Approaches to Comparing Treatments from Meta-Analyses of Single-Arm Studies from a Systematic Literature Review: Case Example of Non-Surgical Technologies for Treatment of Lung Cancer

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Background and Objectives

- Local therapies, such as microwave ablation (MWA), radiofrequency ablation (RFA), and stereotactic body radiation therapy (SBRT), are used in non-small cell lung cancer (NSCLC) patients who are ineligible for surgery or in patients with pulmonary metastases.[1,2]
- More than 85% of studies on these technologies are single arm, making head-to-head analysis methods challenging due to disconnected evidence networks.
- The objective of this research was to explore methods that can be used to pool and compare such large volumes of single-arm data.

Methods

Systematic Literature Review:
- Conducted in MEDLINE®, Embase®, and Cochrane databases, for studies published from January 1, 2005 to January 16, 2022.
- Reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.

Population/Intervention:
- Studies with ≥40 lung cancer patients treated with MWA, RFA, or SBRT.

Outcomes:
- 1-, 2-, and 3-year local tumor progression (LTP).
- 1-, 2-, and 3-year overall survival (OS).
- 1-, 2-, and 3-year progression-free survival (PFS).

Study Design:
- Single-arm studies, comparative studies, and single arms from comparative studies (with a comparator not of interest).

Statistical Methods

1 Single-Arm Pooled Meta-Analysis
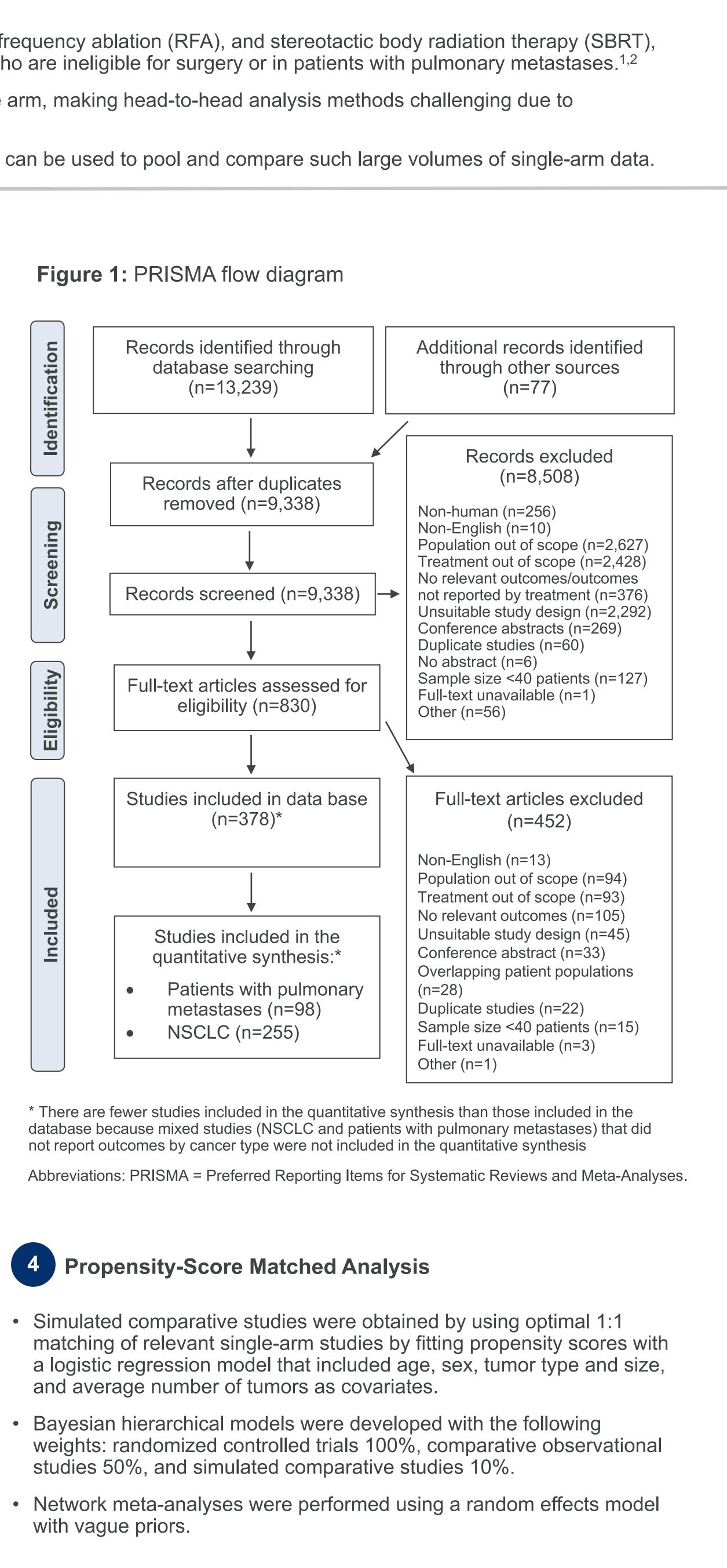- The study-specific point estimates and their confidence intervals (CIs) were combined using a random-effects meta-analytic model.

2 Meta-Regressions
- Univariable and multivariable random-effects meta-regressions were performed after adjusting for the following study-level covariates: age, proportion male, proportion T1a/T1b or Stage IA, average tumor size and number, study design, and geographic region.

3 Single-Arm Bayesian Meta-Analysis
- Unadjusted Bayesian hierarchical random-effects meta-analyses were conducted using pessimistic (Normal (0, 1)) prior on treatment effects.
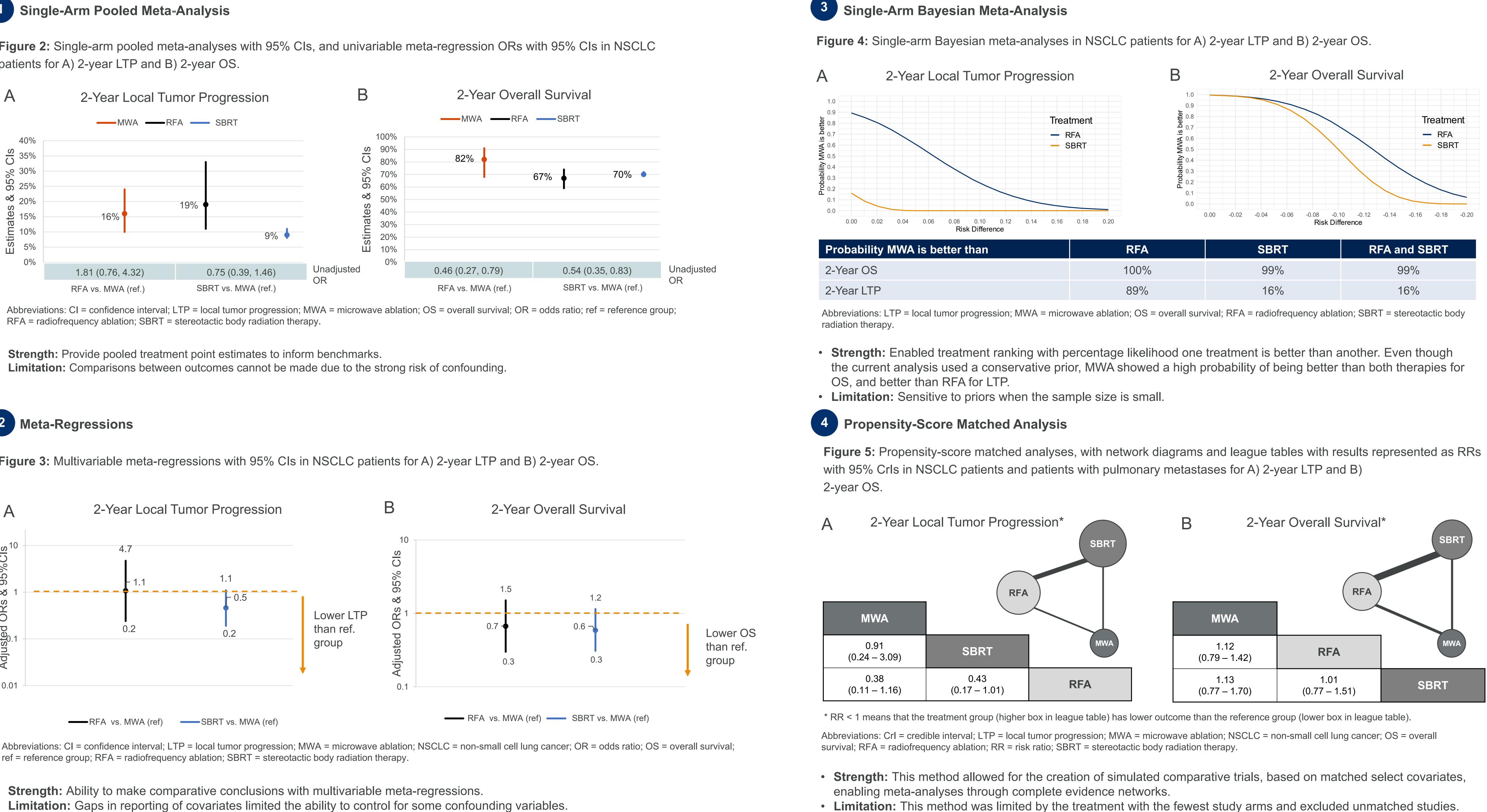- Posterior sampling was conducted with JAGS and convergence monitored across four chains.

4 Propensity-Score Matched Analysis
- Simulated comparative studies were obtained by using optimal 1:1 matching of relevant single-arm studies by fitting propensity scores with a logistic regression model that included age, sex, tumor type and size, and average number of tumors as covariates.
- Bayesian hierarchical models were developed with the following weights: randomized controlled trials 100%, comparative observational studies 50%, and simulated comparative studies 10%.
- Network meta-analyses were performed using a random effects model with vague priors.

Figure 1: PRISMA flow diagram

* There are fewer studies included in the quantitative synthesis than those included in the database because mixed studies (NSCLC and patients with pulmonary metastases) that did not report outcomes by cancer type were not included in the quantitative synthesis

Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Results

1 Single-Arm Pooled Meta-Analysis

Figure 2: Single-arm pooled meta-analyses with 95% CIs, and univariable meta-regression ORs with 95% CIs in NSCLC patients for A) 2-year LTP and B) 2-year OS.

Abbreviations: CI = confidence interval; LTP = local tumor progression; MWA = microwave ablation; OS = overall survival; OR = odds ratio; ref = reference group; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

- **Strength:** Provide pooled treatment point estimates to inform benchmarks.
- **Limitation:** Comparisons between outcomes cannot be made due to the strong risk of confounding.

2 Meta-Regressions

Figure 3: Multivariable meta-regressions with 95% CIs in NSCLC patients for A) 2-year LTP and B) 2-year OS.

Abbreviations: CI = confidence interval; LTP = local tumor progression; MWA = microwave ablation; NSCLC = non-small cell lung cancer; OR = odds ratio; OS = overall survival; ref = reference group; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

- **Strength:** Ability to make comparative conclusions with multivariable meta-regressions.
- **Limitation:** Gaps in reporting of covariates limited the ability to control for some confounding variables.

3 Single-Arm Bayesian Meta-Analysis

Figure 4: Single-arm Bayesian meta-analyses in NSCLC patients for A) 2-year LTP and B) 2-year OS.

Probability MWA is better than	RFA	SBRT	RFA and SBRT
2-Year OS	100%	99%	99%
2-Year LTP	89%	16%	16%

Abbreviations: LTP = local tumor progression; MWA = microwave ablation; OS = overall survival; RFA = radiofrequency ablation; SBRT = stereotactic body radiation therapy.

- **Strength:** Enabled treatment ranking with percentage likelihood one treatment is better than another. Even though the current analysis used a conservative prior, MWA showed a high probability of being better than both therapies for OS, and better than RFA for LTP.
- **Limitation:** Sensitive to priors when the sample size is small.

4 Propensity-Score Matched Analysis

Figure 5: Propensity-score matched analyses, with network diagrams and league tables with results represented as RRs with 95% CrIs in NSCLC patients and patients with pulmonary metastases for A) 2-year LTP and B) 2-year OS.

* RR < 1 means that the treatment group (higher box in league table) has lower outcome than the reference group (lower box in league table).

Abbreviations: CrI = credible interval; LTP = local tumor progression; MWA = microwave ablation; NSCLC = non-small cell lung cancer; OS = overall survival; RFA = radiofrequency ablation; RR = risk ratio; SBRT = stereotactic body radiation therapy.

- **Strength:** This method allowed for the creation of simulated comparative trials, based on matched select covariates, enabling meta-analyses through complete evidence networks.
- **Limitation:** This method was limited by the treatment with the fewest study arms and excluded unmatched studies.

Discussion

The methods assessed enabled the indirect comparison of treatments that have been evaluated primarily by single-arm studies.

Unadjusted Bayesian analyses (method #3) did not control for confounding variables; thus, results are incongruent with the meta-regressions and propensity-score matched analyses (method #2 and #4) which did control for these variables.

Each method has strengths and limitations and by describing those here, we have provided a guide for other researchers to select the most appropriate approach for meta-analyses of single-arm data to allow comparisons between treatments.
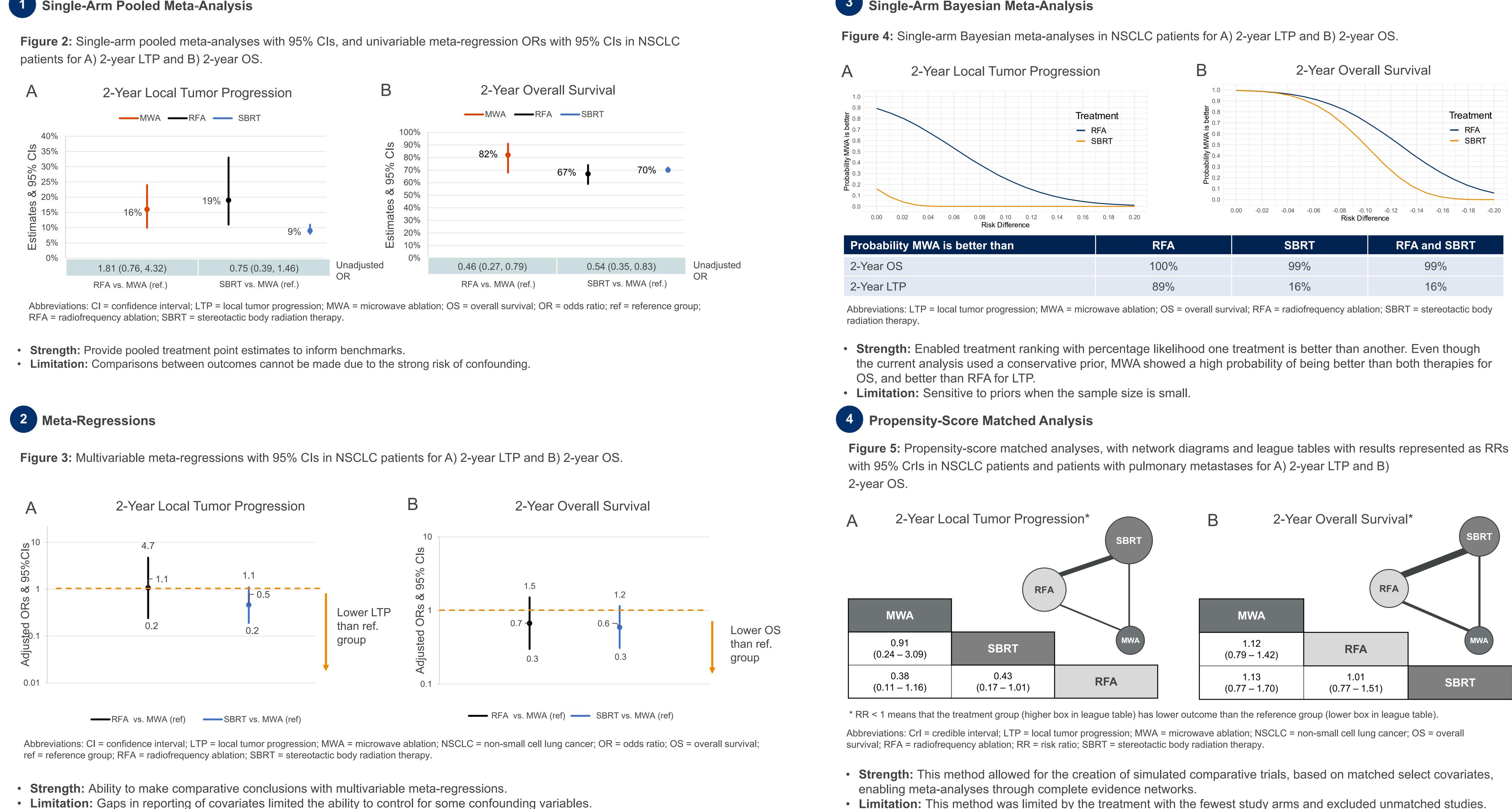
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