

Table 1. Study characteristics of systematic reviews for local therapy in metastatic melanoma

| Author, Year, Study design    | Number of included studies in this literature analyses and study design  | Patients, age   | Intervention vs control   | Follow-up                   | Outcomes  | Author's conclusion   |
|-------------------------------|--|---|---|-----------------------------|---|---|
| <b>Surgical intervention</b>  |  |   |   |                             |   |   |
| Wankhede, 2022<br><br>SR & MA | Total: n=40<br><ul style="list-style-type: none"> <li>Retrospective: n=38</li> <li>Prospective phase 2 trial n=1</li> <li>Multicentric randomized phase 3 trial n=1</li> </ul> | Patients with metastatic melanoma with cutaneous melanoma as the primary subtype.<br>n= 31.282<br><br>Median age: 46 - 70 years | <u>Intervention:</u><br>Curative metastasectomy (complete resection of metastatic deposit from the organ site under investigation)<br>n= 9.958<br><br><u>Control:</u><br>Non-curative treatment (R1/R2 resection, palliative surgery, systemic therapy, radiotherapy, and end-of-life care)<br>n=21.324 | Median:<br>6.3 to 93 months | <ul style="list-style-type: none"> <li>Overall mortality</li> <li>Median survival</li> <li>5-year OS</li> </ul> | <i>“Curative metastasectomy for MM is associated with a lower risk of death than non-curative treatment methods. Selection bias and underlying weakness of studies reduced the strength of evidence in this review. However, CM should be a part of the multimodality treatment of MM whenever technically feasible.”</i> |

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| Yeo, 2022<br>SR & MA                 | Total: n=13<br><ul style="list-style-type: none"> <li>Retrospective: n=11</li> <li>Prospective: n=2</li> </ul>  | Patients with liver metastases from malignant melanoma.<br>n= 3.422<br><br>Mean age, years:<br><ul style="list-style-type: none"> <li>Surgery: 43.5 ± 10.9</li> <li>Non-surgery: 53.1 ± 16.1</li> </ul> | <u>Intervention:</u><br>Liver resection n= 749 (21.9%)<br><br><u>Control:</u><br>Non-surgical arm n= 2.673 (78.1%)   | Mean in months:<br><ul style="list-style-type: none"> <li>Surgery: 54.6 ± 11.6</li> <li>Non-surgery: 52.9 ± 16.4.</li> </ul>   | <ul style="list-style-type: none"> <li>Postoperative mortality</li> <li>30-day mortality</li> <li>median OS</li> <li>1-year OS</li> <li>2-year OS</li> <li>3-year OS</li> <li>4-year OS</li> <li>5-year OS</li> </ul> | <i>“This study suggests that surgical treatment of melanoma liver metastases could offer better OS outcomes compared with non-surgical treatment.”</i>                                   |
| <b>Laser and light-based therapy</b> |   |   |  |  |   |  |
| Austin, 2017<br>SR                   | Total: n=27<br><ul style="list-style-type: none"> <li>Case-report: n=10</li> <li>Not specified: n=17</li> </ul> | Metastatic melanoma patients.<br>n= 397<br><br>Age: NR  | <u>Intervention:</u><br><ul style="list-style-type: none"> <li>Ablative laser therapy: 10 studies including n=318 patients</li> <li>Non-ablative laser therapy: 9 studies including n=50 patients</li> </ul> | <ul style="list-style-type: none"> <li>Ablative laser therapy: Between 1 month – 10 y</li> <li>Non-ablative laser therapy: 8 weeks – 6.5 y</li> <li>Photodynamic therapy: 4 weeks – 2 y</li> </ul> | <ul style="list-style-type: none"> <li>Response</li> <li>Recurrences</li> <li>Adverse events</li> </ul>   | <i>“Additional clinical research with standardized outcome measures involving contemporary LLBT devices may yield promising results. The evidence demonstrates that LLBT could an be</i> |

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|                              |  |  | <ul style="list-style-type: none"> <li>Photodynamic therapy: 8 studies including n=29 patients</li> </ul> <p>Control:<br/>Not applicable</p> |  |  | <i>effective palliative option in combination with standard of care treatment for MM and may improve patient's quality-of-life and MM burden without subjecting patients to costly procedures, long hospital stays and significant AEs."</i> |
| <b>Electrochemotherapy</b>   |  |  |  |  |  |  |
| Aguado-Romeo, 2016<br><br>SR | Total: n=7 <ul style="list-style-type: none"> <li>Systematic reviews=3</li> <li>Spratt (2014): 47 studies of which 11 with ECT</li> <li>AETS (2011): 26 studies (13 case series, 13 with control group)</li> </ul> | Unresectable cutaneous and/or subcutaneous metastatic melanoma (in transit, satellite, distant) at any site. | <u>Intervention:</u><br>ECT as monotherapy and as therapy combined with isolated limb perfusion in patients with high tumor load n=1.181     | <ul style="list-style-type: none"> <li>Systematic reviews: NR</li> <li>Case series range: 6-67 months</li> </ul> | <ul style="list-style-type: none"> <li>Effectiveness</li> <li>Clinical response (measured as complete response, partial response, disease-free)</li> </ul> | <i>"There is no evidence that electrochemotherapy alters the natural course of the disease and it should therefore be considered a palliative treatment. With an evidence</i>  |

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|                            | <p>Mali (2013): 9 studies</p> <ul style="list-style-type: none"> <li>Case series: n=4 (Caracò 2013, Ricotti 2013, Solari 2014, Skarlatos 2011)</li> </ul> | <p>Number of patients, mean age in years</p> <ul style="list-style-type: none"> <li>Sprat (2014): n=176, age: NR</li> <li>AETS (2011) n=693, age 56.9</li> <li>Mali (2013) n=197, age: NR</li> <li>Caracò (2013): n=60, age 62</li> <li>Ricotti (2013): n=30, age 75</li> </ul> | <p>Control:<br/>NR</p>  |           | <p>Period, overall survival, recurrence rate, stable disease)</p> <ul style="list-style-type: none"> <li>Safety</li> <li>Adverse effects associated with the procedure</li> <li>Toxicity</li> </ul> | <p><i>level of 1- (minus), electrochemotherapy can be recommended for the palliative treatment of unresectable, locally advanced melanoma (grade B recommendation)."</i></p> |

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|                            |  | <ul style="list-style-type: none"> <li>Solari (2014): n=20, age 72</li> <li>Skarlatos (2011): n=5, age 69.8</li> </ul>  |   |   |   |  |
| <b>Radioembolization</b>   |  |   |   |   |   |  |
| Jia, 2017<br>SR            | Total: n=3<br><ul style="list-style-type: none"> <li>Observational: n=3 (Piduru, 2012; Memon, 2014; Xing, 2017)</li> </ul> | Patients with unresectable liver metastasis of melanoma.<br><br>Number of patients, age in years<br><ul style="list-style-type: none"> <li>Piduru, 2012: n=12 (5 cutaneous and 7 ocular), age: 53</li> <li>Memon, 2014</li> </ul> | <u>Intervention:</u><br>90Y radioembolization n=56<br><br><u>Control:</u><br>Not applicable | <ul style="list-style-type: none"> <li>Piduru, 2012: NR</li> <li>Memon, 2014: NR</li> <li>Xing, 2017 39.6 months</li> </ul> | <ul style="list-style-type: none"> <li>Disease control rate, %</li> <li>Cases of CR, PR, SD, PD, n</li> <li>Overall survival, mo</li> <li>1-year survival rate %</li> <li>Side effects</li> </ul> | <i>"In conclusion, 90Y radioembolization therapy is an effective treatment for unresectable liver metastases of melanoma, with encouraging effects on disease control and survival. However, prospectively gathered data are needed to further demonstrate the</i> |

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|                            |   | n=16 (4 cutaneous and 7 ocular, 3 rectal, 2 unknown), age: 57<br>• Xing, 2017<br>n=28 (13 cutaneous and 15 ocular), age: 49.5 |                         |           |          | <i>benefit of 90Y radioembolization in this patient population.</i> |

SR: Systematic review; MA: Meta-analysis; NR: Not reported; ICI: Immunotherapy; stereotactic radiation therapy (SRS/SBRT); ECT: Electrochemotherapy