for detailed categorization. In the OS comparison, pooled ORs were 3.981 (95% CI: 2.835–5.590, $p < 0.001$), 3.355 (95% CI: 1.955–5.760, $p < 0.001$), and 1.726 (95% CI: 0.519–5.739, $p = 0.373$) in the synchronous, oligopersistence, oligoprogression, and oligo-recurrence subgroups, respectively. Regarding the PFS comparison, the pooled ORs were 5.631 (95% CI: 2.452–12.934, $p < 0.001$), 3.484 (95% CI: 2.344–5.178, $p < 0.001$), and 1.777 (95% CI: 0.953–3.315, $p = 0.07$), respectively.

In the subgroup analyses according to the metastatic burden category, the pooled ORs for OS were 3.243 (95% CI: 1.748–6.017, $p < 0.001$) and 3.532 (95% CI: 2.523–4.946, $p < 0.001$) in the low and high metastatic burden subgroups, respectively. The pooled ORs for PFS were 5.129 (95% CI: 3.186–8.256, $p < 0.001$) and 3.259 (2.010–5.283, $p < 0.001$) in the low and high metastatic burden subgroups, respectively. The results of all subgroup analyses are summarized in Table 2.

Complications

Eight studies provided clinical information regarding grade ≥3 toxicities. Ni et al. [31] reported that four of 34 (9.3%) patients who underwent RFA required chest tube drainage,

with no grade ≥3 toxicities reported in the control arm. No other study has reported excessive grade ≥3 complications due to LAT. Common toxicities due to LAT include esophagitis, pneumonitis, and myelosuppression. Although grade 5 toxicity has rarely been reported, Shang et al [27]. reported a case of pneumonitis (1 of 105, 0.9%).

Discussion

The present study successfully reported the role of LAT in NSCLC oligometastasis with respect to both endpoints of OS and PFS. The pooled OR of pooled analyses including all studies was significant with low or low to moderate heterogeneity, and further confirmed by sensitivity analyses including only RCTs. In the subgroup analyses regarding disease specificity, although LAT showed benefits for both OS and PFS in the synchronous and oligopersistence subgroups, it was not significantly beneficial in the subgroup analyses of the oligoprogression and recurrence subgroups. Subgroup analyses regarding metastatic burden did not show distinctively different results regarding OS and PFS, although the pooled OR for PFS was higher in the low metastatic burden subgroup than in the other subgroups. Heterogeneity in pooled analyses was mostly moderate or low, and possible publication bias was not noted.

The role of LAT in improving the oncologic prognosis of early metastatic disease has been the most researched subject in oligometastasis. The past studies were mostly limited to single-arm series, which obtained “better than previously expected” survival results [40]. However, several researchers have shown the benefit of LAT in a recent controlled series, and four randomized studies to date have demonstrated the role of LAT in NSCLC oligometastasis [6-8, 41]. Of the 20 studies included in our meta-analysis, 90% of them reported a benefit in OS or PFS. Except for one study that used RFA [31], none of the studies

mentioned additional serious complications with LAT. Rather, it is expected that LAT could confer symptomatic relief or reduce the toxicities of chemotherapy [42], which might be underreported. Therefore, the results of the present systematic review support the active clinical application of LAT.

The clinical role of LAT has been clarified based on the consistent results of controlled studies, including a recent randomized series. Subsequently, a more detailed clinical topic has arisen to optimize clinical decisions. Oligometastasis encompasses a range of clinical situations; in early oligometastasis studies, it was divided into synchronous and metachronous diseases in terms of temporal consideration [5, 43]. However, detailed classification based on the metastatic burden, disease characteristics, and temporal considerations has been increasingly used and researched [10]. Willman et al [12]. Reported shorter PFS for repeat and induced oligometastasis than for de novo disease. Chen et al. also reported that oligoprogression was associated with a significantly shorter OS than oligopersistence [11]. In the subgroup analysis of this study, LAT was related to OS or PFS benefits in the synchronous and oligopersistence subgroups, but the benefit was not significant in the oligoprogression and recurrence subgroups. The results of our study suggest the need to consider the disease category of oligometastasis in clinical decisions in accordance with the relevant series.

The definition of oligometastasis varies among researchers, and the borderline at which LAT is considered beneficial has not been clearly defined [44, 45]. We hypothesized that among the studies included in this study, those that used a stricter definition (3 or fewer metastatic foci) or had less metastatic burden would be associated with a more significant LAT benefit. However, there was no clear difference in the results between the study groups classified according to metastatic burden. This may be because oligometastasis, which has a relatively

large metastatic burden, still benefits from LAT owing to the reduced disease burden and symptom relief [46]. Another limitation is that the numerical definition of oligometastasis alone cannot accurately evaluate the metastatic burden of patients. In addition to the number of metastases, the size and location of metastases have an impact on prognosis. The identification of related biological markers, such as cell-free DNA and circulating tumor cells, is urgently needed to identify the disease characteristics of oligometastasis that may benefit from LAT [45, 47].

The limitations of the present study include heterogeneity in the pooled analyses. Considering that oligometastasis includes a spectrum of diseases and the diversity in the clinical details of treatment modalities, some degree of heterogeneity is inevitable. Nevertheless, clinical decisions regarding the application of LAT can be supported by the integrated information investigated herein. Several analytical methods have been used to obtain reliable pooled results. In the present study, the main pooled results were confirmed by sensitivity analyses using RCT, and subgroup analyses helped identify the cause of heterogeneity and obtain useful information for more clinical decisions. Another limitation is the difficulty in identifying the specific disease categories of oligometastasis. Among the authors, only those of one of the 20 studies identified the disease category. Due to limited information, we could perform a more simplified classification than the full nine-category classification suggested by ESTRO-EORTC [10]. Another limitation is that the regimen of systemic treatment in the control group was not unified. Since included studies recruited patients from 1994-2016, the regimen of chemotherapy varies and novel agent (e.g. durvalumab) was not used. An updating meta-analysis is necessary including future studies. We found a meta-analysis on a similar subject in a preliminary search [48]. The meta-analysis included six oligometastases and one polymetastasis NSCLC studies; therefore, some heterogeneity was considered. A systematic review should collect all available evidence, and the purpose of a meta-analysis is

to provide integrated information based on extensive literature to help clinical decisions, as referenced in the Cochrane manual [46, 47]. The previous study included only six oligometastasis studies, which required a more extensive search, and no subgroup analyses were performed. Our systematic review extensively searched for all available evidence, and we believe that more clinically useful information can be provided through subgroup analyses.

Conclusion

The present systematic review and meta-analysis support the oncologic role of LAT in treating NSCLC oligometastases. Oligoprogression and/or oligorecurrence disease could have less benefit from LAT than synchronous or oligorecurrence disease. The difference in the clinical role of LAT according to the metastatic burden should be further investigated, along with studies identifying the clinical definition of oligometastasis.

Provenance and peer review

Not commissioned, externally peer-reviewed

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Figure 1. Study inclusion plot.

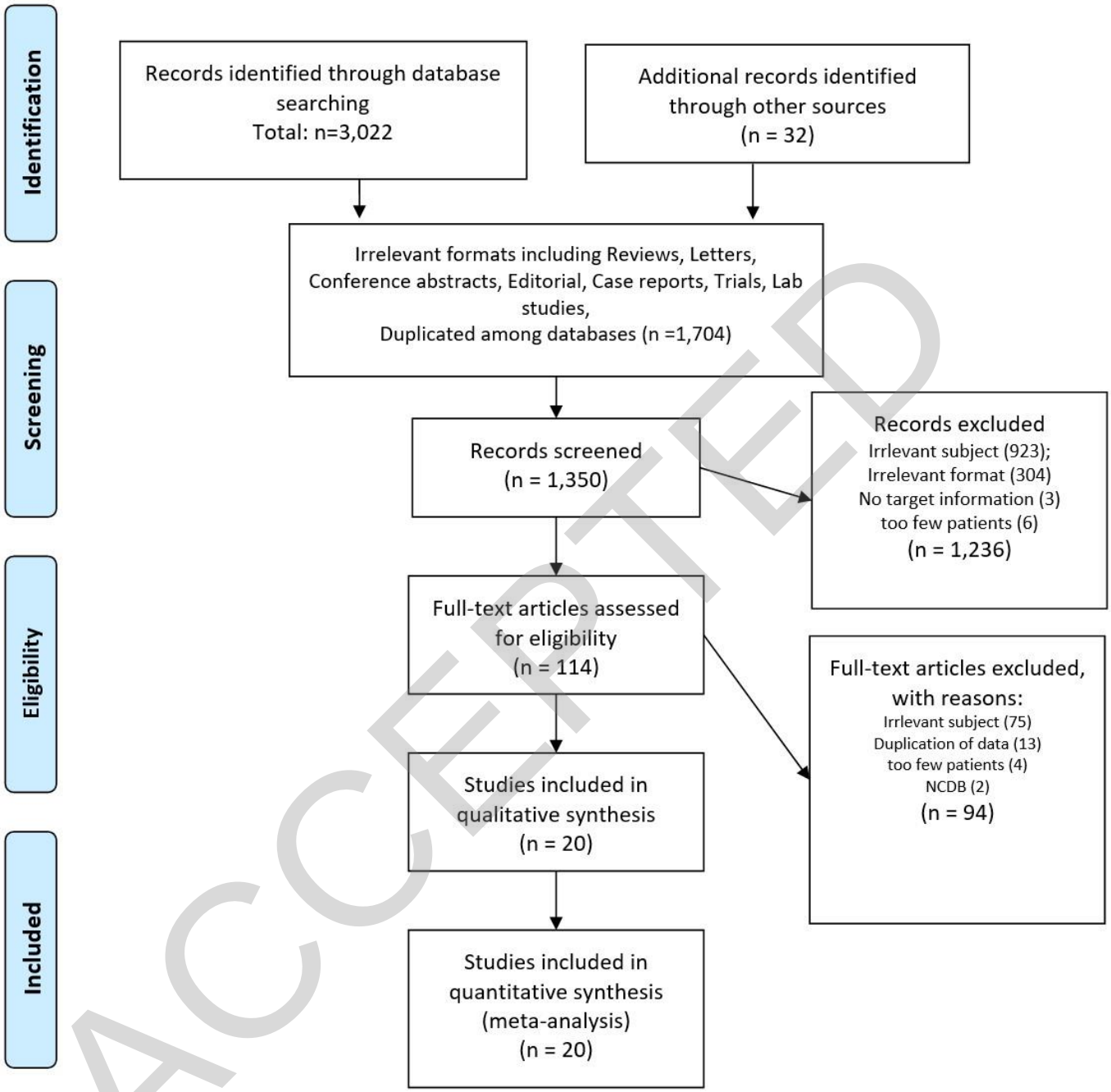

Figure 2. Forest plots of pooled analyzing (A) overall survival of all studies (above) and randomized studies (below) (B) progression-free survival of all studies (above) and randomized studies (below).

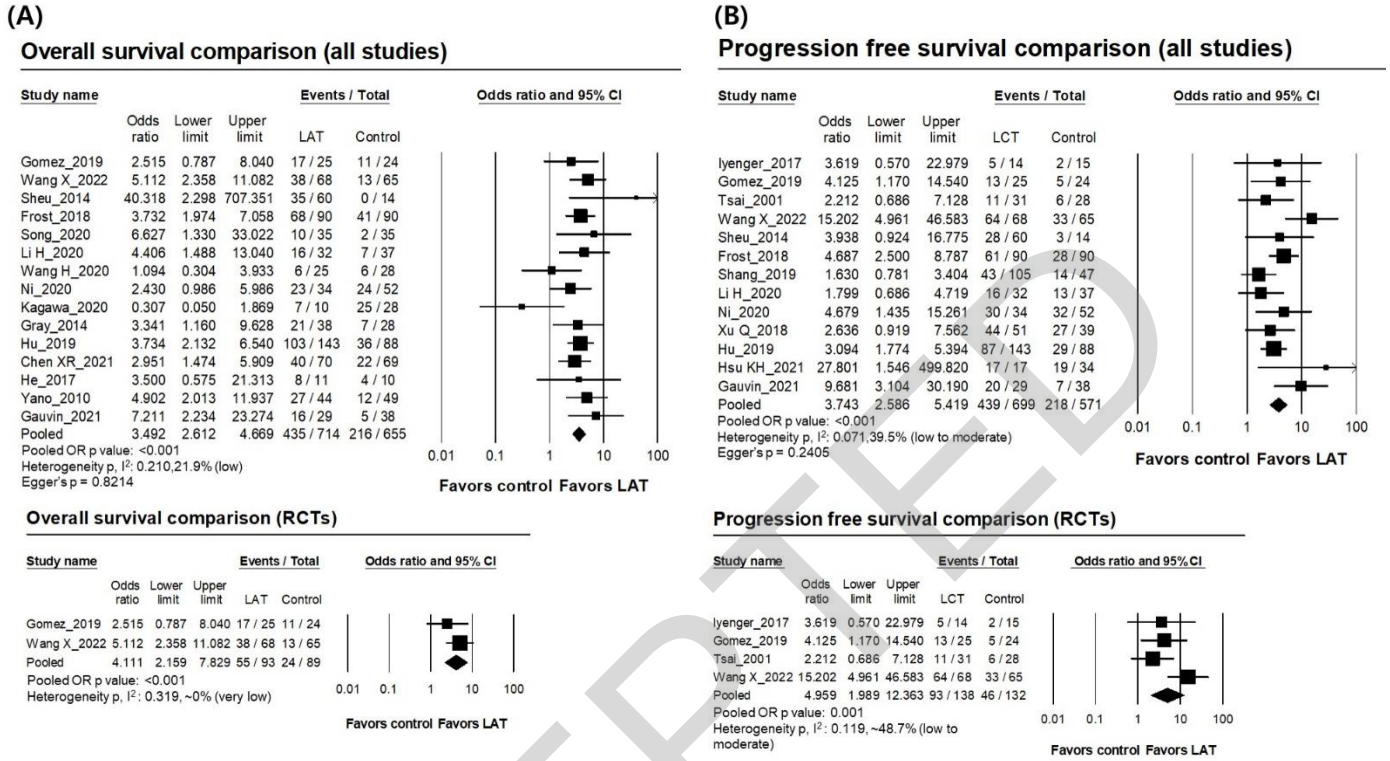

Figure 3. Pooled percentile of (A) overall survival and (B) progression-free survival

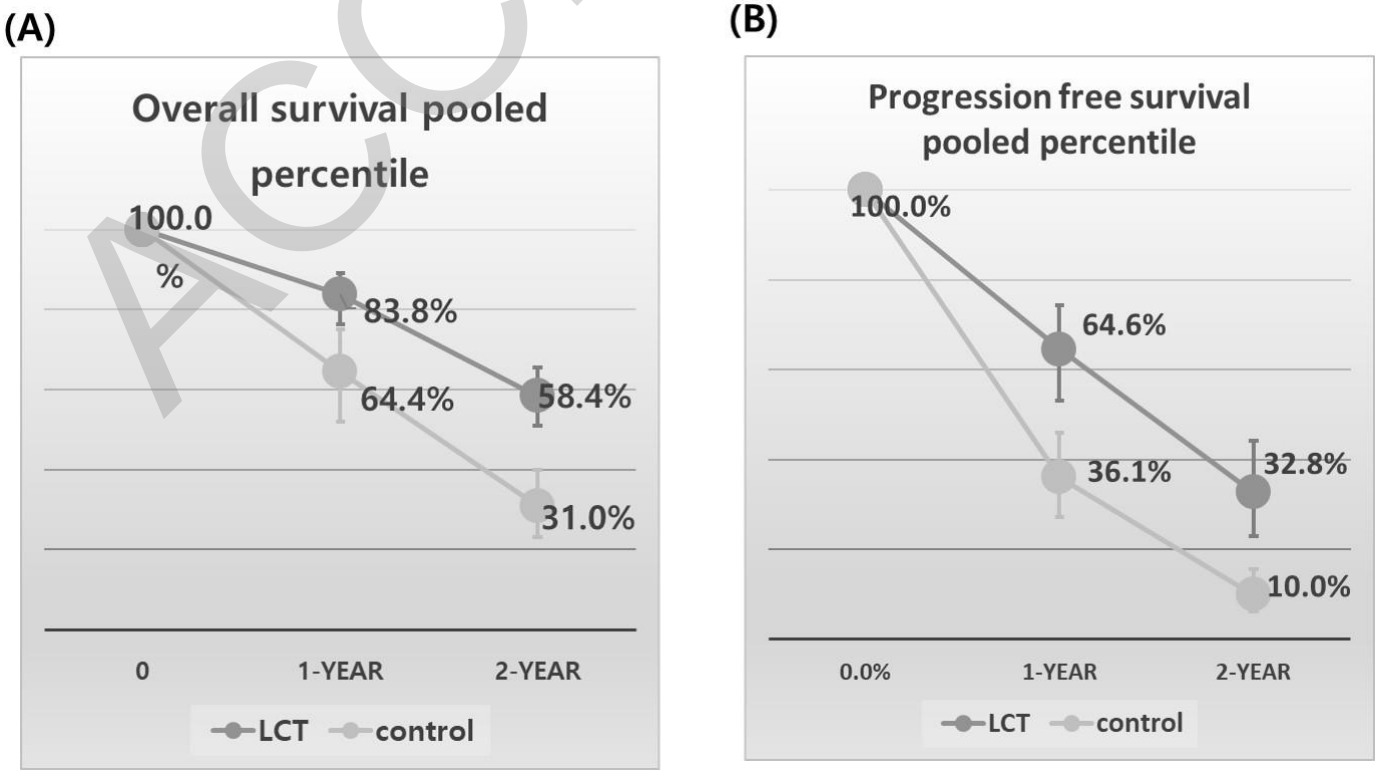

Table 1. General information of included studies

Author, publication year, country	Patient recruit	LCT group compared to control	No. of patients	Specific disease entity of OM	Category of OM	Defined No. of oligomets.	LCT modality	OS benefit (Median months, p)	PFS benefit (Median months, p)	Conflicts of interest
Iyenger, 2017 US	2014–2016	RCT	29	SD or PR after 1st line CTx.	Oligopersistence	≤6 (including primary) in 3 organs	SBRT		9.7 vs 3.5, 0.01	None
Gomez, 2019 US & UK	2012–2016	RCT	49	SD or PR after 1st line CTx.	Oligopersistence	≤3	SBRT, hypofx., CCRT or surgery	41.2 vs. 17, p=0.017	14.2 vs. 4.4, 0.022	None
Tsai, 2021 US	2019–2021	RCT	59	PD after 1st line CTx.	Oligoprogression	≤5 extracranial lesions	SBRT		10.3 vs. 2.1, 0.001	Industrial
Wang X, 2022, China	2016–2018	RCT	133	Treatment naïve	Synchronous	≤5 in ≤2 organs	SBRT	25.5 vs. 17.6, <0.001	20.2 vs. 12.5, <0.001	Government, academic
Sheu, 2014 US	1998–2012	PSM	74	Persistence after CTx. Or CCRT	Oligopersistence	≤3	RT and/or surgery		46.7 % vs. 18.2 % at 1 year, <0.01	None
Frost, 2018 Germany	2000–2016	PSM	180	Dx. Of OM within 90 days of initial Dx.	Synchronous	1–4 in one organ	SBRT, CCRT, or surgery	60.4 vs 22.5, <0.001	25.1 vs. 8.2, <0.001	None
Song, 2020 China	2005–2019	PSM	70	N/A	N/A	≤5	RT and/or surgery			None
Shang, 2019 China	2005–2016	no significant difference except mets. locatio	152	≥6 months DFI after surgery	Oligorecurrence	≤5	RT or RFA	19 vs. 20, 0.519	10 vs. 7, 0.006	None

		n								
Li H, 2020 China	2014–2018	no significant difference	69	Synchronous	Synchronous	≤5	Brachtherapy	17.6 vs 11.2, 0.042	11.6 vs. 6.3, 0.036	Government
Wang H, 2020 China	2013–2018	no significant difference	53	Repeat oligoprogression	Oligoprogression	≤5	Brachtherapy	12.8 vs. 15.2, 0.847		Government
Ni, 2020 China	2015–2018	no significant difference	86	SD or PR after 1st line CTx.	Oligopersistence	≤5	RFA (MWA)	34.8 vs. 22.7, 0.04	16.7 vs. 12.9, 0.02	None
Kagawa, 2020 Japan	2013–2018	no significant difference	38	PD after 1st line CTx.	Oligoprogression	≤3, single organ	RT or surgery			Industrial
Gray, 2014 US	2000–2011	younger age (p=0.027)	66	Primary and synchronous brain mets	Synchronous	≤4, brain only	RT (thorax and brain) or surgery	26.4 vs. 10.5, <0.001		Industrial
Xu Q, 2018 China	2010–2016	Lower T and N stage	90	SD or PR after 1st line CTx.	Oligopersistence	≤5	RT and/or surgery	40.9 vs. 30.8, <0.001	20.6 vs. 13.9, <0.001	None
Hu, 2019 China	2010–2016	more brain mets, fewer lung mets. (P<0.001)	231	SD or PR after 1st line CTx.	Oligopersistence	≤5, single organ	RT and/or surgery	34 vs. 21, 0.001	15 vs 10, <0.001	None
Chen XR, 2021 China	2004–2018	less advanced primary, more neurologic symptom	139	Synchronous brain mets. at Dx.	Synchronous	≤3	RT and/or surgery	33.2 vs. 16.8, 0.002		Government
He, 2017 China	2003–2013	N/A	21	Synchronous and oligorecurrence after	Oligorecurrence and/or synchronous	≤3, lung	Surgery	37 vs. 11.6, 0.026		None

surgery

Yano, 2010 Japan	1994–2004	N/A	93	Postoperative recurrence	Oligorecurrence	controllable with LCT	RT or surgery	74 vs 10.9, <0.05		None
Hsu KH, 2021 Taiwan	2010–2018	N/A	51	SD or PR after 1st or 2nd line CTx.	Oilgopersistence	≤5	SBRT or RT (50-70 Gy)		Not reached vs 14.3, <0.001	None
Gauvin, 2021 Canada	2005–2015	N/A	67		Synchronous	1 M1b mets or ≤3 cerebral mets	SBRT or RT (>60 Gy) and/or surgery	26 vs 5, 0.0001	17.5 vs. 3.4, 0.001	Industrial

Abbreviations: NOS, Newcastle-Ottawa scale; NSCLC, non-small cell lung cancer; R, retrospective; N/A, not assessable; OP, operation; P, prospective; RCT, randomized controlled trial; PR, partial remission; SD, stable disease; CTx., chemotherapy; PSM, propensity score matching; TKI, tyrosine kinase inhibitor; PSA, prostate-specific antigen; RTx, radiotherapy; PS, performance status

Table 2. Subgroup analyses of endpoints

	No.studies	No. patients	Heterogeneity *p*, I^2	Heterogeneity assessment	OR (95% CI, *p*-value)
Overall survival comparison					
Synchronous	6	654	0.809, ~0%	Very low	3.981 (2.835–5.590, <0.001)
Oligopersistence	4	440	0.288, 20.2%	Low	3.355 (1.955–5.760, <0.001)
Oligoprogression/recurrence	4	205	0.029, 66.9%	Moderate	1.726 (0.519–5.739, 0.373)
Low metastatic burden	7	568	0.068, 48.9%	Low to moderate	3.243 (1.748–6.017, <0.001)
High metastatic burden	7	708	0.474, ~0%	Very low	3.532 (2.523–4.946, <0.001)
Progression-free survival comparison					
Synchronous	4	449	0.024, 68.2%	Moderate	5.631 (2.452–12.934, <0.001)
Oligopersistence	7	610	0.837, ~0%	Very low	3.484 (2.344–5.178, <0.001)
Oligoprogression/recurrence	2	211	0.666, ~0%	Very low	1.777 (0.953–3.315,

					0.07)
Low metastatic burden	4	370	0.678, ~0%	Very low	5.129 (3.186–8.256, <0.001)
High metastatic burden	9	900	0.060, 46.6%	Low to moderate	3.259 (2.010–5.283, <0.001)

Abbreviations: OR, odds ratio, CI, confidence interval