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Application of Propensity Score Matching and Bayesian Hierarchical Design Methods to Integrate Single-Arm Studies into Network Meta-Analyses (NMAs):

Opportunities and Pitfalls Illustrated in a Case Study Assessing Ablation/Radiation Therapies in Lung Cancer

Conflicts of Interest

- This work was supported by Ethicon, Inc., manufacturer of the NeuWave microwave ablation system.
- Rana A. Qadeer is an employee of EVERSANA, who were sponsored to perform this study by Ethicon, Inc.

P13: COMPARATIVE EFFECTIVENESS STUDIES & METHODS

Application of Propensity Score Matching and Bayesian Hierarchical Design Methods to Integrate Single-Arm Studies into Network Meta-Analyses (NMAs):

Opportunities and Pitfalls Illustrated in a Case Study Assessing Ablation/Radiation Therapies in Lung Cancer

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Outline

1. Introduction

Burden of lung cancer

Treatment options

Problems and objectives

2. Methods

Systematic literature review

Data synthesis and statistical methods

3. Results

Systematic literature review

Primary and exploratory analyses

4. Discussion

Summary

Opportunities and pitfalls

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Burden of Lung Cancer

Among all cancer types, lung cancer is the ***leading cause of death*** worldwide[1]

In 2020, ***>228,000 new cases*** and ***>135,000 deaths*** in the United States[2]

In 2010, prevalence costs estimated to be ***$12.1 billion*** in the United States[3]

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Treatment Options

- Key treatment option is surgical resection; however, only 20% to 25% eligible[4,5]
- Radiation and minimally-invasive ablation therapies are commonly used:[6-19]
  - Stereotactic Body Radiotherapy (SBRT)
  - Radiofrequency Ablation (RFA)
  - Microwave Ablation (MWA)

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Problems and Objectives

TWO KEY PROBLEMS

1. Lack of analyses (e.g., network meta-analyses [NMAs]) that compare all three treatment modalities (SBRT, RFA, and MWA)
2. NMAs generally include direct comparative evidence (RCTs, observational studies); however, availability of direct comparative evidence was low

OBJECTIVES

- Compare the efficacy of SBRT, RFA, and MWA using a NMA incorporating **direct comparative and single-arm studies**
- Discuss opportunities/pitfalls of incorporating single-arm studies into NMAs

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Systematic Literature Review

1

- MEDLINE®, Embase®, EBM Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews searched for RCTs, comparative observational studies, and/or single-arm studies

2

- Studies screened according to PICOS defined *a priori* (e.g., ≥18 years of age with primary or metastatic lung cancer)

3

- Baseline characteristics from the included studies were extracted

4

- Outcomes (local tumor recurrence [LTR], 1-, 2-, and 3-year overall survival [OS], and complications) from the included studies were extracted

5

- Risk of bias assessment using the Cochrane Risk of Bias tool (RoB) and Newcastle-Ottawa scale (NOS)

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Data Synthesis and Statistical Methods

- Bayesian hierarchical NMAs were conducted:[20]

PRIMARY ANALYSES	EXPLORATORY ANALYSES
• Included RCTs and comparative observational studies	• Included RCTs, comparative observational studies, and **simulated comparative studies**
• Down-weighted lower quality evidence to provide adjusted treatment effects across treatments	• Down-weighted lower quality evidence to provide adjusted treatment effects across treatments

• RCTs received a weight of 100%, while comparative observational studies received a weight of 50%
  • Other weights were tested in sensitivity analyses
	• Weights: RCTs 100%, comparative observational studies 50%, simulated comparative studies 10%
	  • Other weights were tested in sensitivity analyses

• Fixed effect model due to limited number of studies
  • Other models were tested in sensitivity analyses
	• Random effects model with vague priors
	  • Other models were tested in sensitivity analyses

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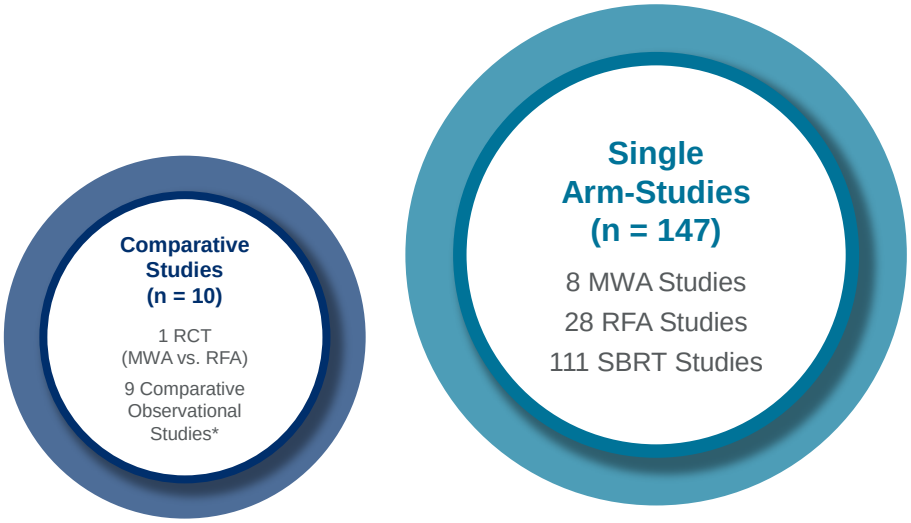
Systematic Literature Review



*5 studies compared MWA with RFA and 4 studies compared RFA with SBRT

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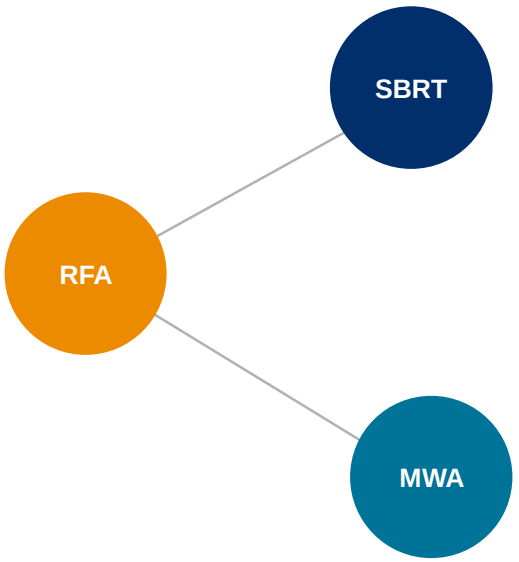
Primary Analyses (1 of 2)

- Number of comparative studies included in each analysis varied based on the outcome:
  - **LTR:** 4 comparative observational studies
  - **1-year OS:** 1 RCT and 7 comparative observational studies
  - **2-year OS:** 5 comparative observational studies
  - **3-year OS:** 4 comparative observational studies
  - **Complications:** 1 RCT and 5 comparative observational studies
- Network diagram for all outcomes was a variation of the diagram shown on right (varied by sample sizes and number of studies included)



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Primary Analyses (2 of 2)

LTR

- MWA was ranked first and RFA was ranked last
- Statistically significant reduction with MWA vs. RFA

1-Year OS

- No differences between treatments

2-Year OS

- No differences between treatments

3-Year OS

- No differences between treatments

Complications

- SBRT was ranked first and RFA was ranked last
- Statistically significant reductions with SBRT and MWA vs. RFA

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Exploratory Analyses

Results observed in **exploratory analyses were similar to those from the primary analyses:**

	Number of Studies	Treatment Rankings	Treatment Effect Sizes
LTR			
Primary analyses	4	**Same**	Varied by 6% - 44%
Exploratory analyses	11		
1-, 2-, and 3-Year OS			
Primary analyses	8, 5, 4	**Some Variation**	Varied by 0% - 16%
Exploratory analyses	23, 17, 16		
Complications			
Primary analyses	6	**Same**	Varied by 3% - 16%
Exploratory analyses	22		

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Sensitivity Analyses

Results from sensitivity analyses for the primary and exploratory analyses were aligned with results presented on previous slides

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Summary

Problems:

- Lack of analyses that compare all three treatment modalities (SBRT, RFA, and MWA) for patients with inoperable lung cancer
- Paucity of direct comparative evidence but many single-arm studies available

Methods:

- Conducted Bayesian hierarchical NMAs:
  - Primary analyses included direct comparative evidence
  - Exploratory analyses included direct comparative and simulated comparative (generated through PSM of single-arm studies) evidence

Findings:

- Results observed in exploratory analyses were similar to those from the primary analyses

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Opportunities and Pitfalls

OPPORTUNITIES

- May offer opportunities to utilize all available evidence
- Useful in disease/treatment areas with many single-arm studies and limited direct comparative evidence and incomplete evidence networks
- Can **up/down-weight** based on study design

PITFALLS

- Sub-optimal matching between single-arm studies limiting the ability to sufficiently **adjust** for cross-study differences
- **Limited** guidance regarding similarity
- **Limited** guidance regarding weighting of **lower quality evidence**

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Conclusions

- NMAs typically consider comparative RCT evidence
- In therapeutic areas where RCT evidence is limited, Bayesian hierarchical NMAs integrating non-RCT evidence may allow for a more **fulsome consideration of all evidence and allow down-weighting of low quality evidence**
- Important that studies leveraging this methodology present results in a **transparent manner, including the stratification of results by study design**

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