Article:
Chan, V.W.-S. orcid.org/0000-0002-6108-9315, Ng, H.H.-L., Zhong, J. orcid.org/0000-0001-5325-3739 et al. (1 more author) (2025) Meta-analysis on SBRT and ablation for localised RCC. The Lancet Oncology, 26 (5). e235-e236. ISSN 1470-2045

https://doi.org/10.1016/s1470-2045(25)00147-0

Title: Reply to "Comparative Efficacy and Safety of Ablative Therapies in the Management of Primary Localised Renal Cell Carcinoma: A Systematic Review and Meta-Analysis"

Authors:

Vinson Wai-Shun Chan, MBChB[1,2], Helen Hoi-Lam Ng, MBChB[1,2], Jim Zhong, PhD[1,2], Prof Tze Min Wah PhD[1,2*]

[1] Leeds Institute of Medical Research, Faculty of Medicine and Health, University of Leeds, United Kingdom

[2] Division of Diagnostic and Interventional Radiology, Institute of Oncology, St James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

*Corresponding Author:

Prof Tze Min Wah

Department of Diagnostic and Interventional Radiology, Institute of Oncology, St. James's University Hospital, Leeds Teaching Hospitals NHS Trust, Leeds LS9 7TF, UK. Tel.: +44 1132066043

Email: tze.wah@nhs.net

Dear Editor,

The article titled “Comparative Efficacy and Safety of Ablative Therapies in the Management of Primary Localised Renal Cell Carcinoma: A Systematic Review and Meta-Analysis” by Huang and colleagues[1] was read with interest. However, additional discussion of the methodological approach is necessary before drawing conclusions.

The authors performed single-arm meta-analyses comparing the efficacy and safety of the three ablative therapies (AT) to stereotactic body radiotherapy (SBRT) for primary localised renal cell carcinomas (RCCs). Firstly, an individual data meta-analysis[2] (IPDMA) was included as a primary study for meta-analysis and the results may have been double-counted. Table 1 describes the possible duplicated studies compared against the published IPDMA (see supplementary page 7 of the cited study)[2]. Hereby, we re-present the meta-analysis (Supplementary Figure 1) with the IPDMA excluded. Studies with misclassification of follow-up duration were also excluded. For instance, the study by Kirste (2022) with follow-up range of 18-54 months was incorrectly included in the 5-year local control (LC) forest plot. The revised meta-analysis found 1-year, 2-year and 5-years LC rate of SBRT to be 97% (95%CI 95-99%; I^2=15·53%); 96% (95%CI 93-98%; I^2=39·93) and 94% (95%CI 88-100%; I^2=69·73%), respectively. Adverse events also suffered from double counting, with revised meta-analysis showing a higher 5% (95%CI 3-7%, I^2=0%) rate of grade 3-4 adverse events, or 5·9% (23/393) in raw proportions.

Moreover, the use of single arm meta-analyses for comparison is primarily flawed. Despite subgroup analyses, substantial heterogeneity persisted. Furthermore, interpretation was challenging with unreported meta-regression results, especially residual heterogeneity (e.g. I^2-residual)[3]. Due to the scarcity of oncological events from small RCCs, the sample size of 612 patients (450 in repeated meta-analysis) from SBRT is insufficient to detect substantial differences against AT in local recurrence (LR) and cancer-specific survival; evidenced by wide 95% confidence-intervals. LC in radiotherapy is also a conceptually different endpoint to LR in AT. Consequently, the authors’ suggestion that SBRT may be advantageous for treating larger RCCs is premature due to methodological flaw. Additionally, the ROBINS-I tool was incorrectly applied to assess the risk of bias on non-comparative studies rather than comparative studies[4].

It is crucial to reflect on the methodological limitations of this article and its use of largely retrospective and possibly biased datasets. Randomised trials remain vital in determining optimal treatment for localised RCCs, for example a recent study comparing AT and partial nephrectomy showing feasibility in recruitment[5]. However, phase two/three trials comparing SBRT and AT are lacking.

Reference:

1. Huang RS, Chow R, Benour A, et al. Comparative efficacy and safety of ablative therapies in the management of primary localised renal cell carcinoma: a systematic review and meta-analysis. *The Lancet Oncology*.
2. Siva S, Ali M, Correa RJM, et al. 5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney). *The Lancet Oncology* 2022; **23**(12): 1508-16.
3. Panityakul T, Bumrungsup C, Knapp G. On Estimating Residual Heterogeneity in Random-Effects Meta-Regression: A Comparative Study. *Journal of Statistical Theory and Applications* 2013; **12**: 253.
4. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; **355**: i4919.
5. Neves JB, Warren H, Santiapillai J, et al. Nephron Sparing Treatment (NEST) for Small Renal Masses: A Feasibility Cohort-embedded Randomised Controlled Trial Comparing Percutaneous Cryoablation and Robot-assisted Partial Nephrectomy. *Eur Urol* 2024; **85**(4): 333-6.

Legends of Figures

Table 1: Studies Included in the meta-analysis potentially double counted from the IPDMA

Supplementary Figure 1: Repeated meta-analysis of (a) Local Control at 1 year; (b) Local Control at 2 years; (c) Local Control at 5 years; (d) Grade 3-4 adverse events with the individual patient data meta-analysis excluded and Siva et al 2024 (Siva S, Bressel M, Sidhom M, et al. Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): a non-randomised phase 2 trial. The Lancet Oncology 2024; 25(3): 308-16.) added in attempt of complete meta-analysis.

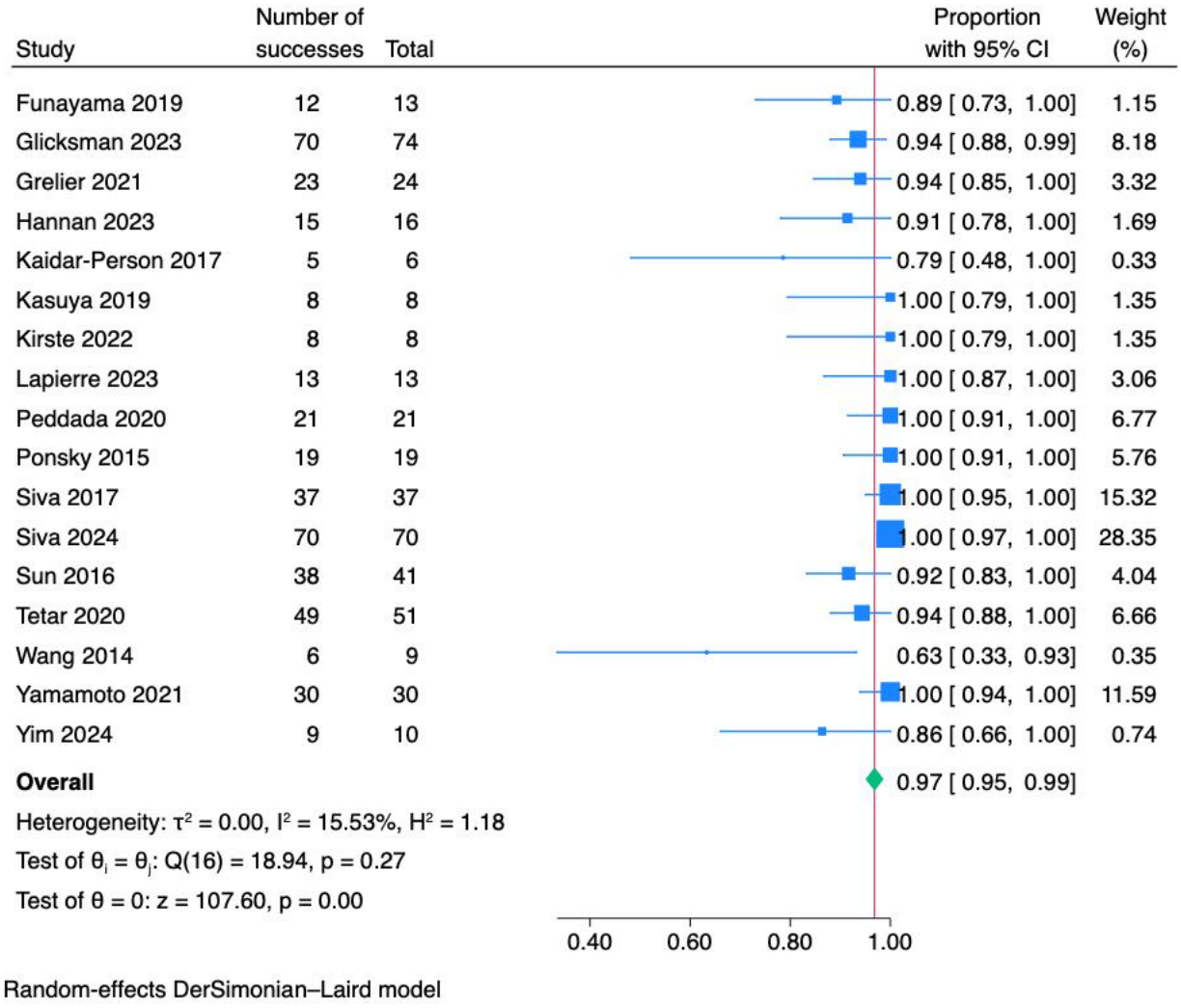
Example of centre included in IPDMA (supplementary table 7 of IPDMA)	Corresponding reference in study by Huang et al.	Study	Recruitment/ Inclusion Period	Note
University of Yamanashi	33	Funayama 2019	August 2007 - June 2016	
University Hospitals Seidman Cancer Center	37,27	Grubb 2021 and Ponsky 2015	Since May 2011; June 2006 - August 2011	Grubb 2011 included a pooled local control rate of patients in Grubb 2011 and Ponsky 2015
University of Texas Southwestern	18	Hannan 2023	September 2014 - October 2019	
Juravinski Cancer Centre and Sunnybrook Health Sciences Centre	17, 28	Glicksman 2023 and Chang 2016	2012-2020; 1 January 2012 - 1 April 2015	Glicksman 2023 reported an extended cohort of Chang 2016
Beth Israel Deaconess Medical Center	29	Sun 2016	May 2006 - May 2011	
Peter MacCallum Cancer Centre	31	Siva 2017	2012-2014	

*Note individual patient data meta-analysis by Siva et al. in 2022 included retrospective and prospective patients from 2007 – 2018.

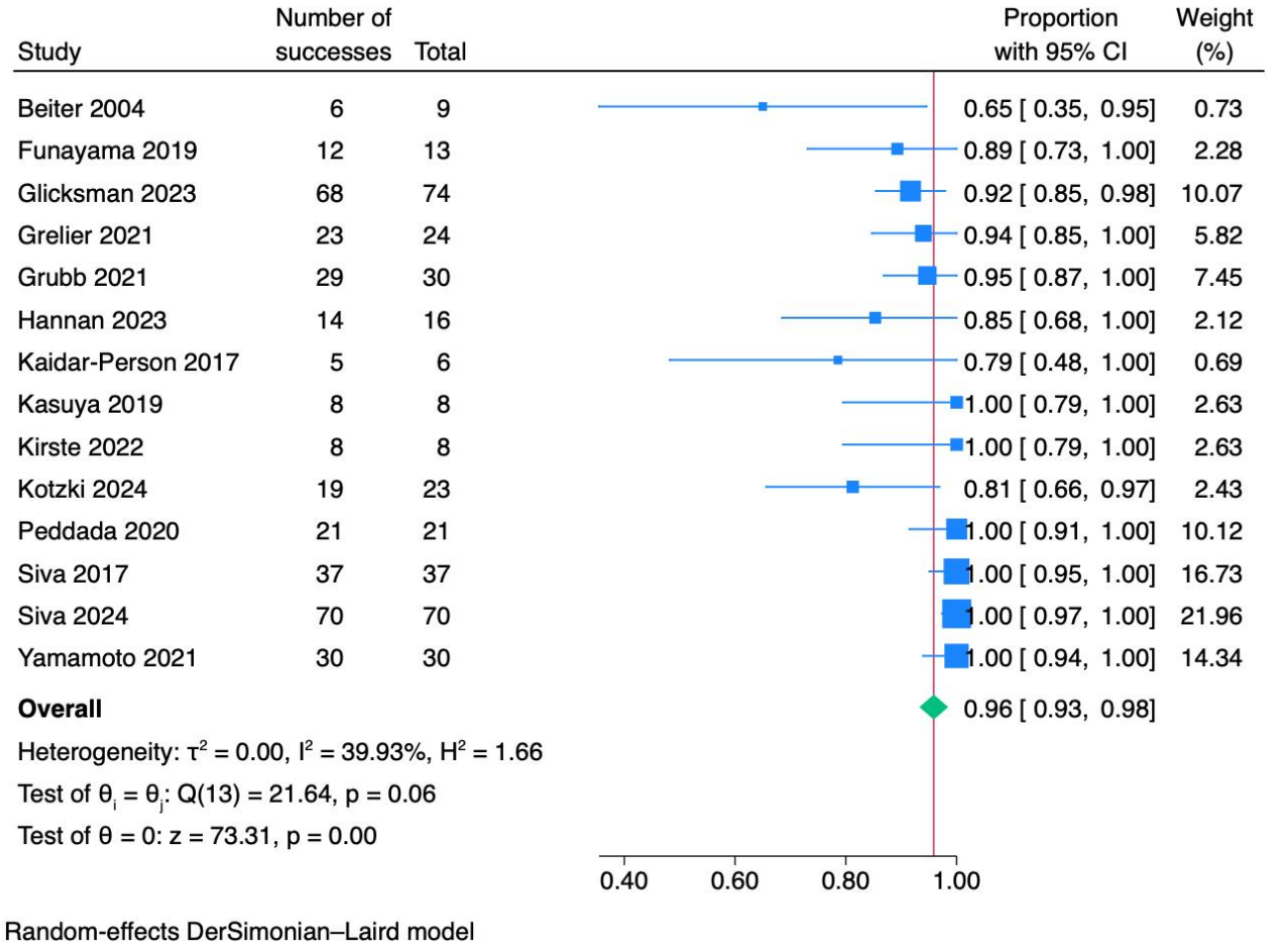
Table 1: Studies Included in the meta-analysis potentially double counted from the IPDMA

Supplementary Figure 1: Repeated meta-analysis of (a) Local Control at 1 year; (b) Local Control at 2 years; (c) Local Control at 5 years; (d) Grade 3-4 adverse events with the individual patient data meta-analysis excluded and Siva et al 2024 (Siva S, Bressel M, Sidhom M, et al. Stereotactic ablative body radiotherapy for primary kidney cancer (TROG 15.03 FASTRACK II): a non-randomised phase 2 trial. The Lancet Oncology 2024; 25(3): 308-16.) added in attempt of complete meta-analysis.

(a)

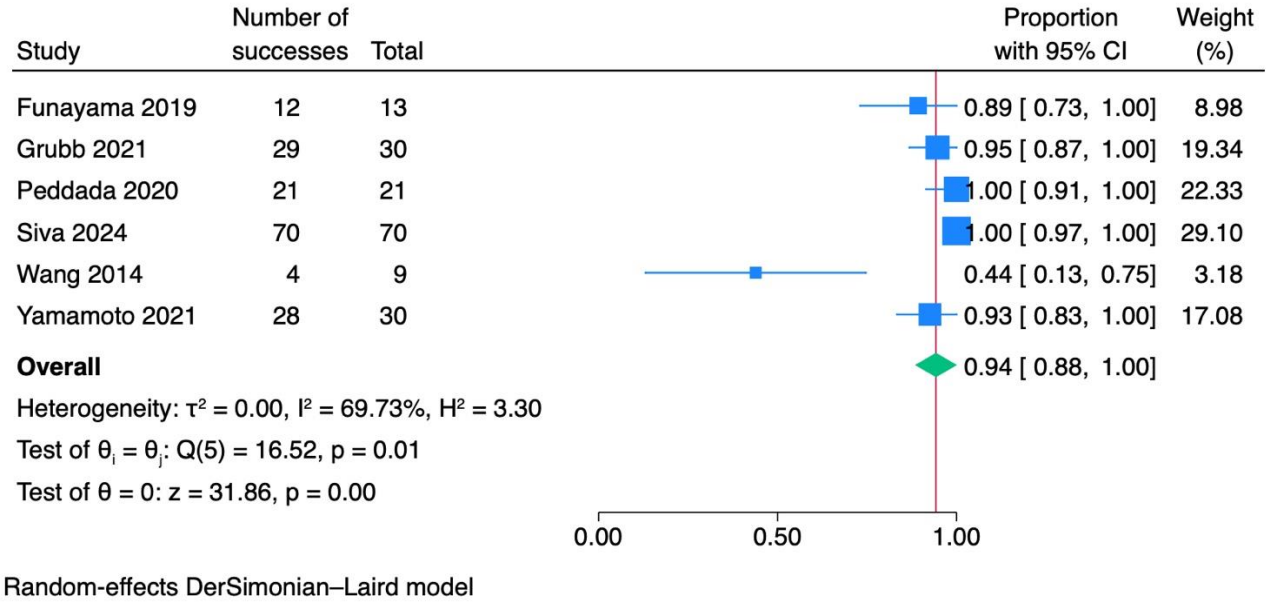


(b)



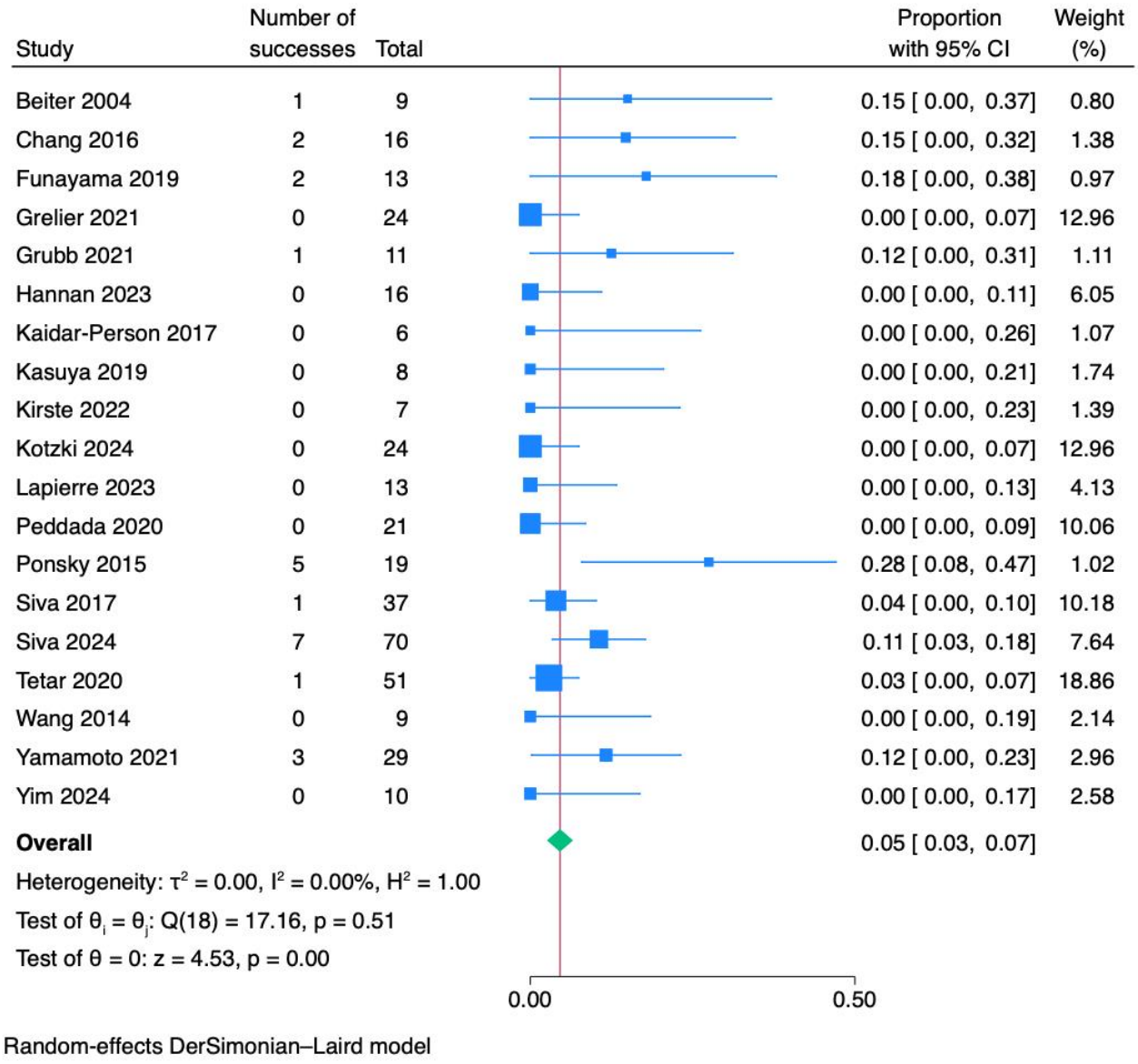
Random-effects DerSimonian–Laird model

(c)



Random-effects DerSimonian–Laird model

(d)


Study
Number of successes
Total
Proportion with 95% CI
Weight (%)
Beiter 2004 1 9 0.15 [0.00, 0.37] 0.80
Chang 2016 2 16 0.15 [0.00, 0.32] 1.38
Funayama 2019 2 13 0.18 [0.00, 0.38] 0.97
Grelier 2021 0 24 0.00 [0.00, 0.07] 12.96
Grubb 2021 1 11 0.12 [0.00, 0.31] 1.11
Hannan 2023 0 16 0.00 [0.00, 0.11] 6.05
Kaidar-Person 2017 0 6 0.00 [0.00, 0.26] 1.07
Kasuya 2019 0 8 0.00 [0.00, 0.21] 1.74
Kirste 2022 0 7 0.00 [0.00, 0.23] 1.39
Kotzki 2024 0 24 0.00 [0.00, 0.07] 12.96
Lapierre 2023 0 13 0.00 [0.00, 0.13] 4.13
Peddada 2020 0 21 0.00 [0.00, 0.09] 10.06
Ponsky 2015 5 19 0.28 [0.08, 0.47] 1.02
Siva 2017 1 37 0.04 [0.00, 0.10] 10.18
Siva 2024 7 70 0.11 [0.03, 0.18] 7.64
Tetar 2020 1 51 0.03 [0.00, 0.07] 18.86
Wang 2014 0 9 0.00 [0.00, 0.19] 2.14
Yamamoto 2021 3 29 0.12 [0.00, 0.23] 2.96
Yim 2024 0 10 0.00 [0.00, 0.17] 2.58
Overall 0.05 [0.03, 0.07]
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00
Test of $\theta_i = \theta_j$: Q(18) = 17.16, p = 0.51
Test of θ = 0: z = 4.53, p = 0.00
0.00
0.50
Random-effects DerSimonian–Laird model