APPENDIX B

Should MIS vs. Open be used for resectable Colorectal Liver Metastases (CRLM), when performed separately from resection of primary cancer ?

POPULATION:	resectable Colorectal Liver Metastases (CRLM), when performed separately from resection of primary cancer
INTERVENTION:	MIS
COMPARISON:	Open
MAIN OUTCOMES:	Perioperative Complications - Clavien dindo Grade 3+; Disease Free Survival - 1 year; Hospital Length of Stay; Mortality - 5yr; Estimated Blood Loss ; R0 Resection; Perioperative Transfusion;
SETTING:	
PERSPECTIVE:	**PATIENT-CENTERED**
BACKGROUND:	
CONFLICT OF INTERESTS:	

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know		

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	*Outcomes used by the panel for decision making	The panel felt that as there although DFS 1yr and 5yr Overall Mortality would be most important to patients, the range estimated effects was similar between MIS and Open Hepatectomy. However, the panel felt that there was considerable benefit from decreased complications and hospital length of stay with MIS hepatectomy. Ultimately, there was consensus that MIS hepatectomy conferred moderate benefit.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with Open	Risk difference with MIS
				Study population	

Perioperative Complications - Clavien dindo Grade 3+*	506 (3 RCTs)	⊕⊕⊕◯ Moderate[a]	**RR 0.62** (0.38 to 1.00)	153 per 1,000	**58 fewer per 1,000** (95 fewer to 0 fewer)
Disease Free Survival - 1 year*	233 (2 RCTs)	⊕◯◯◯ Very low[b,c]	**RR 1.03** (0.70 to 1.50)	Study population	
				632 per 1,000	**19 more per 1,000** (190 fewer to 316 more)
Hospital Length of Stay*	506 (3 RCTs)	⊕⊕⊕⊕ High	-	The mean hospital Length of Stay was **0** days	MD **6.61 days lower** (10.19 lower to 3.03 lower)
Mortality - 5yr*	316 (3 RCTs)	⊕⊕◯◯ Low[d]	**RR 0.98** (0.75 to 1.27)	Study population	
				482 per 1,000	**10 fewer per 1,000** (120 fewer to 130 more)
Estimated Blood Loss	506 (3 RCTs)	⊕⊕⊕◯ Moderate[e]	-	The mean estimated Blood Loss was **0** cc	MD **251.61 cc lower** (555.45 lower to 52.23 higher)
R0 Resection	193 (1 RCT)	⊕⊕◯◯ Low[c]	**RR 1.08** (1.00 to 1.17)	Study population	
				887 per 1,000	**71 more per 1,000** (0 fewer to 151 more)
Perioperative Transfusion	466 (2 RCTs)	⊕⊕◯◯ Low[c]	**RR 0.81** (0.45 to 1.49)	Study population	
				95 per 1,000	**18 fewer per 1,000** (52 fewer to 47 more)

a. There was a small event size which introduces some fragility.
b. Using this Cochrane Risk of Bias tool, this study was found to have an unclear risk of bias due to some concern over randomization. After randomization the open arm had larger tumors.
c. There was a small sample size and an even smaller sample size. Additionally, a wide 95% CI around absolute effect crosses several clinically relevant thresholds (i.e. important benefits to trivial or no benefit to important harms)
d. There is a small sample size which increases the imprecision

	e. Although there is a wide confidence interval there is clear benefit across all studies that the effect favors the intervention. The degree to which there is less blood loss with MIS is somewhat uncertain.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	There are no undesirable effects found for any of the important or critical outcomes.	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	<table><tr><th>Outcomes</th><th>Importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>Perioperative Complications - Clavien dindo Grade 3+</td><td>CRITICAL</td><td>⨁⨁⨁◯ Moderate[a]</td></tr><tr><td>Disease Free Survival - 1 year</td><td>CRITICAL</td><td>⨁◯◯◯ Very low[b,c]</td></tr><tr><td>Hospital Length of Stay</td><td>CRITICAL</td><td>⨁⨁⨁⨁ High</td></tr><tr><td>Mortality - 5yr</td><td>CRITICAL</td><td>⨁⨁◯◯ Low[d]</td></tr></table> a. There was a small event size which introduces some fragility.	The panel judged the overall benefit favored MIS because of overall moderate benefits across the critical and important outcomes with no observed evidence of differential harms, however, the imprecision for net benefit was deemed substantial. Therefore, the overall certainty of evidence for critical outcomes was downgraded to low.

	b. Using this Cochrane Risk of Bias tool, this study was found to have an unclear risk of bias due to some concern over randomization. After randomization the open arm had larger tumors. c. There was a small sample size and an even smaller sample size. Additionally, a wide 95% CI around absolute effect crosses several clinically relevant thresholds (i.e. important benefits to trivial or no benefit to important harms) d. There is a small sample size which increases the imprecision	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know		As the available evidence demonstrated moderate benefit and no undesirable effects were revealed, the panel felt that the balance of effects probably favors the intervention. The uncertainty in the decision came from the low certainty of evidence of the available data.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	**No important uncertainty or variability**			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	●	○

CONCLUSIONS

Recommendation

The panel suggests that patients with CRLM undergo an MIS rather than open hepatectomy for resectable colorectal liver metastases being resected separately from resection of the primary cancer when feasible (conditional recommendation, low certainty evidence)

Justification

The panel judged there are moderate desirable effects of MIS Hepatectomy over Open which outweighed trivial undesirable effects. This balance favoring MIS hepatectomy would likely apply to most adult patients with CRLM. However, due to low certainty evidence, only a conditional recommendation could be made.

Subgroup considerations

Implementation considerations

The data from included studies came from relatively high-volume centers and operations were performed by well-trained surgeons, well past their learning curve. In addition, these trials included mostly patients with only one or two lesions, and very few major hepatectomies. This must be considered in the implementation of these recommendations, which do not necessarily apply to complex liver resections, particularly when surgeons and institutions do not have the training and expertise to safely perform these operations. In general, the recommendation for MIS hepatectomy should be applied only in situations where the surgeons and the facility have the training and experience to perform the resection safely with an appropriate oncologic outcome.

Monitoring and evaluation

Research priorities

- Research regarding differences between staged resection of CRLM combined with colon resection vs rectal resection.
- Differences in rates and consequences of incisional hernia after open vs MIS hepatectomy
- Quality of life, short and long-term after open vs MIS hepatectomy
- Return to intended oncologic therapy after open vs MIS hepatectomy
- RCTs better powered to address long term oncologic outcomes