Evaluation of the Prognostic Role of Liver Metastases on Patient Outcomes: Systematic Review and Meta-Analysis

Jessica J. Waninger, MD, PhD[1], **Vincent T. Ma, MD**[2,3], **Zoey Chopra, BS**[4], **Ashley N. Pearson, BS**[5,6], **Michael D. Green, MD PhD**[5,6,7,8]

[1]Department of Ophthalmology, University of Michigan, Ann Arbor, MI.

[2]Department of Internal Medicine, Division of Hematology, Medical Oncology, and Palliative Care, University of Wisconsin, Madison, WI.

[3]Department of Internal Medicine, Division of Hematology and Medical Oncology, University of Michigan, Ann Arbor, MI

[4]Department of Economics, University of Michigan, Ann Arbor, MI,

[5]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI.

[6]Rogel Cancer Center, University of Michigan, Ann Arbor, MI.

[7]Department of Microbiology and Immunology, University of Michigan, Ann Arbor, MI 48109, USA

[8]Department of Radiation Oncology, Veterans Affairs Ann Arbor Healthcare System, Ann Arbor, MI 48109, USA

Abstract

The liver is a common site of metastasis for many primary malignancies, but the quantitative impact on survival is unknown. We performed a systematic review and meta-analysis of 83 studies (604,853 patients) assessing the overall hazard associated with liver metastases by primary tumor type and treatment regimen. The pooled overall survival HR (95% CI) for all included studies was 1.77 (1.62, 1.93). Patients with breast cancer primaries fared the worst (HR: 2.37, 95% CI: 1.64, 3.44), as did patients treated with immunotherapies (HR: 1.86, 95% CI: 1.42, 2.42). Liver metastases negatively impact survival, necessitating new approaches to disease management.

Introduction

The primary cause of cancer related deaths are due to metastasis—the dissemination and colonization of tumor cells to distant body sites[1,2]. As such, the clinical and pathological staging systems for most solid tumors take into account distant metastases and thereby stratify patients into separate prognostic and treatment groups[3]. One of the most common metastatic sites regardless of primary malignancy is the liver[4,5]. Though many studies

Correspondence: Michael D. Green, 1301 Catherine Street Ann Arbor MI 48104; Phone: 734-936-4300; Fax: 734-763-7371 migr@med.umich.edu.

have shown liver metastases to be a poor prognostic feature[6–8], formal analysis of their contribution to patient survival outcomes is limited.

Furthermore, the advent of immune checkpoint inhibitors (ICIs), such as those targeting cytotoxic T-lymphocyte-antigen 4 (CTLA-4) and programed death 1 (PD-1) have changed cancer care. Recent studies have demonstrated a negative association between liver metastasis and efficacy of ICI[9–14]. The liver is known to create an immunosuppressive environment[15] and recent work in our lab has shown that liver metastases modulate anti-tumoral immunity and thereby reduce the efficacy of ICI[16]. Despite a growing body of literature pointing to the negative prognostic role of liver metastases in patient survival, there are, to our knowledge, no systematic reviews or meta-analyses evaluating this effect.

Here we performed a systematic review of the literature for studies documenting the hazard associated with liver metastases. Given what we know about how the liver engages with the immune system we expect that all patients with liver metastases, regardless of their primary malignancy, will have poorer outcomes compared to patients with metastatic involvement at other body sites. To assess this, we performed a subset analysis by primary malignancy. We also stratified studies by the treatment type to understand if patients with liver metastases on particular therapies, whether it be cytotoxic, targeted, or ICI, fare worse. Finally, since non-small-cell lung cancers (NSCLC) frequently metastasize to the liver and this is one of the primary histologies for which ICI is approved, we analyzed the relative effect of liver involvement by treatment type.

Methods

Search Strategy and selection criteria

We performed a systematic search of published literature by primary malignancy from September 2020 to February 2021 in three databases: MEDLINE, EMBASE, and ClinicalTrials.gov. We also reviewed abstracts from major conference proceedings. To be included in this meta-analysis the study had to provide overall survival outcomes data in the form of hazard ratios (HR) for patients with liver metastases compared to other sites of disease. In the event that a hazard ratio was not reported median survival times were used as an approximation of hazard. All study types, including clinical trials, prospective and retrospective/observational studies, were included in the search. Three reviewers (JW, MG, VM) independently searched the databases using predefined MESH or EMTree search terms. Pubmed MESH terms used included: "Liver Neoplasms/Secondary" AND "Prognosis" AND "[primary malignancy]" and Embase EMTree terms used included: "cancer prognosis/exp" AND "[primary malignancy]." For specific primary malignancy terms used see Table 1. Using these terms, 14,788 studies were identified. Following de-duplication and initial title and abstract screen for the appropriate search terms, 1,240 studies were included. Of these, 472 studies contained overall survival outcome measures on patients with liver metastases and were included for full text analysis. Three reviewers (JW, VM, ZC) independently assessed if studies met the predetermined criteria and a fourth reviewer, MG, was consulted in case of disagreement. All discrepancies were discussed and resolved with the consensus of all investigators. Three reviewers (JW, VM, ZC) extracted data from each study.

Data analysis

Detailed study information (first author and year of publication, study design/trial phase, number of patients, and exclusion criteria) and patient characteristics (primary cancer type, percent female, percent preserved performance status (ECOG 0–1, KPS >80%), percent of patients with liver metastases, and type of therapy) were collected. When duplicate publications were identified, only the most recent and completed reports were included. For studies with both a training and validation cohort, only the validation cohort was used. Multiple independent cohorts were used within a single study if outcomes criteria were met. The Newcastle-Ottawa Scale (NOS) was used for assessing the quality of nonrandomized studies. This system assesses the patient selection, cohort comparability, and outcome of each study using a point-based system where a maximum of 4, 2, and 3 points can be awarded in each category, respectively.

The primary endpoint was the difference in overall survival log hazard ratio between patients with liver metastases and those with other sites of metastatic disease. HRs and their 95% CI and/or p-value comparing survival outcomes between the two groups were extracted for each study. These data had to be directly accessible or computable in order for a study to be included in the final analysis. Review Manager (RevMan) as part of the Cochrane Collaboration was used to compute all pooled HRs (using a random-effects model) and tests of heterogeneity[17]. The I^2 statistic describing the percentage of the variability in effect estimate due to heterogeneity was calculated for each pooled estimate[18].

Role of the funding source

Investigator grant support did not influence the data interpretation, and the corresponding author had full access to all of the study data and had the final responsibility in submission for publication.

Results

Following our database search, 14,788 studies were identified. Ultimately 83 articles between 1982 and 2021 were selected for inclusion (Figure 1). Some articles analyzed multiple cohorts, leading to a total of 98 data points included in this analysis. 15 of 98 (15%) datapoints were extracted from prospectively conducted studies, while 83 of 98 (85%) were collected from retrospective studies. Each dataset had overall survival comparisons between patients with liver metastases and those with other sites of metastatic involvement.

The most prevalent primary malignancies included lung cancer (27.6%), prostate cancer (15.3%), breast cancer (15.3%), pancreatic cancer (7.4%) and melanoma (7.4%). Other primary histologies represented can be seen in Figure 2. Of the 604,853 patients included in this meta-analysis 40% were female, 82% had preserved performance status, and 29% had documented liver metastases. The majority of patients were treated with either cytotoxic chemotherapy (43.9%) or immunotherapy (18.4%), however, 26.5% of studies either did not report or did not stratify by treatment regimen.

All patients with liver metastases had worse survival outcomes (pooled HR: 1.77, 95% CI: 1.62, 1.93) (Figure 2). Heterogeneity was assessed using an interaction test where I^2

was 94% (Figure 3). To assess if a particular tumor type that metastasizes to the liver fare worse we calculated pooled estimates for each (Figure 4). Of the primaries with   2 studies, patients with breast cancer have more than double the risk of death associated with the development of liver metastases (HR: 2.37, 95% CI: 1.64, 3.44). Similarly, patients with pancreatic cancer (HR: 1.76, 95% CI: 2.20) and melanoma (HR: 1.73, 95% CI: 1.22, 2.44) with liver involvement had worse outcomes. Primary malignancies that had less overall hazard associated with liver metastases included nasopharyngeal carcinoma (HR: 1.38, 95% CI: 1.17, 1.61) and sarcoma (HR: 1.12, 95% CI: 0.87, 1.43), though only 3 studies for each were identified and included in the analysis.

Patients with liver involvement have been shown to have poorer survival outcomes regardless of treatment types. However, more recently, multiple studies have demonstrated that liver metastases are not only negatively prognostic but also predictive of poor responses to ICI[10,16,19]. This meta-analysis confirms poor outcomes to ICI in all patents with liver metastases compared to other metastatic sites of disease (HR: 1.86, 95% CI: 1.42, 2.42) (Figure 5). Given that immunotherapy is routinely used in patients with NSCLC, we wanted to assess if treatment with ICI vs other therapy types had a greater effect on survival in patients with liver metastases (Figure 6). Patients treated with ICI had better outcomes (HR: 1.69, 95% CI: 1.06, 2.70) compared to those treated with either chemotherapy (HR: 1.75, 95% CI: 1.22, 2.51) or targeted therapy (HR: 1.91, 95% CI: 1.22, 2.75).

Discussion

The liver serves critical functions in metabolism, detoxification, and synthesis of proteins and factors critical for fluid balance and blood clotting. We observed that the presence of liver metastases was associated with poor prognoses across all solid cancer types. Liver metastases can contribute to cancer mortality by disrupting the physiological organ functions. Pooled, prospective clinical trials in breast cancer patients treated with chemotherapy have demonstrated that liver metastases are associated with increased treatment-related adverse events, presumably secondary to altered chemotherapy metabolism[20]. In colorectal cancer patients, increases in the number and volume of liver metastases is associated with elevations in liver function tests indicative of organ damage[21]. Consistent with this, however, clinically significant alterations in liver function tests indicative of organ failure are uncommon. In a breast cancer series, less than 5% of patients presented with obstructive jaundice and only 6% of patients had abdominal ascites[22]. Registry data suggests only 1–10% of liver-related mortality is secondary to liver failure[23]. Thus, it remains unclear whether other mechanisms contribute to the poorer prognosis of patients with liver metastases.

We also observed that liver metastases are associated with poor clinical outcomes in patients receiving immunotherapy. In addition to its metabolic and synthetic functions, the liver also acts as a secondary lymphoid organ, housing a large number of innate and adaptive immune cells. The liver is uniquely capable of promoting immune tolerance to antigens through a variety of mechanisms[24]. Unexpectedly, immune tolerance mechanisms within the liver can regulate systemic immune function. This was first described more than fifty years ago when it was found that liver transplants suppressed graft rejection of other organs

both in preclinical models and patients. In cancer, hepatic immune tolerance has long been thought to be a factor which supports metastatic seeding of the liver[25]. Preclinical modeling has also found that liver metastases[20] can coopt hepatic immune tolerance mechanisms to induce resistance to immunotherapy through a variety of mechanisms. We and others have found that liver metastases can cause loss of dendritic cells and CD8^{+} T cells as well as upregulate immunosuppressive T regulatory cells and macrophages[16,26,27]. Thus, hepatic immune tolerance may contribute to the morbidity and mortality associated with liver metastases.

To our knowledge this is the first analysis comprehensively and clearly showing the negative prognostic role of liver metastases on patient outcome, however, there are limitations to consider.

Individual patient clinical, pathologic, and radiographic features were not available, preventing multivariable modeling and accounting for potential confounding variables. These variables, in addition to the inclusion of different primary tumor histologies and treatment types, added to the considerable heterogeneity seen in this analysis. Therefore, to generate more conservative estimates we used a random effects model. Additionally, all literature reviews are susceptible to positive publication bias. Nevertheless, both prospective and retrospective clinical trials consistently have found that liver metastases are associated with poor cancer outcomes. Advances in understanding how liver metastases influence cancer outcomes are needed. This knowledge is critical to the development of innovative combination treatment strategies to improve the prognosis of patients with liver metastases.

References

1. Steeg PS. Targeting metastasis. Nat Rev Cancer 2016;16(4):201–18. [PubMed: 27009393]

2. Mehlen P, Puisieux A. Metastasis: a question of life or death. Nat Rev Cancer 2006;6(6):449–58. [PubMed: 16723991]

3. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67(2):93–9. [PubMed: 28094848]

4. Budczies J, Winterfeld von M, Klauschen F, et al. The landscape of metastatic progression patterns across major human cancers. Oncotarget 2015;6(1):570–83. [PubMed: 25402435]

5. Disibio G, French SW. Metastatic patterns of cancers: results from a large autopsy study. Arch Pathol Lab Med 2008;132(6):931–9. [PubMed: 18517275]

6. Yamamoto N, Tamura T, Fukuoka M, Saijo N. Survival and prognostic factors in lung cancer patients treated in phase I trials: Japanese experience. Int J Oncol 1999;15(4):737–41. [PubMed: 10493956]

7. Selzner M, Morse MA, Vredenburgh JJ, Meyers WC, Clavien PA. Liver metastases from breast cancer: long-term survival after curative resection. Surgery 2000;127(4):383–9. [PubMed: 10776428]

8. Engstrand J, Nilsson H, Strömberg C, Jonas E, Freedman J. Colorectal cancer liver metastases - a population-based study on incidence, management and survival. BMC Cancer 2018;18(1):78–11. [PubMed: 29334918]

9. Bilen MA, Shabto JM, Martini DJ, et al. Sites of metastasis and association with clinical outcome in advanced stage cancer patients treated with immunotherapy. BMC Cancer 2019;19(1):142. [PubMed: 30755167]

10. Tumeh PC, Hellmann MD, Hamid O, et al. Liver Metastasis and Treatment Outcome with Anti-PD-1 Monoclonal Antibody in Patients with Melanoma and NSCLC. Cancer Immunol Res 2017;5(5):417–24. [PubMed: 28411193]

11. Topalian SL, Hodi FS, Brahmer JR, et al. Five-Year Survival and Correlates Among Patients With Advanced Melanoma, Renal Cell Carcinoma, or Non-Small Cell Lung Cancer Treated With Nivolumab. JAMA Oncol 2019;5(10):1411. [PubMed: 31343665]

12. Nosrati A, Tsai KK, Goldinger SM, et al. Evaluation of clinicopathological factors in PD-1 response: derivation and validation of a prediction scale for response to PD-1 monotherapy. Br J Cancer 2017;116(9):1141–7. [PubMed: 28324889]

13. Vokes EE, Ready N, Felip E, et al. Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases. Annals of Oncology 2018;29(4):959–65. [PubMed: 29408986]

14. Kitadai R, Okuma Y, Hakozaki T, Hosomi Y. The efficacy of immune checkpoint inhibitors in advanced non-small-cell lung cancer with liver metastases. Journal of Cancer Research and Clinical Oncology 2020;146(3):777–85. [PubMed: 31828427]

15. Crispe IN. Liver antigen-presenting cells. J Hepatol 2011;54(2):357–65. [PubMed: 21084131]

16. Yu J, Green MD, Li S, et al. Liver metastasis restrains immunotherapy efficacy via macrophage-mediated T cell elimination. Nat Med 2021;27(1):152–64. [PubMed: 33398162]

17. Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.

18. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60. [PubMed: 12958120]

19. Kitadai R, Okuma Y, Hakozaki T, Hosomi Y. The efficacy of immune checkpoint inhibitors in advanced non-small-cell lung cancer with liver metastases. Journal of Cancer Research and Clinical Oncology 2020;146(3):777–85. [PubMed: 31828427]

20. Macpherson IR, He Y, Palmieri C. Eribulin, Child-Pugh score, and liver-function tests: lessons from pivotal breast cancer studies 301 and 305. Breast Cancer Res 2021;23(1):33–9. [PubMed: 33736675]

21. Jiang Z, Li C, Zhao Z, et al. Abnormal Liver Function Induced by Space-Occupying Lesions Is Associated with Unfavorable Oncologic Outcome in Patients with Colorectal Cancer Liver Metastases. Biomed Res Int 2018;2018:9321270. [PubMed: 29862297]

22. Wyld L, Gutteridge E, Pinder SE, et al. Prognostic factors for patients with hepatic metastases from breast cancer. Br J Cancer 2003;89(2):284–90. [PubMed: 12865918]

23. Sheu M-J, Liang F-W, Lin C-Y, Lu T-H. Changes in liver-related mortality by etiology and sequelae: underlying versus multiple causes of death. Popul Health Metr 2021;19(1):22–8. [PubMed: 33926463]

24. Lee JC, Green MD, Huppert LA, Chow C, Pierce RH, Daud AI. The Liver-Immunity Nexus and Cancer Immunotherapy. Clin Cancer Res 2022;28(1):5–12. [PubMed: 34285059]

25. Brodt P Role of the Microenvironment in Liver Metastasis: From Pre- to Prometastatic Niches. Clin Cancer Res 2016;22(24):5971–82. [PubMed: 27797969]

26. Lee JC, Mehdizadeh S, Smith J, et al. Regulatory T cell control of systemic immunity and immunotherapy response in liver metastasis. Sci Immunol 2020;5(52).

27. Ho WW, Gomes-Santos IL, Aoki S, et al. Dendritic cell paucity in mismatch repair-proficient colorectal cancer liver metastases limits immune checkpoint blockade efficacy. Proc Natl Acad Sci U S A 2021;118(45):e2105323118. [PubMed: 34725151]
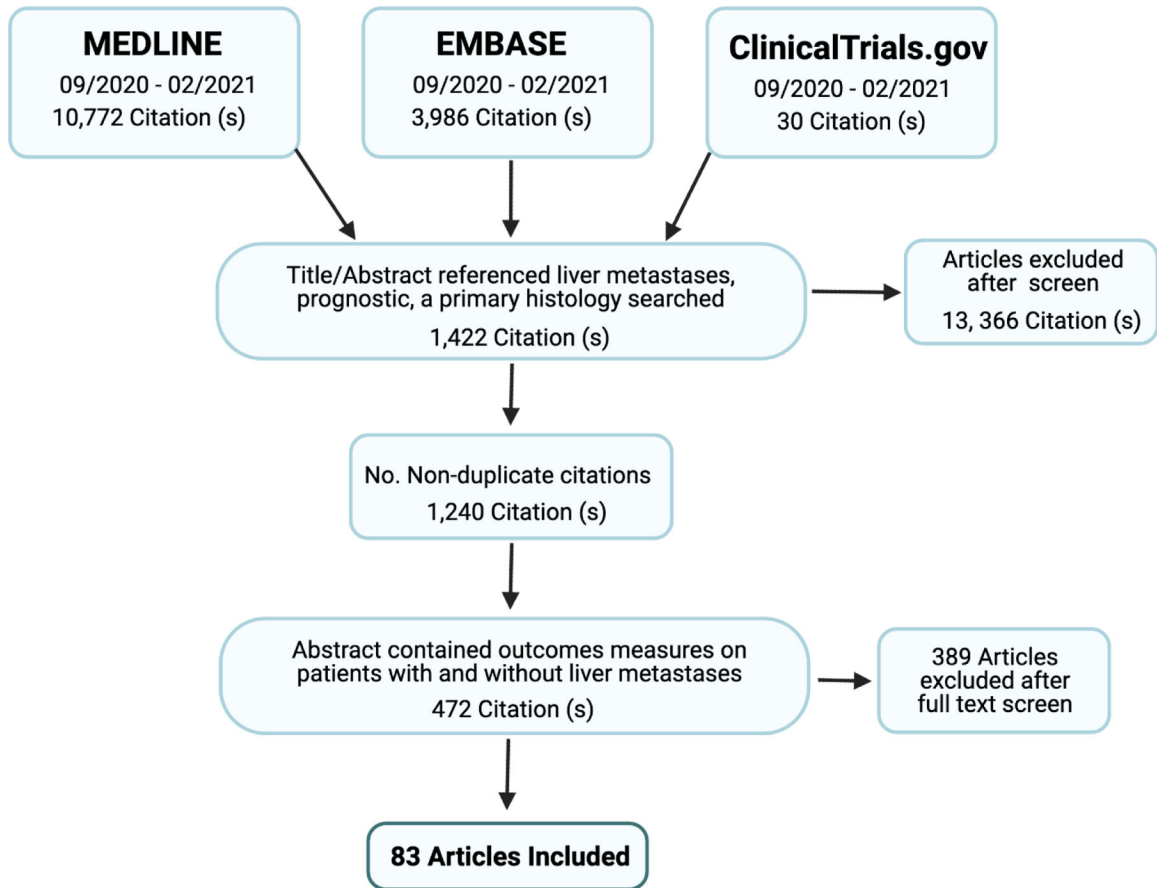
Figure 1: PRISMA Analysis
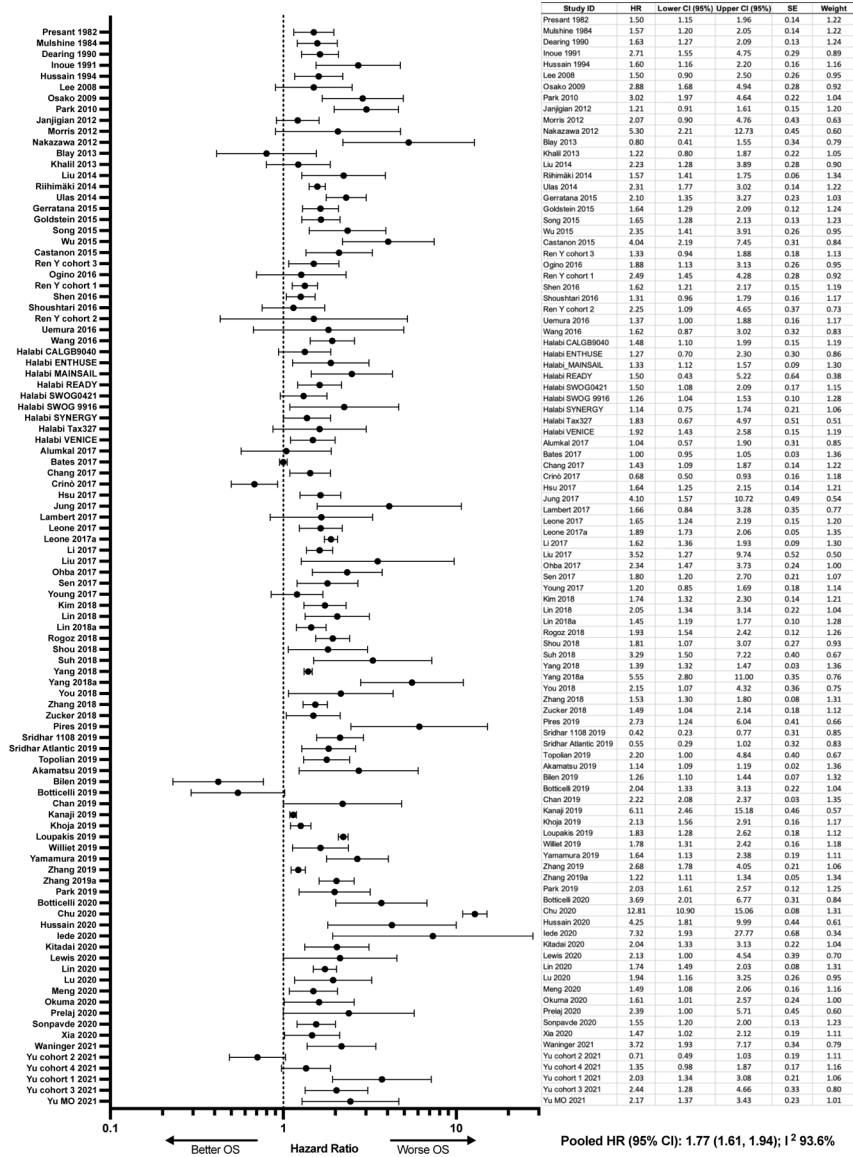Flowchart of study selection.

Study ID	HR	Lower CI (95%)	Upper CI (95%)	SE	Weight
Presant 1982	1.50	1.15	1.96	0.14	1.22
Mulshine 1984	1.57	1.20	2.05	0.14	1.22
Dearing 1990	1.63	1.27	2.09	0.13	1.24
Inoue 1991	2.71	1.55	4.75	0.29	0.89
Hussain 1994	1.60	1.16	2.20	0.16	1.16
Lee 2008	1.50	0.90	2.50	0.26	0.95
Osako 2009	2.88	1.68	4.94	0.28	0.92
Park 2010	3.02	1.97	4.64	0.22	1.04
Janjigian 2012	1.21	0.91	1.61	0.15	1.20
Morris 2012	2.07	0.90	4.76	0.43	0.63
Nakazawa 2012	5.30	2.21	12.73	0.45	0.60
Blay 2013	0.80	0.41	1.55	0.34	0.79
Khalil 2013	1.22	0.80	1.87	0.22	1.05
Liu 2014	2.23	1.28	3.89	0.28	0.90
Riihimäki 2014	1.57	1.41	1.75	0.06	1.34
Ulas 2014	2.31	1.77	3.02	0.14	1.22
Gerratana 2015	2.10	1.35	3.27	0.23	1.03
Goldstein 2015	1.64	1.29	2.09	0.12	1.24
Song 2015	1.65	1.28	2.13	0.13	1.23
Wu 2015	2.35	1.41	3.91	0.26	0.95
Castanon 2015	4.04	2.19	7.45	0.31	0.84
Ren Y cohort 3	1.33	0.94	1.88	0.18	1.13
Ogino 2016	1.88	1.13	3.13	0.26	0.95
Ren Y cohort 1	2.49	1.45	4.28	0.28	0.92
Shen 2016	1.62	1.21	2.17	0.15	1.19
Shoushtari 2016	1.31	0.96	1.79	0.16	1.17
Ren Y cohort 2	2.25	1.09	4.65	0.37	0.73
Uemura 2016	1.37	1.00	1.88	0.16	1.17
Wang 2016	1.62	0.87	3.02	0.32	0.83
Halabi CALGB9040	1.48	1.10	1.99	0.15	1.19
Halabi ENTHUSE	1.27	0.70	2.30	0.30	0.86
Halabi MAINSAIL	1.33	1.12	1.57	0.09	1.30
Halabi READY	1.50	0.43	5.22	0.64	0.38
Halabi SWOG0421	1.50	1.08	2.09	0.17	1.15
Halabi SWOG 9916	1.26	1.04	1.53	0.10	1.28
Halabi SYNERGY	1.14	0.75	1.74	0.21	1.06
Halabi Tax327	1.83	0.67	4.97	0.51	0.51
Halabi VENICE	1.92	1.43	2.58	0.15	1.19
Alumkal 2017	1.04	0.57	1.90	0.31	0.85
Bates 2017	1.00	0.95	1.05	0.03	1.36
Chang 2017	1.43	1.09	1.87	0.14	1.22
Crinò 2017	0.68	0.50	0.93	0.16	1.18
Hsu 2017	1.64	1.25	2.15	0.14	1.21
Jung 2017	4.10	1.57	10.72	0.49	0.54
Lambert 2017	1.66	0.84	3.28	0.35	0.77
Leone 2017	1.65	1.24	2.19	0.15	1.20
Leone 2017a	1.89	1.73	2.06	0.05	1.35
Li 2017	1.62	1.36	1.93	0.09	1.30
Liu 2017	3.52	1.27	9.74	0.52	0.50
Ohba 2017	2.34	1.47	3.73	0.24	1.00
Sen 2017	1.80	1.20	2.70	0.21	1.07
Young 2017	1.20	0.85	1.69	0.18	1.14
Kim 2018	1.74	1.32	2.30	0.14	1.21
Lin 2018	2.05	1.34	3.14	0.22	1.04
Lin 2018a	1.45	1.19	1.77	0.10	1.28
Rogoz 2018	1.93	1.54	2.42	0.12	1.26
Shou 2018	1.81	1.07	3.07	0.27	0.93
Suh 2018	3.29	1.50	7.22	0.40	0.67
Yang 2018	1.39	1.32	1.47	0.03	1.36
Yang 2018a	5.55	2.80	11.00	0.35	0.76
You 2018	2.15	1.07	4.32	0.36	0.75
Zhang 2018	1.53	1.30	1.80	0.08	1.31
Zucker 2018	1.49	1.04	2.14	0.18	1.12
Pires 2019	2.73	1.24	6.04	0.41	0.66
Sridhar 1108 2019	0.42	0.23	0.77	0.31	0.85
Sridhar Atlantic 2019	0.55	0.29	1.02	0.32	0.83
Topolian 2019	2.20	1.00	4.84	0.40	0.67
Akamatsu 2019	1.14	1.09	1.19	0.02	1.36
Bilen 2019	1.26	1.10	1.44	0.07	1.32
Botticelli 2019	2.04	1.33	3.13	0.22	1.04
Chan 2019	2.22	2.08	2.37	0.03	1.35
Kanaji 2019	6.11	2.46	15.18	0.46	0.57
Khoja 2019	2.13	1.56	2.91	0.16	1.17
Loupakis 2019	1.83	1.28	2.62	0.18	1.12
Williet 2019	1.78	1.31	2.42	0.16	1.18
Yamamura 2019	1.64	1.13	2.38	0.19	1.11
Zhang 2019	2.68	1.78	4.05	0.21	1.06
Zhang 2019a	1.22	1.11	1.34	0.05	1.34
Park 2019	2.03	1.61	2.57	0.12	1.25
Botticelli 2020	3.69	2.01	6.77	0.31	0.84
Chu 2020	12.81	10.90	15.06	0.08	1.31
Hussain 2020	4.25	1.81	9.99	0.44	0.61
Iede 2020	7.32	1.93	27.77	0.68	0.34
Kitadai 2020	2.04	1.33	3.13	0.22	1.04
Lewis 2020	2.13	1.00	4.54	0.39	0.70
Lin 2020	1.74	1.49	2.03	0.08	1.31
Lu 2020	1.94	1.16	3.25	0.26	0.95
Meng 2020	1.49	1.08	2.06	0.16	1.16
Okuma 2020	1.61	1.01	2.57	0.24	1.00
Prelaj 2020	2.39	1.00	5.71	0.45	0.60
Sonpavde 2020	1.55	1.20	2.00	0.13	1.23
Xia 2020	1.47	1.02	2.12	0.19	1.11
Waninger 2021	3.72	1.93	7.17	0.34	0.79
Yu cohort 2 2021	0.71	0.49	1.03	0.19	1.11
Yu cohort 4 2021	1.35	0.98	1.87	0.17	1.16
Yu cohort 1 2021	2.03	1.34	3.08	0.21	1.06
Yu cohort 3 2021	2.44	1.28	4.66	0.33	0.80
Yu MO 2021	2.17	1.37	3.43	0.23	1.01

Pooled HR (95% CI): 1.77 (1.61, 1.94); I² 93.6%

Figure 2: Forest Plot of Included Studies
Hazard Ratio (HR) of Overall Survival (OS) for each included study.

Figure 3: Heterogeneity Analysis
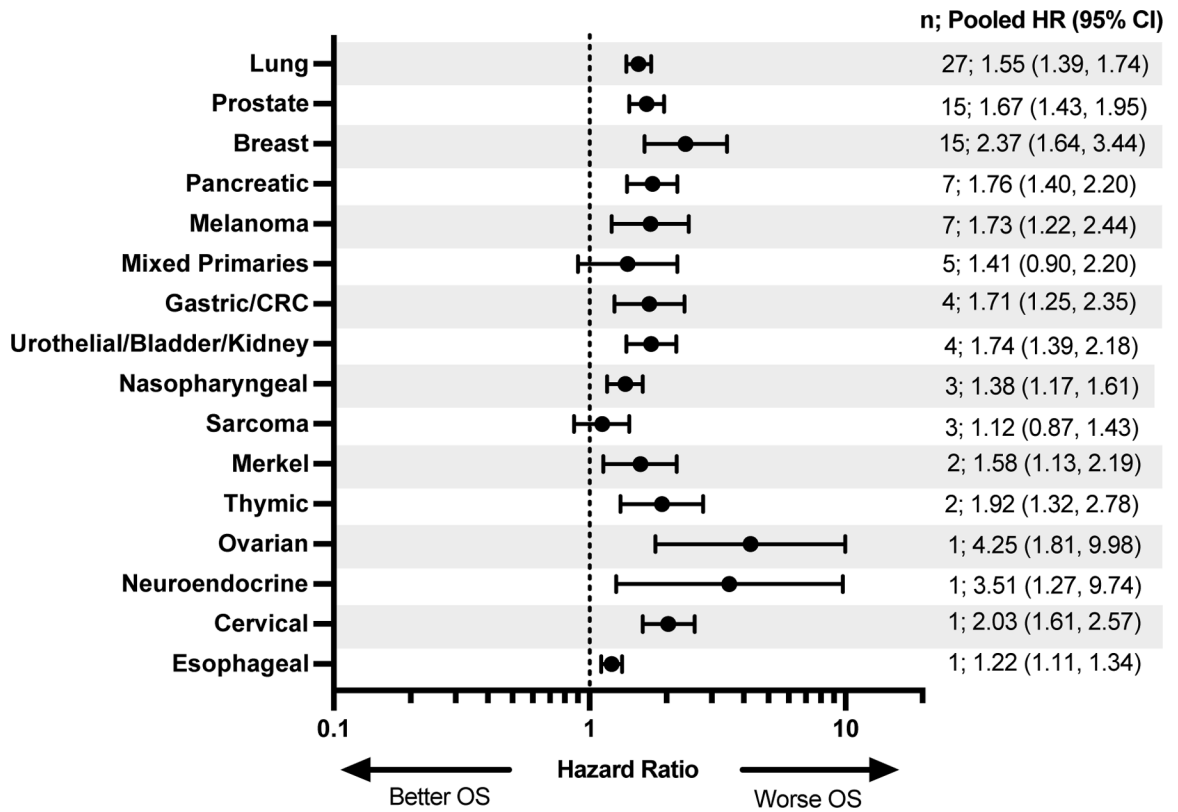Funnel Plot evaluating potential publication bias in meta-analysis.

Figure 4: Liver metastases are negatively prognostic regardless of primary histology.
Forest plot of summary hazard ratios of liver metastases vs. other metastases by primary histology. OS: overall survival, HR: hazard ratio.
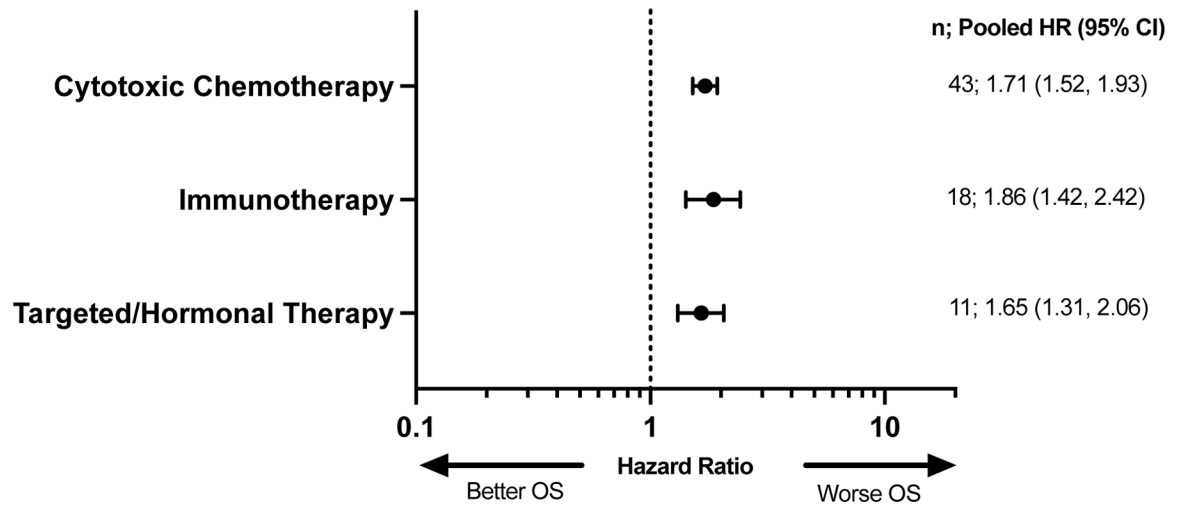
Figure 5: Patients with liver metastases have worse overall survival regardless of therapeutic intervention.

Forest plot of summary hazard ratios by therapy type. OS: overall survival, HR: hazard ratio.
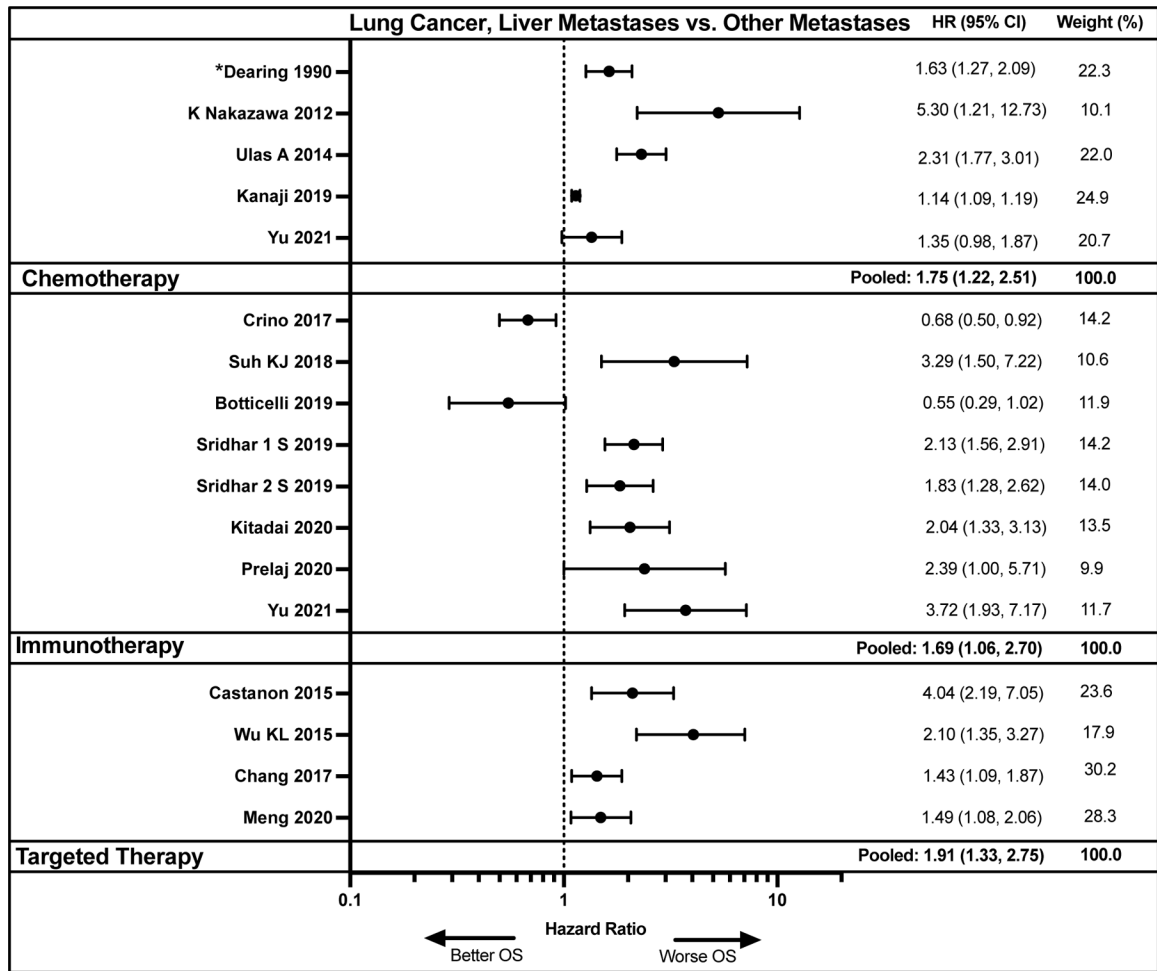
Figure 6: Liver metastases portend worse overall survival in lung cancer patients irrespective of therapeutic intervention.

Forest plot of summary hazard ratios of liver metastases vs. other metastases in patients with NSCLC by treatment type. OS: overall survival, HR: hazard ratio. *Indicates this study analyzed small cell lung cancer.

Table 1:

Search Terms

Primary Malignancy	MESH term	EMTree term
Anal	Anus Neoplasms	anus cancer
Bladder	Urinary Bladder Neoplasms	bladder cancer
Breast	Breast Neoplasms	breast cancer
Cervical	Uterine Cervical Neoplasms	uterine cervix cancer
Colon	Colonic Neoplasms	colon cancer
Esophagus	Esophageal Neoplasms	esophagus cancer
Gastric	Stomach Neoplasms	stomach cancer
Head and Neck	Head and Neck Neoplasms	head and neck cancer
Melanoma	Melanoma	melanoma
Merkel	Carcinoma, Merkel Cell	merkel cell carcinoma
Non-small cell	Carcinoma, Non-Small-Cell Lung	non-small cell lung cancer
Small cell	Carcinoma, Small Cell	small cell lung cancer
Ovarian	Ovarian Neoplasms	ovary cancer
Pancreatic	Pancreatic Neoplasms	pancreas cancer
Prostate	Prostatic Neoplasms	prostate cancer
Rectal	Rectal Neoplasms	rectum cancer
Small Bowel	Intestinal Neoplasms	small intestine cancer
Sarcoma	Sarcoma	sarcoma
Testicular	Testicular Neoplasms	testis cancer
Thymic	Thymus Neoplasms	thymus cancer
Thyroid	Thyroid Neoplasms	thyroid cancer
Vulvar	Vulvar Neoplasms	vulva cancer
Skin Cancer	Skin Neoplasms	skin cancer