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META-ANALYSIS

Multimodal treatment improves survival in patients with lung metastases from colorectal cancer: A network meta-analysis

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Abstract

Aim: The lungs represent the second most common site of colorectal cancer metastases. Although surgery is commonly considered the best treatment, many other invasive and noninvasive procedures and treatments have been adopted to improve patient survival and there is no clear evidence in the literature of which is the more effective. The aim of this work was to identify which treatment confers the best gain in overall survival for patients with pulmonary metastases from colorectal cancer.

Method: A systematic review and network meta-analysis of survival hazard ratio (HR) including 11 studies was conducted following the PRISMA guidelines and the Cochrane protocol on PubMed, Scopus, Embase, Web of Science and Cochrane Library up to 31 December 2023. Surgery, image-guided thermoablation, stereotactic body radiotherapy, chemotherapy and best standard care, associated or alone, were evaluated. Chemotherapy was adopted as the treatment reference to define survival HRs. Network metaregression was then performed considering patients with pulmonary only or multisite metastases from colorectal cancer.

Results: In patients with pulmonary metastases, the association of surgery, stereotactic body radiotherapy and chemotherapy is the best performing (HR 0.22), while the most effective components alone are image-guided thermoablation (HR 0.53) and surgery (HR 0.57), although this was not significant. After metaregression, multimodal treatments still represent the strategy conferring the best survival gain. However, while surgery (incremental HR 0.26) has the most important role in patients with isolated pulmonary metastatic disease, chemotherapy (incremental HR 0.3) leads for patients with multimetastatic disease.

Conclusion: Multimodal treatment confers the best gain in overall survival in patients with pulmonary metastases from colorectal cancer. Combining multiple therapeutic strategies improves survival, with oligometastatic patients benefiting more from surgery and local therapies while multimetastatic patients mainly benefit from chemotherapy, although ablation and surgery can enhance outcomes when feasible.

KEYWORDS
chemotherapy, colorectal cancer, imaging-guided thermoablation, meta-analysis, pulmonary metastases, radiotherapy, surgery, survival

INTRODUCTION

Colorectal cancer (CRC) represents one of the most frequent cancers after breast and lung cancer and is one of the leading causes of cancer worldwide [1].

Although several invasive and noninvasive screening tests have been adopted to identify CRC at an early stage, 25% of patients with CRC receive their diagnosis at an advanced stage [2]. The most common metastatic site for CRC is the liver, but 15% of patients with metastatic disease present one or more lung secondary localizations [3]. Patients with pulmonary metastases from CRC have better survival outcomes than those with metastases in other sites such as the liver, brain or peritoneum. However, it is important to acknowledge that making definitive statements on this topic can be challenging due to the substantial heterogeneity among patients with oligometastatic or polymetastatic CRC [4].

Recent advances in diagnostic and therapeutic approaches have contributed to improving survival rates. The 5-year overall survival (OS) rate for patients with pulmonary metastases from CRC now exceeds 50%. In cases of isolated lung metastases, the 5-year OS rate can reach up to 68% following surgical metastasectomy [5].

The surgical resection of pulmonary metastases from CRC has been traditionally regarded as the gold standard treatment whenever feasible. However, the medical literature lacks high-quality evidence demonstrating the benefits of surgery, with most support coming from retrospective studies.

Recently, alternative procedures and treatments, such as image-guided thermoablation (IGTA), stereotactic body radiotherapy (SBRT) and chemotherapy, have attracted growing interest in this field. They have shown promising results in improving disease-free survival and OS. A recent meta-analysis [4] has evaluated the survival benefits of surgery compared with local ablative treatments, chemotherapy and simple observation, but did not estimate the survival results for each individual procedure compared with surgery or each other.

The purpose of this systematic review and network meta-analysis (NMA) is to determine which treatment is most effective in extending survival for patients with pulmonary only or multimetastatic CRC.

METHOD

The systematic review and NMA protocol were registered on PROSPERO (ID CRD42023431392).

Search strategy

We screened the Embase, PubMed, Cochrane Library, Scopus and Web of Science databases up to 28 February 2023 as suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines [5, 6]. The corresponding checklists were completed showing full compliance of our research to both protocols. We additionally searched for further studies eligible for inclusion in the references of the reviews and meta-analyses on the topic.

Selection criteria

A specific population (P), intervention (I), comparator (C), outcome (O) and study design (S) (PICOS) framework was specified to define study eligibility, as recommended:

- Population (P): patients affected by single or multiple lung metastasis from CRC.
- Intervention (I) and comparison (C): any procedure proposed with curative or palliative intent, including surgery, IGTA, chemotherapy, SBRT and best standard care (BSC).
- Outcomes (O): survival hazard ratio (HR).
- Study design (S): retrospective and prospective comparative studies.

Exclusion criteria

All noncomparative research and comparative studies evaluating different specificities in the same type of procedure (e.g. comparison of the efficacy of different means of IGTA) were deemed not eligible for inclusion [7]. Studies not clearly specifying the history of the treatments received by patients for the management of CRC and metastases were not included. Furthermore, studies not reporting at least one of the outcomes of interest were excluded. Finally, studies without available full text or with full text in a language other than English were not included.

Systematic review process

All the studies selected in the systematic review process were gathered in the Mendeley reference software (Mendeley Ltd, London, UK) which was then used to identify and remove duplicates among the initially identified records.

Information about study design and methodology, participant demographics and baseline characteristics, OS and survival HR were collected in a computerized spreadsheet (Microsoft Excel 2021; Microsoft Corporation, Redmond, WA, USA).

Primary and secondary endpoints

The primary endpoint was to determine the survival HR of each treatment compared with chemotherapy, which was outlined as the reference treatment.

Risk of bias assessment

The risk of bias was assessed using the ROBINS-I tool [8], the CINeMA framework [9] and the ROB-MEN tool [10].

Statistical analysis

Outcome measures were expressed as HR with 95% CI. When the included studies did not directly report HR with their 95% CI this was indirectly obtained from Kaplan–Meier curves and corresponding *p*-values as described by Liu et al. [11]. In multiarm trials, every intervention was included in pairwise comparisons with each treatment arm. As some treatment arms consisted of the association of multiple treatments, we conducted a component network meta-analysis (CNMA) to evaluate the effect of each component when suitable. This could also be applied to disconnected networks whose composite treatments contain common components [12]. HR resulting from CNMA was reported as incremental HR (iHR) with the corresponding 95% CI.

Heterogeneity was quantified by the I^2 statistic and Cochran's *Q*-test; cut-off values of 25%, 50% and 75% were considered as low, moderate and high, respectively [13]. Moreover, the within-design heterogeneity and between-design inconsistency were evaluated with the full design-by-treatment interaction random-effects model [14]. A fixed-effect model was chosen to compute outcomes in case of low heterogeneity; otherwise, a random-effects model was adopted. When high overall heterogeneity was found, influence analysis through the forward search algorithm by Petropoulou et al. [15] was performed to detect extreme study effects; after the exclusion of those studies, sensitivity analysis was conducted.

The number and numerosity of study designs as well as the treatments they described were graphically represented through network graphs. Direct evidence plots were produced to display the proportion of direct and indirect evidence for each network estimate. To rank the treatments for each outcome, we used P-scores [16] and the comparison between different treatments for each outcome was visually rendered through forest plots defining a comparison intervention group. Then, we conducted metaregression in order to further reduce inconsistency.

Netheat plots allowed the representation of inconsistency in our network model, and which designs mostly contributed to it. Inconsistency between direct and indirect estimates and whether it was significant or not was estimated through net splitting.

Funnel plots were developed to explore publication bias and Egger's test of the intercept was used to quantify the asymmetry of funnel plots when feasible.

Statistical analysis was conducted with R statistical software (The Comprehensive R Archive Network—CRAN, ver. 4.0.0 x64) [17], using "meta", "netmeta", and "NMAoutlier", "dmetar", and "IPDfromKM" packages [11, 18–21].

RESULTS

The initial search selected 9219 articles for the initial screening. The whole systematic review process is reported in Figure S1 and the characteristics of the included studies are summarized in Table 1.

We conducted HR NMA on 11 studies [22–32] including 3100 patients. Analysis evaluated five different components (surgery, chemotherapy, IGTA, SBRT, BSC) in eight treatments (surgery alone, surgery + chemotherapy, surgery + chemotherapy + SBRT, IGTA, IGTA + chemotherapy, chemotherapy alone, SBRT alone, BSC). Sixteen pairwise comparisons made up the NMA structure, which is visually rendered in Figure 1.

As heterogeneity and inconsistency were elevated (I^2 = 73.7%, 95% CI 48.7%–86.5%), a random-effects model was adopted. Treatment ranking, based on P-scores, showed that the best treatment to confer increased survival in patients with lung metastases from CRC was the association of surgery, SBRT and chemotherapy (P-score = 0.9453). For this treatment, NMA resulted in a survival HR = 0.22 (95% CI 0.09–0.53; p = 0.0006) compared with chemotherapy, which was defined as the reference treatment. Survival HR for each of the other treatments compared with chemotherapy was: 0.39 for IGTA + chemotherapy, 0.41 for surgery + chemotherapy, 0.53 for IGTA alone, 0.57 for surgery alone, 0.73 for SBRT alone and 3.57 for BSC. HR NMA results are visually reported in Figure 2.

CNMA permitted us to further evaluate survival iHR for each component without the effect of associations in multiple treatments. IGTA was the component with the lowest iHR (0.39, 95% CI 0.15–0.99) followed by surgery (0.41, 95% CI 0.27–0.64), SBRT (0.54, 95% CI 0.27–1.01), chemotherapy (0.73, 95% CI 0.29–1.83) and BSC (2.61, 95% CI 0.69–9.90).

Sensitivity analysis was not performed as we failed to identify one or more specific studies which were mainly responsible for high heterogeneity and inconsistency.

In a further attempt to reduce inconsistency, we conducted metaregression using metastasis site information as the regressor. Thus, new NMA were conducted including

1. 1022 patients with colorectal metastases isolated to the lungs
2. 2078 patients with lung and at least one other site of metastatic disease (liver, peritoneum, brain, etc.) from CRC.

Details concerning the HR NMA result and P-scores for each treatment are provided in Table 2.

Pulmonary-only metastatic disease

The analysis, exclusively including patients with metastatic disease isolated to the lungs, was performed on five studies [22–26] reporting 10 pairwise comparisons of four components (surgery, chemotherapy, SBRT and BSC) associated in five treatments (surgery + chemotherapy, surgery alone, chemotherapy alone, SBRT alone, and

TABLE 1 Characteristics of the included studies.

Author	Year	Country	Procedure, *n*	3-year OS (%)	5-year OS (%)	Study characteristics
Andres et al.	2015	Switzerland, France, Spain, Portugal, Belgium	Surgery + CT 149 CT 285	69.8 40	40.7 9.4	Retrospective, multicentric
Chua et al.	2010	Austria	IGTA 41 IGTA + CT 59	24.4 66.1	– –	Retrospective, monocentric
Hansdotter et al.	2023	Sweden	Surgery + CT 29 Surgery 33 CT 27 BSC 10	93.1 75.8 25.9 10	72.4 54.6 7.4 0	Retrospective, monocentric
Filippi et al.	2016	Italy	Surgery 142 SBRT 28	– –	– –	Retrospective, monocentric
Karam et al.	2022	France	Surgery 66 IGTA 81	80 80.2	72 64	Retrospective, monocentric (PSM)
Lee et al.	2022	Korea	Surgery + SBRT + CT 463 CT 670	86 28	71.2 14.2	Retrospective, monocentric
Meimarakis et al.	2013	Germany	Surgery + CT 30 CT 30	83 38	59 20	Retrospective, monocentric (PSM)
Milosevic et al.	2020	Serbia, United Kingdom	Surgery + CT 46 CT 47	70 69	36.4 29.6	RCT, multicentric
Tampellini et al.	2012	Italy	Surgery + CT 50 CT 104	92 45	70 11	Retrospective, multicentric
Tselikas et al.	2020	France	Surgery 78 IGTA 126	67.2 72.1	56 38	Retrospective, bicentric
Widder et al.	2013	Netherlands	Surgery 68 SBRT 42	62 60	41 49	Retrospective, monocentric

Abbreviations: BSC, best standard care; CT, chemotherapy; IGTA, image-guided thermoablation; PSM, propensity-score match; RCT, randomized clinical trial; SBRT, stereotactic body radiation.

BSC) with three different designs (Figure 3A). Heterogeneity and inconsistency were still elevated (I^2=83.2%, 95% CI 57.2%–93.4%) and a random-effects model was adopted.

Surgery + chemotherapy had the lowest HR (HR=0.26) compared with chemotherapy alone. SBRT resulted in HR=0.34, surgery was associated with HR=0.34 and for BSC HR=2.92. Figure 4A reports the forest plot of HR NMA for all the treatments compared with chemotherapy.

After CNMA, SBRT had the lowest iHR (iHR=0.26, 95% CI 0.04–1.57; p=0.1419) followed by surgery (iHR=0.26, 95% CI 0.08–0.85; p=0.0262), chemotherapy (iHR=0.77, 95% CI 0.13–4.65; p=0.7795) and BSC (iHR=2.26, 95% CI 0.23–22.40; p=0.4866).

Multimetastatic disease

For patients with multimetastatic disease, we included six studies in the NMA [27–32] reporting six pairwise comparisons of six different treatments (chemotherapy alone, IGTA alone, IGTA + chemotherapy, surgery alone, surgery + chemotherapy, and surgery + SBRT + chemotherapy) constituting four components (chemotherapy, IGTA, surgery, and SBRT) that were compared in four different study designs structured in two detached subnetworks (Figure 3B). As chemotherapy and surgery were evaluated in both subnetworks as single components of different treatment associations it was possible to compare all treatments and components for multimetastatic patients through CNMA. No inconsistency or heterogeneity were found (I^2=0%, 95% CI 0%–89%) so a common effect model was used.

The best advantage in survival, compared with chemotherapy, was associated with surgery + SBRT + chemotherapy (HR=0.33, 95% CI 0.25–0.43; p=0.0001; P-score=0.9405) followed by IGTA + chemotherapy (HR=0.41, 95% CI 0.26–0.64; p=0.0001), surgery + chemotherapy (HR=0.48, 95% CI 0.34–0.67; p=0.0001), IGTA (HR=1.35, 95% CI 0.38–4.85; p=0.6428) and surgery (HR=1.59, 95% CI 0.46–5.5; p=0.4646). The P-score for chemotherapy alone was 0.2893. The effects on survival of each treatment compared with chemotherapy are summarized in Figure 4B.

Analysis of the incremental effect of each component showed that chemotherapy had the lowest iHR (iHR=0.3, 95% CI 0.09–0.99; p=0.0478) followed by IGTA (iHR=0.41, 95% CI 0.26–0.64; p=0.0001), surgery (iHR=0.48, 95% CI 0.34–0.67; p=0.0001) and SBRT (iHR=0.69, 95% CI 0.45–1.07; p=0.1002).

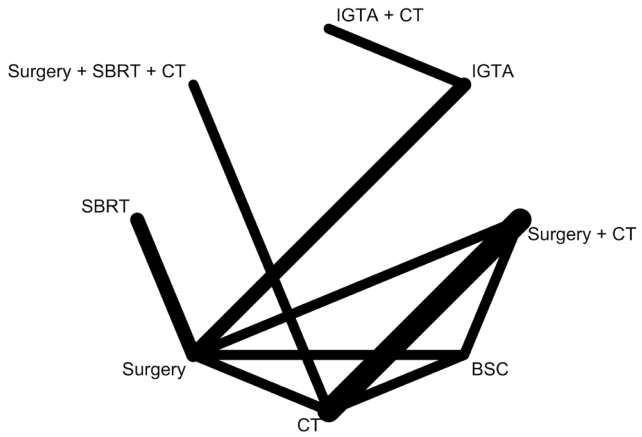

FIGURE 1 Netgraph summarizing the study designs of the 11 studies included in the network meta-analysis. BSC, best standard care; CT, chemotherapy; IGTA, image-guided thermoablation; SBRT, stereotactic body radiotherapy.

Risk of bias and publication bias

The analysis of risk of bias showed the presence of overall low and moderate risk through the different treatment comparisons. When risk was moderate, this was mainly due to moderate and high risk of within-study bias and to the presence of incoherence.

To assess publication bias we produced a comparison-adjusted funnel plot, which is reported in Figure S2. The corresponding Egger's test of the intercept did not show funnel plot asymmetry (p=0.3816).

DISCUSSION

Pulmonary metastases from CRC represent a frequent issue, and their management is still a subject of debate. Various strategies have

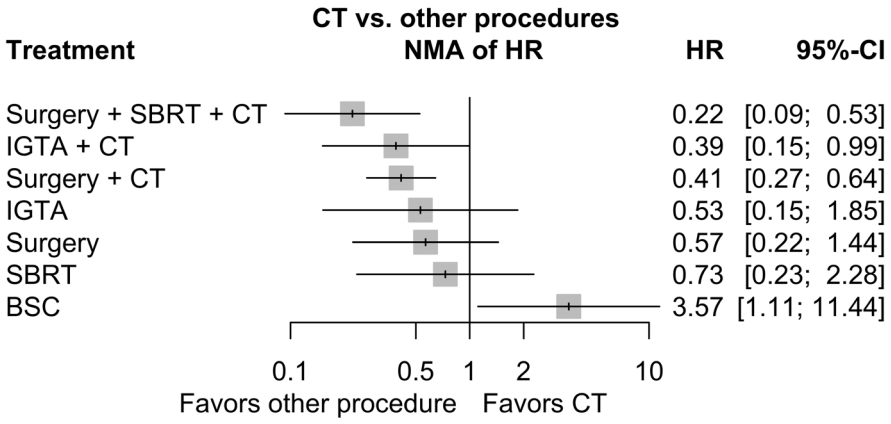

FIGURE 2 Forest plot showing the results of hazard ratio (HR) network meta-analysis (NMA) for all the included treatments compared with chemotherapy (CT). BSC, best standard care; IGTA, image-guided thermoablation; SBRT, stereotactic body radiotherapy.

TABLE 2 Results of hazard ratio (HR) network meta-analysis.

	All patients			Lung only			Multimetastatic		
Treatment	**P-score**	**HR**	***p***	**P-score**	**HR**	***p***	**P-score**	**HR**	***p***
Surgery + SBRT + CT	**0.9453**	0.22 (0.09–0.52)	0.0006				**0.9405**	0.33 (0.25–0.43)	0.0001
IGTA + CT	0.7086	0.38 (0.15–0.99)	0.0485				0.8074	0.41 (0.26–0.64)	0.0001
Surgery + CT	0.6694	0.41 (0.27–0.64)	0.0001	**0.7948**	0.26 (0.08–0.85)	0.0262	0.625	0.48 (0.34–0.67)	0.0001
IGTA	0.546	0.53 (0.15–1.85)	0.3197				0.2527	1.35 (0.38–4.85)	0.6428
Surgery	0.5204	0.57 (0.22–1.44)	0.2328	0.6903	0.34 (0.06–1.92)	0.2208	0.0851	1.59 (0.46–5.5)	0.4646
SBRT	0.3781	0.73 (0.23–2.28)	0.5883	0.6775	0.34 (0.04–3.05)	0.3321			
CT	0.2255	Reference treatment	–	0.2923	Reference treatment	–	0.2893	Reference treatment	–
BSC	0.0065	3.57 (1.11–11.44)	0.0324	0.0451	2.92 (0.49–17.44)	0.2406			

Note: The highest P-score for each category of patients is reported in bold.

Abbreviations: BSC, best standard care; CT, chemotherapy; IGTA, image-guided thermoablation; SBRT, stereotactic body radiation.

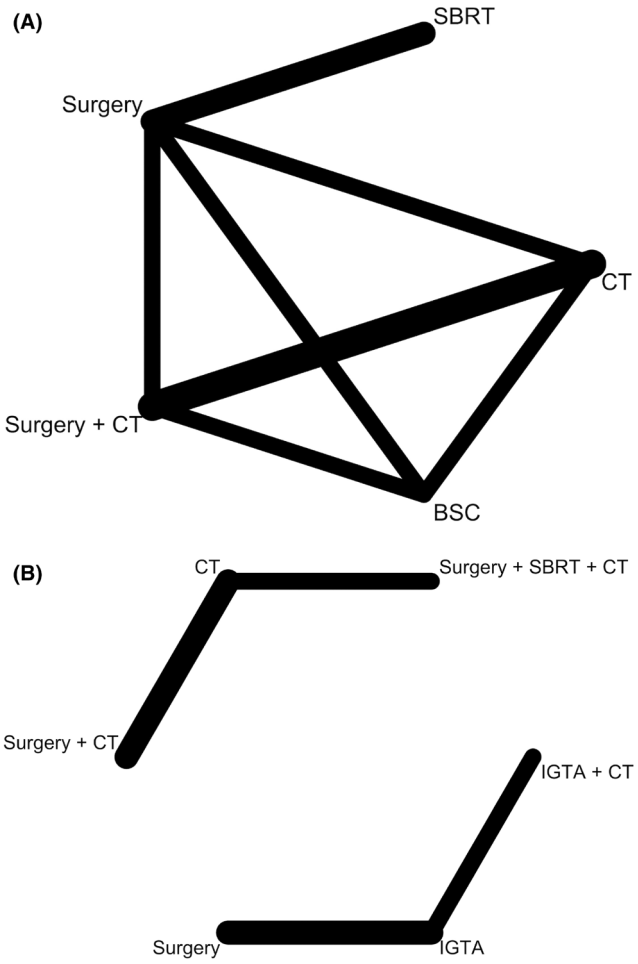

FIGURE 3 (A) Netgraph summarizing the study designs of the five studies concerning patients with pulmonary-only metastases included in network meta-analysis (NMA). (B) Netgraph summarizing the study designs of the five studies concerning patients with multimetastatic disease included in NMA. BSC, best standard care; CT, chemotherapy; IGTA, image-guided thermoablation; SBRT, stereotactic body radiotherapy.

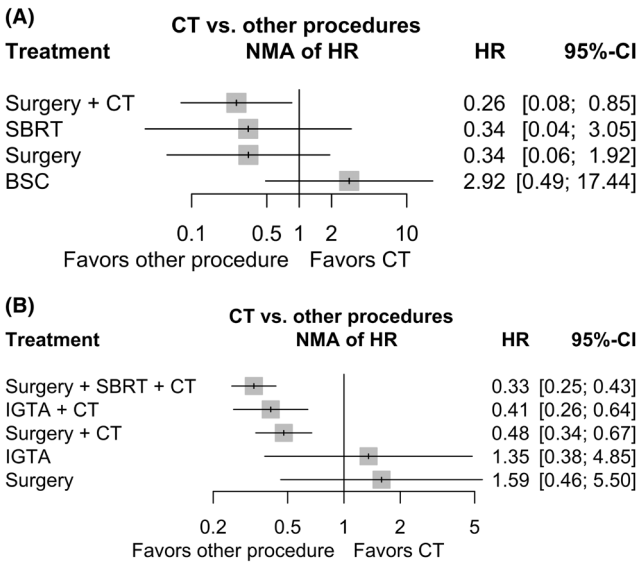

FIGURE 4 (A) Forest plot showing the results of hazard ratio (HR) network meta-analysis (NMA) for all the included treatments for patients with pulmonary-only metastases compared with chemotherapy (CT). (B) Forest plot showing the results of HR NMA for all the included treatments for patients with multimetastatic disease compared with CT. BSC, best standard care; CT, chemotherapy; IGTA, image-guided thermoablation; SBRT, stereotactic body radiotherapy.

been proposed in single- and multicentre retrospective series, but strong evidence on the most advantageous procedure is lacking. Consequently, we conducted this NMA with the intention of identifying which treatment combination most extends survival for patients with pulmonary metastases from CRC to determine whether an aggressive multimodal approach, entailing repeated local and systemic treatments, is superior to a more conservative approach. Furthermore, we sought to determine if a specific local treatment is more effective than others in improving survival.

First, the results of this NMA underline the importance of both systemic and local treatments and their association. As a matter of fact, all the strategies including chemotherapy and surgery, SBRT or IGTA had lower HR than the single treatments alone. It is important to highlight how this was true when considering both patients with metastatic disease confined to the lung and those with extrapulmonary metastatic disease. Multimodal treatment has progressively become the reference for most cancers and advanced CRC appears to adhere to this trend. As metastatic disease to the liver represents the most common condition, most of the research has focused on finding the best strategy to improve survival for these patients. The combination of chemotherapy, surgery, IGTA and other local ablative treatments such as SBRT, transarterial chemoembolization and transarterial radioembolization is now what is globally recommended in international guidelines, and the strategy is evolving towards personalized individual treatment [33]. However, except for some chemotherapy regimens, the evidence sustaining the superiority of one approach over another for hepatic and, especially, extrahepatic CRC metastases remains limited to moderate, low and very low grade recommendations [34, 35] based on retrospective series.

One of the largest contributions to this topic is a recent study by Zhang et al. [36] on 82 609 patients from the US National Cancer Database; this reported the best advantage in survival being obtained with the association of chemotherapy and lung metastasis resection for either isolated pulmonary (HR = 0.33) or simultaneous pulmonary and liver CRC metastases (HR = 0.51). This study was excluded from our analysis as some included patients underwent metastatic treatment without having surgery for the primitive CRC and this group of patients was used as reference for survival analysis.

The only randomized clinical trial focused on pulmonary CRC metastases treatment has increased the uncertainty around the utility of surgical metastasectomy. The PulMiCC multicentre randomized clinical trial aimed to compare the 3- and 5-year OS of patients with pulmonary CRC metastases (without liver metastases or with already treated and fully controlled liver metastases) undergoing lung resection(s) or active monitoring, which could include systemic treatment but no local ablative therapies. Due to recruitment difficulties, the study was closed early, thereby preventing the extrapolation of definitive results. Although the authors reported a nonsignificant HR of 0.82 (0.43–1.56) favouring surgical treatment, and suggested that surgery could possibly confer a survival advantage [37], further analysis on this cohort of patients published just 1 year later revealed no survival advantage between the surgical and active monitoring groups (HR = 0.93, 0.56–1.56) [24]. Nevertheless, the reliability of these results is quite low due to the small size of the included population and the fact that, after initial randomization, patients could receive systemic and local ablative treatments in both arms, depending on local management strategies.

In contrast, our NMA demonstrates that surgical, nonsurgical local and systemic treatments play a crucial role in extending patient survival, with different efficacy depending on disease characteristics. For patients with isolated pulmonary metastases, surgery and local ablative treatments perform better than chemotherapy alone; in particular, the combination of surgery and chemotherapy is the only treatment associated with a significant 74% gain in survival compared with chemotherapy alone. Moreover, incremental analysis confirmed the leading role of surgery, which was the only component associated with a significant survival gain. SBRT and chemotherapy had a nonsignificant tendency towards survival gain, while BSC was associated with worse outcomes. These findings probably depend on the fact that patients with isolated pulmonary metastases are more likely to have limited disease spread that can be controlled through a complete R0 metastasectomy, with chemotherapy playing a role of reinforcement. Unfortunately, the role of IGTA and its association with chemotherapy could not be evaluated in this setting.

Concerning patients with multimetastatic disease, our research further highlights the importance of multidisciplinary discussion and management for this disease. The combination of surgery, SBRT and chemotherapy showed the best results, with a significant 67% survival benefit. The other component associations also had significant favourable outcomes: IGTA + chemotherapy (HR = 0.41) and surgery + chemotherapy (HR = 0.48). However, when considered alone, surgery and local ablative treatments were inferior to chemotherapy. This was confirmed by incremental analysis that showed that chemotherapy was the component associated with the best increase in survival (iHR = 0.3) in this specific population. This is not surprising considering that these patients already experienced a more extensive spread of the disease and systemic treatment is the most suitable approach for controlling overall disease progression, while surgery and local ablative treatments can contribute to localized disease management.

To the best of our knowledge, this systematic review and NMA is the first research to analyse the contribution of each treatment component to survival gain and the second meta-analysis on this subject. However, it has several notable limitations.

Firstly, most of the included studies were retrospective, thereby increasing the risk of within-study bias. Low and moderate risk of bias were identified using the CINeMA framework. Two items primarily contributed to the increased risk of bias where overall moderate risk was identified: within-study bias and incoherence. The presence of within study bias solely depended on bias due to confounding. As a matter of fact, in some of the included studies the assigned treatment depended on some baseline patient characteristics that could affect survival (e.g. the number, size and contact with major vessels of the pulmonary metastases). Therefore, populations receiving different treatments were dissimilar in cancer-related baseline characteristics. This aspect, although not predominantly, may have also influenced the choice of the type of chemotherapy delivered, adding an additional factor of heterogeneity in the populations considered. On the other hand, the included studies detailing which chemotherapy protocols were used in the study populations showed no differences between treatment groups. Concerning incoherence, this was mainly detected in those treatment comparisons supported by direct

evidence from only one included study. Incoherence is defined as disagreement between direct and indirect evidence in NMA and can be determined by limitations in study design, publication bias, and differences in patients, treatments and evaluated outcome characteristics [38]. The latter was likely the most common source of incoherence in our research.

Secondly, considering populations that are inherently varied, increased heterogeneity was found in the analysis. This represents a common issue concerning meta-analysis, especially when focusing on oncological diseases whose characteristics can vary depending on a multitude of features and treatment strategies that change among different centres. However, this issue was addressed through metaregression which allowed us to reduce heterogeneity and identify different survival benefit patterns for each treatment component depending on patient characteristics.

The treatment of lung metastases from CRC presents several knowledge gaps, including unclear criteria for selecting patients for metastasectomy and varying definitions of resectability. The optimal use of local therapies such as SBRT and IGTA, compared with surgery, remains uncertain, and the best combination of surgery, local therapies and systemic treatments is still not well-defined. Additionally, the role of biomarkers (e.g. RAS, BRAF) in predicting treatment response and survival is limited, and the timing of systemic therapies, particularly neoadjuvant versus adjuvant chemotherapy, is debated. The effectiveness of immunotherapy in this context is also unclear, and there are limited long-term data on survival and quality of life. Our systematic review and network meta-analysis found that combining multiple therapeutic strategies improves survival, with oligometastatic patients benefiting more from surgery and local therapies, while multimetastatic patients mainly benefit from chemotherapy, although ablation and surgery can enhance outcomes when feasible.

Despite these limitations, this is the first systematic review and NMA on this topic, performed following the most up-to-date methodological findings and recommendations, using multiple tools to extrapolate unpublished survival data to increase the number of included studies and improve the quality of our results. Further prospective and randomized trials evaluating the effects on survival of surgery, local ablative treatments and chemotherapy, either alone or in combination, are needed to confirm these results.

CONCLUSION

Multimodal treatment involving surgery, local ablative procedures and chemotherapy provides survival benefits to patients with pulmonary metastases from CRC. For patients with metastases confined to the lungs, surgery is the most effective procedure, especially when combined with systemic treatment. Patients with multimetastatic disease have the best survival improvement with chemotherapy compared with surgery and local ablative procedures alone, and their association gives further gain in survival.

As these findings are primarily derived from retrospective research, additional high-quality studies are needed to investigate the efficacy of surgery, local ablative treatments and chemotherapy on lung CRC metastases.

AUTHOR CONTRIBUTIONS

Andrea Chierici: Conceptualization; methodology; formal analysis; writing – original draft. **Danilo Vinci:** Investigation; data curation. **Guido Liddo:** Visualization; writing – review and editing. **Stefano Granieri:** Writing – review and editing; supervision. **Mauro Loi:** Supervision; validation. **Marco Alifano:** Writing – review and editing; supervision. **Antonio Iannelli:** Project administration; writing – review and editing.

FUNDING INFORMATION

Nothing to declare.

CONFLICT OF INTEREST STATEMENT

Nothing to declare.

DATA AVAILABILITY STATEMENT

All relevant data are within the manuscript and its supporting information files. Any complemental data is available through direct and motivated request to the corresponding author.

ETHICS STATEMENT

Ethical committee approval was deemed unnecessary due to the anonymous nature of data.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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