Table 1: NHMRC Evidence Statement for clinical question: MNG16 “What is the impact of different liver directed therapies in patients with incurable metastatic colorectal cancer?”

**PICO Question MNG16:** In patients with incurable metastatic colorectal cancer, what are the effects of liver-directed therapies on survival and quality-of-life outcomes, compared with standard care?

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<th>Evidence base (number of studies (quantity), level of evidence and risk of bias in the included studies – see body of evidence tables in report)</th>
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<td><strong>A</strong> One or more level I studies with a low risk of bias or several level II studies with a low risk of bias</td>
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<td><strong>B</strong> One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias</td>
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Seven Level II studies were found comparing liver directed therapies to systemic chemotherapy only in colorectal cancer patients with metastatic incurable liver disease. Six of the studies looked at ablative therapies with or without systemic chemotherapy in comparison to systemic chemotherapy alone. The final study looked at hepatic arterial infusion (HAI).

Three studies provided Selective Internal Radiation Therapy (SIRT) using Yttrium-90 resin microspheres in addition to a systemic chemotherapy. The systemic chemotherapies used were mFOLFOX6 (Van hazel 2016), intravenous fluorouracil (FU) (Hendlisz 2010) and systemic FULV (Van hazel 2004). The median follow up between two studies ranged from 10.2 (van hazel 2016) to 24.8 months (Hendlisz2010). The final follow up for the third study was 36 months (Van hazel 2004). All patients were previously untreated and chemotherapy naïve or were resistant to previous chemotherapies. The two other studies had small sample sizes of 21 (Van Hazel 2004) and 44 (Hendlisz2010).

One study provided radiofrequency ablation (RFA) in addition to FOLFOX4 with a median follow up of 4.4 years (Ruers2012) in a cohort of 119 participants. 85.7% of the total 119 had undergone previous chemotherapy and 16% had previous liver surgery. Patients who received previous adjuvant chemotherapy were included if it was terminated at least 12 months before detection of metastatic disease.

Another study provided drug eluting beads with irinotecan (DEBIRI) in addition to mFOLFOX with a median follow up of 19 to 24 months (Martin 2015). This was a study of 70 patients. Patients were chemotherapy naïve but may have had prior surgery with 54% having undergone past surgery on the primary colon or rectal tumor.
One study with a total of 74 patients reported DEBIRI on its own in comparison to FOLFIRI with median follow up of 50 months (Fiorentini 2012). Patients who had previously received chemotherapy were included if it had been completed 3 months before protocol therapy. 65% of the total 74 patients had undergone previous chemotherapy.

The final study where HAI was provided as treatment in comparison to systemic chemotherapy had a final follow up of 15 months. Of the total 135 participants, 97% of patients had received previous chemotherapy 12 months prior.

For patients in SIRFLOX, 88.6% of patients in the treatment group were of synchronous metastases with 90.3% in the control group. Most patients had ≤25% liver tumour involvement with 73% in the treatment group and 69.3% in the control group. Similarly in Van Hazel (2004)'s SIRT and FULV study, 71% of patients had liver metastases size <25%. 24% of patients also had extrahepatic metastases. In the study which looked at SIRT and FU, 45% of patients measured 2-4 liver lesions and 41% had ≥5 lesions measured (Hendlisz 2010).

In the RFA study, most patients were of metachronous metastases with 61.7% in the treatment arm (Ruers2012). Those with metachronous or synchronous metastases were fairly balanced in the control arm, 52.5% with metachronous metastases and 47.5% with synchronous.

The balance between synchronous and metachronous disease seemed similar with the DEBIRI and mFOLFOX study (Martin 2015). Out of 70 participants, 53% in the treatment arm and 57% in the control were with synchronous metastases. More patients receiving the combination therapy had extrahepatic disease with 55% in the treatment arm and 31% in the control arm.

For the DEBIRI only study, all patients had metachronous disease and 70% had ≤25% liver involvement (Fiorentini 2012). In the HAI study, the median liver involvement was 40% and 79% of all patients were of synchronous disease (Kemeny 2006).

Only one Level II study had low risk of bias (Van Hazel 2016). The largest study was the SIRFLOX trial (Van Hazel 2016) which held 530 patients. For the remaining studies, participant patient sizes ranged from 21 to 135. In five studies (Van Hazel 2016, martin 2015, Ruers 2012, Hendisz 2010, Kemeny 2006), the
median age of participants ranged from 57 – 63 years at the time of recruitment. The mean age for two studies ranged from 63 to 65 years (Fiorentini 2012, Van Hazel 2004).

Two Level II studies (Kemeny 2006; Van Hazel 2004) were at risk of bias, for the reported outcomes of survival, adverse events and toxicity, time to progression or progression free survival and tumour response. Another Level II study was at risk of bias for the same outcomes (Fiorentini 2012). This was due to randomisation processes involving sequence generation, allocation concealment or blinding were not made clear in these studies.

Two other Level II studies at risk of bias (Martin 2015; Hendlisz 2010) looked at the same outcomes with one study also reporting the resection rate (Martin 2015). In one study, 10 participants were purposively placed in the treatment group and allocation was not concealed appropriately (Martin 2015). The other study was an open-label design and did not explain incomplete data (Hendlisz 2010). Another Level II study reported only adverse events, progression free survival and overall survival and was at risk of bias (Ruers 2012). Blinding processes were not reported and potentially selective reporting may have occurred with results for tumour response not reported despite it being pre-specified.

Four Level II studies reported quality of life outcomes (Fiorentini 2012; Ruers 2012; Kemeny 2006; Van Hazel 2004). Three were at risk of bias as randomisation processes were not made clear (Ruers 2012; kemeny 2006; Van Hazel 2004). For one study, it was also unclear whether there was incomplete data for these outcomes (Ruers 2012). One Level II study did not explain incomplete data for their quality of life outcomes which put it at risk of bias (Fiorentini 2012).

All studies included patients with histologically confirmed colorectal cancer and unresectable liver metastases.

Grade D

2. Consistency (If only one study was available, rank this component as ‘not applicable’) See body of evidence tables in report – results and p value (95% CI)
**Tumour Response**

Two studies reported generally improved tumour response rate for patients who received SIRT in addition to a systemic chemotherapy (Van Hazel 2016; Van Hazel 2004). At 60 months follow up, the SIRFLOX trial (Van Hazel 2016) reported improved tumour response rate in treated patients, 76.4% in comparison to 68.1% in those who received only systemic chemotherapy (p=0.113).

In greater detail, there were more reports of complete response (p=0.054) and partial response in treated patients (Van Hazel 2016). While no complete response was reported in Van Hazel's (2004) study, this trend was also seen in the first integrated response and best confirmed response. At 36 months follow up, no improvement in response was seen in patients who did not receive SIRT at either first integrated or best confirmed response. In patients who additionally received SIRT, 91% at the first integrated response and 73% at best confirmed response reported a partial response. There was strong significance to the differences between the two arms (p<0.001).

Consequently, fewer patients in the treatment arm had only stable disease. In the SIRFLOX trial, 10.5% reported stable disease in the treatment arm compared to 18.3% in the control arm (Significance was not reported). In Van Hazel's (04) study, at first integrated response, 9% of SIRT patients reported stable disease compared to 60% of those who did not receive SIRT. At best confirmed response, 27% of SIRT patients were reported with stable disease compared to 60% of those who did not receive SIRT. (Significance was not reported for either outcome).

Unlike the previous patterns, more SIRT patients in the SIRFLOX trial experienced progressive disease although this was a small percentage in both groups. 9.4% of patients who received SIRT experienced progressive disease in comparison to 6.5% of patients in the control arm (Significance of this was not reported). However returning to previous trends, Van Hazel's (2004) study reported progressive disease in systemic chemotherapy patients only, 40% at both first integrated and best confirmed response (Significance of this was not reported).

The improved tumour response was reflected in the hepatic or liver response rate, reported in two studies. In the SIRFLOX trial, 78.7% of SIRT patients reported significant improvement of the liver tumour versus 68.8% of control patients (p=0.042).

Again, more patients in the treatment arm showed a complete and partial response in the

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liver than those in the control arm (Van hazel 2016). In the SIRFLOX trial, 6% of SIRT patients reported significantly improved complete response in the liver than 1.9% of control patients (p=0.02). In Hendlisz (2010)'s study, no patients experienced complete response at 24.8 months median follow up. However, it was seen that only SIRT patients reported partial response to treatment in the liver (p=0.22, 95%CI -0.10 – 0.32 in difference).

Continuing from this, the SIRFLOX trial found fewer SIRT patients with stable disease of the liver than systemic chemotherapy patients, 10.9% in comparison to 17.9% respectively at 60 months follow up (Significance of these were not reported). In contrast, Hendlisz (2010) found significantly more SIRT patients with stable disease than systemic chemotherapy patients, 76% in comparison to 35% respectively (p=0.001, 95% CI 0.19 – 0.71).

Diverging from the overall tumour response rate, the SIRFLOX trial found a slightly higher proportion of SIRT patients who reported progressive disease in the liver. There were 6.7% in the treatment arm compared to 6.1% in the control arm at 60 months follow up. Significance was not reported. Hendlisz (2010) found substantially fewer SIRT patients with progressive disease of the liver than systemic chemotherapy patients, 10% and 61% respectively (Significance was also not reported).

Generally, the two studies agreed that the addition of SIRT to systemic chemotherapy was able to improve both overall tumour and hepatic response. This was reflected in the complete and partial response rates. This was much the same of stable disease rates in the primary tumour response. However the two studies contradict the other when looking at stable disease and progressive disease in the liver response. It is not clear the direction of improvement as significance was rarely reported or only one study reported significance while the other did not.

One study looked at the overall tumour response rate in patients who received DEBIRI in addition to systemic chemotherapy (Martín 2015). There was significant improvement of overall response rate in DEBIRI patients in comparison to systemic chemotherapy patients at 2 months, 4 months and 6 months (p=0.01, p=0.03 and p=0.05 respectively) although the endpoints were not reported specifically. When reviewed with RECIST v1.1, the proportion appeared similar across the two groups and at the 2, 4 6 months with no significance found. When reviewed with Choi's Criteria, DEBIRI patients showed more improvement in tumour response than systemic chemotherapy patients. At 2 months, 90% of DEBIRI patients reported a significantly greater response compared to 82% of systemic chemotherapy patients (p=0.01). While this was the same at 4 and 6 months,
these were not statistically significant (p=0.09 and p=0.12 respectively). At 12 months, the overall response rate of DEBIRI patients were reported at 50% while those who received only systemic chemotherapy was at 24%. This was reportedly statistically significant although the p-value was not reported.

Although endpoints and significance were not specifically reported in the study, the target lesion response of DEBIRI patients were significantly better than those who did not receive DEBIRI at 2, 4 and 6 months (p=0.02, p=0.03, p=0.05 respectively). Overall, it appeared the addition of DEBIRI significantly improved tumour response. It should be kept in mind that the treatment group within Martin’s (2015) study may be heavily biased to an effect as 25% of the patients were purposively placed to receive DEBIRI.

One study reported the overall tumour response in patients who received only DEBIRI compared to those who received systemic chemotherapy only. At median follow up of 50 months, greater DEBIRI patients reported an overall tumour response and fewer were with stable disease. Tumour response was reported in 68.6% of DEBIRI patients compared to 20% in systemic chemotherapy patients. Stable disease was reported in 11.4% of DEBIRI patients compared to 34.3% in those did not receive DEBIRI. Fewer DEBIRI patients also reported progression of the tumour in comparison to systemic chemotherapy patients, 20% and 45.7% respectively. The significance of these was not known as they were not reported.

The studies agreed that patients who received DEBIRI in addition to standard care or on its own still resulted in a general improved tumour response.

One study reported greater tumour response rate at 6 years follow up in patients who received HAI (Kemeny 2006). Overall tumour response was reported in 49% of HAI patients and 24% of those who received only systemic chemotherapy (p=0.012). This was as 3% of HAI patients reported a complete response while none occurred in systemic chemotherapy patients and 44% of HAI patients reported a partial response with 24% tumour response being partial in the systemic chemotherapy arm. There was also fewer HAI patients who reported stable disease at 17% and 21% reported in systemic chemotherapy patients. The significance of these was not reported.

Tumour response rate was not a reported outcome in the RFA study (Ruers 2012).

These studies generally agree the use of SIRT and DEBIRI with or without chemotherapy mostly provide a benefit for overall tumour response rate in colorectal cancer patients with incurable liver disease. Inconsistencies between the two arms are minimal and relate
to the hepatic response.

**GRADE C**

**Progression Free Survival**

Mean progression free survival was significantly longer for those who were treated with RFA and systemic chemotherapy than just chemotherapy alone at 4.4 years median follow up, HR=0.63 (65% CI 0.42 – 0.95, p=0.025). In Ruers (2012) study, RFA patients reported 16.8 months (95% CI 11.7 – 22.1) and systemic chemotherapy patients reported 9.9 months (95% CI 9.3 -13.7). The rate of progression free survival was also significantly higher (p=0.025) in the treatment arm at 27.6% (95% CI 16.9 – 39.5%) and 10.6% in the control arm (95% CI 4.2 – 20.5%).

For patients who received SIRT and systemic chemotherapy, progression free survival generally showed an improvement. In the SIRFLOX trial, median progression free survival at 60 months follow up were similar between the two arms with a weak benefit suggested by an HR of 0.93 (95% CI 0.77 – 1.12). SIRT patients reported 10.7 months and systemic chemotherapy only patients reported 10.2 months (p=0.43). Hendlisz (2010) found a significantly longer median time to progression for SIRT patients at 26 months follow up (p=0.03). SIRT patients reported 4.5 months and systemic chemotherapy only patients reported 2.1 months with a HR of 0.51 (95% CI 0.28 – 0.94). Likewise, Van Hazel (2004) found significantly longer median time to disease progression for SIRT patients than systemic chemotherapy patients at 36 months follow up (p<0.0005). They were reported at 18.6 months and 3.6 months respectively. This was the same for liver progression free survival outcomes. In the SIRFLOX trial, the median liver PFS for SIRT patients were significantly longer than those who received only systemic chemotherapy, 20.5 months and 12.6 months respectively (p=0.002). Hendlisz (2010) observed reduced events of liver progression in SIRT patients than systemic chemotherapy only patients, 18 and 23 respectively (significance not reported). The censored median TTLP also showed SIRT patients to be significantly longer at 5.6 months with systemic chemotherapy patients reporting 2.1 months, (HR = 0.35, 95% CI 0.19 – 0.69, p = 0.002).

Significantly longer PFS was also reported for patients who received DEBIRI only
At 50 months follow up, DEBIRI patients reported 7 months (95% CI 3 – 11 months) and systemic chemotherapy patients reported 4 months (95% CI 3 – 5 months), p=0.006. The median time to hepatic progression was also longer in DEBIRI patients at 7 months while systemic chemotherapy patients reported 4 months (p=0.006). This was the same of the median time to extra-hepatic progression although there was poor significance (p=0.64). This was reported at 13 months (95% CI 10 – 16 months) and 9 months (95% CI 5 – 13 months) respectively.

Unlike patients who received RFA or SIRT in addition to chemotherapy, those who received DEBIRI in addition to chemotherapy reported a slightly shorter median PFS than systemic chemotherapy only patients at 24 months median follow up in Martin (2015)’s trial. This was 12 months (95% CI 9 – 15.4) and 15 months (95% CI 10.4 – 20) respectively, (p=0.18). Overall extra-hepatic median PFS was also shorter, 7 months (95% CI 9- 38 months) and 16 months (95% CI 10 – 38 months) respectively (p=0.35). This may be explained by the greater extrahepatic disease in the treatment group compared to the control and this may been due to the addition of non-randomised participants. However, longer median liver non-target-liver-only was observed. DEBIRI patients reported 21 months (95% CI 12 – 28 months) in comparison to 15 months (95% CI 10.8 – 24 months) reported for systemic chemotherapy patients (p=0.68). While the liver target median PFS was not reported, any benefit given was reportedly not significant. The median liver PFS was also longer in DEBIRI patients at 17 months (95% CI 12 – 23 months) with 12 months (95% CI 11-24) reported for systemic chemotherapy only patients (p=0.05).

Similarly, Kemeny (2006) found a slightly shorter median TTP for patients who received HAI at 3 years follow up (p=0.95) despite 76% of treated patients having received primary tumour resection. This was reported at 5.3 months while systemic chemotherapy patients reported 6.8 months. However, following other liver directed therapies above, median time to hepatic progression was significantly longer (p=0.034). This was reported at 9.8 months for HAI patients and 7.3 months for systemic chemotherapy only patients. Median time to extra-hepatic progression was significantly shorter with HAI patients reporting 7.7 months and systemic chemotherapy patients reporting 14.8 months (p=0.029).

With SIRT and RFA in addition to systemic chemotherapies and DEBIRI alone, there were consistent findings overall for an improved PFS for the primary and hepatic tumour. A benefit given by HAI and the addition of DEBIRI was observed only for time to hepatic progression and median liver PFS. There was little to no benefit observed for median PFS. Significance varied across the studies.
**Grade B**

**Overall Survival**

In patients who received RFA in addition to systemic chemotherapy, median overall survival was slightly longer at 4.4 years median follow up. RFA patients reported 45.3 months while systemic chemotherapy only patients reported 40.5 months (95% CI 29.5 – 50.1). This had weak significance with the HR at 0.74 (95% CI 0.45 – 1.19, p=0.22). Overall survival at 30 months was also found improved in the RFA patients than systemic chemotherapy patients (p=0.218). This was 61.75% (95% CI 48.2 – 73.9) and 57.6% (95% CI 44.1 – 70.4) respectively.

For patients receiving SIRT in addition to systemic chemotherapy, median overall survival was reported to be longer in treated patients at 24.8 median months follow up (Hendlisz 2010). Although this had weak strength to the evidence with HR = 0.92 (95% CI 0.47 – 1.78), SIRT patients reported 10 months while systemic chemotherapy patients were reported at 7.3 months (p=0.8). Median survival was significantly longer for treated patients at 36 months follow up in Van Hazel’s (2004) study (p=0.025). They reported 29.4 months for SIRT patients and 12.8 months for systemic chemotherapy patients (HR = 0.33, 95% CI 0.12 – 0.91). The censored median survival also showed the same with weaker strength (HR=0.39, 95% CI 0.14 – 1.13, p=0.07).

For patients who received only DEBIRI, overall median survival were significantly longer in comparison to those who received systemic chemotherapy only at 50 months median follow up (p=0.031). This was reported at 22 months (95% CI 21 – 23) and 15 months (95% CI 12 – 18 months) respectively. This was reflected at 2 years, 30 months and 50 months follow up although the significance of these was not reported. At two years, 56% was reported for DEBIRI patients and 32% was reported for systemic chemotherapy patients. At 30 months, 34% were reported for DEBIRI patients and 9% were reported for systemic chemotherapy patients. At 50 months, 15% were reported for DEBIRI patients and 0% were reported for systemic chemotherapy patients.

Survival was not a reported outcome in Martin (2015)’s study which looked at DEBIRI in addition to systemic chemotherapy.

For patients who received only HAI, overall survival was significantly longer than systemic chemotherapy patients at 6 years follow up (p=0.0034). This was 24.4 months and 20 months respectively. This was also seen at 2 years follow up where overall survival was reported for HAI patients at 51% and 25% for systemic chemotherapy patients.
Studies agree that the use of SIRT with chemotherapy and DEBIRI or HAI alone, extend the overall survival of colorectal cancer patients with unresectable liver disease although significance varied.

GRADE C

Reection Rate

Only the SIRFLOX trial and Martin (2015) reported resection rate.

At 60 months follow up, there was slight improvement for the SIRT arm relative to the systemic chemotherapy only arm in the SIRFLOX trial (p=0.857). The resection rate for SIRT patients was 14.2% and 13.7% for systemic chemotherapy only patients. Martin (2015) reported a substantially greater resection rate for DEBIRI patients at 35% compared to 6% in systemic chemotherapy only patients (p=0.05).

Addition of SIRT or DEBIRI to systemic chemotherapy appears to show little to some benefit over standard care in improving the resection rate. There is poor strength to the evidence.

GRADE D

Adverse Events

For patients who received RFA in addition to systemic chemotherapy, there were higher reports of adverse events than non-RFA patients after 4.4 years median follow up (Ruers2012). The significance of these was not reported but among these the most commonly reported event was neutropenia which was 28.5% of RFA patients and 20.3% in non-RFA patients. Diarrhoea was reported in 19.6% of RFA patients and 16.9% of non-RFA patients. Grade 3 neuropathy was reported in 17.6% of RFA patients and 13.6% of non-RFA patients. Grade 3 nausea also occurred in 13.7% of RFA patients and 10.2% of non-RFA patients and there were reports of Grade 3 fatigue in 13.7% of RFA patients and 6.8% of non-RFA patients.

For patients who received SIRT in addition to systemic chemotherapy, there were also more reports of adverse events than non-SIRT patients. Greater total adverse events (≥
Grade 3) than non-SIRT patients were reported in SIRFLOX at 60 months follow up (Van Hazel 2016). This was reported at 85.4% and 73.4% respectively (p=0.516). There were significantly more incidence of neutropenia (p=0.004), febrile neutropenia (p=0.02), thrombocytopenia (p<0.001), fatigue (p=0.019) and abdominal pain (p=0.009). Incidences of other events held little to no difference between the two arms and were not significant findings. There were also slightly higher total Grade 5 events in SIRT patients at 3.7% with 1.9% in non-SIRT patients (p=0.279). This was the same of treatment related Grade 5 events. A majority of these were SIRT associated events with SIRT patients reporting gastric/duodenal ulcers (p=0.001), ascites (p=0.005), hepatic failure and radiation hepatitis. Although endpoints were not reported, there was a significant difference between the groups in terms of haemotologic toxicities (p<0.05). There were also significantly greater serious adverse events reported in SIRT patients (p=0.005). 54.1% were reported in SIRT patients and 41.6% reported in non-SIRT patients.

This was supported by findings in Hendlisz (2010). After 24.8 months median follow up, there were greater reports of gastrointestinal events, neurology and other toxicities in SIRT patients compared to non-SIRT patients. Gastrointestinal events were reported in 71% of SIRT patients and 68% of non-SIRT patients. Pain was reported in 29% of SIRT patients and 23% of non-SIRT patients. The significance of these were not reported. However, fewer SIRT patients reported constitutional effects at 52% with 64% in non-SIRT patients. There were also fewer dermatology/skin events, pulmonary, cardiac arrhythmia and allergies in SIRT patients but the significance of these were not reported either. In opposition to the SIRFLOX findings, fewer Grade 3 or 5 toxicities were reported for SIRT patients. This was reported in 5% of SIRT patients compared to 27% of non-SIRT patient, however this was not significant (p=0.1).

In Van Hazel’s (2004) study, more Grade 3 and 4 toxicity events occurred in SIRT patients than non-SIRT patients, 13 and 5 respectively. There were particularly greater reports of granulocytopenia, anorexia, cirrhosis, mucositis and diarrhoea. One death out of the entire trial was attributed to SIRT. No significance was reported for any of these outcomes in Van Hazel’s (2004) trial.

For patients who received DEBIRI in addition to systemic chemotherapy, there were greater total adverse incidences (Martin 2015). At 38 months follow up, 973 incidences occurred in DEBIRI patients and 459 incidences occurred in non-DEBIRI patients (p=0.15). In a subgroup analysis, this was reflected across mild, moderate, severe and life threatening categories of adverse events. The significance of these was not reported. Most incidences were mild with 540 in DEBIRI patients and 316 in non-DEBIRI patients. There were high rates of Grade 3-4 adverse events in DEBIRI patients, reported in 80%
of treated patients and 60% in non-DEBIRI patients. These events included neutropenia, abdominal, procedural hypertension and hepatobiliary events among others. There were higher incidences of gastrointestinal events with 26 incidences reported in DEBIRI patients and 9 in non-DEBIRI patients. The significance of these was not reported. There were also high incidences of specific adverse events with 90 reported in DEBIRI patients and 27 in non-DEBIRI patients (p=0.14). Most were gastrointestinal with 206 reported in DEBIRI patients and 120 in non-DEBIRI patients (p=0.12). The rest of these specific adverse events were reportedly non-significant.

For patients who received DEBIRI only, there were significantly fewer grade ≥ 3 neutropenia events after 50 months median follow up (Fiorentini 2012). This was reported at 4% in DEBIRI patients and 44% in systemic chemotherapy patients (p<0.0001). This was the same of mucositis events (p=0.0002) and diarrhoea (p=0.073). However there were also significantly greater liver enzyme elevations in DEBIRI patients at 58% and 8% in systemic chemotherapy patients (p<0.0001) as well as greater bilirubin elevation, 18% and 1% respectively (p<0.00002). Haematological toxicity as well as haematological and gastrointestinal side effects were reported 7 times in DEBIRI patients and 11 times in systemic chemotherapy only patients. It is not clear how this compares to DEBIRI patients as it was not reported. Liver relapse was reported in fewer DEBIRI patients at 49% with 66% in systemic chemotherapy patients. However there were higher rates of extra-hepatic relapse in DEBIRI patients at 51% compared to 34% in systemic chemotherapy patients. Significance of this was not reported.

Similar to patients who received DEBIRI alone, those who were treated with HAI alone reported fewer grade ≥ 3 neutropenia (Kemeny 2006). There were no reports in HAI patients compared to 45% reported in systemic chemotherapy patients (p<0.0001) at 6 years follow up. Likewise, there were fewer reports of diarrhoea and stomatitis. Diarrhoea occurred in 5% of HAI patients and 16% of systemic chemotherapy patients (p=0.075). There were no incidences of stomatis in HAI patients but was reported in 24% of systemic chemotherapy patients (p<0.00002). However, there were significantly greater reports of bilirubin elevation ≥ 3mg/dL in HAI patients (p=0.006). This was reported in 18.6% of HAI treated patients with no occurrences reported in systemic chemotherapy only patients. Alkaline phosphate and aminotransferase elevation ≥ 3mg/dL were also reported at 33.8% and 27% of HAI patients respectively. This could not be compared between the two arms as the same outcome was not reported for systemic chemotherapy only patients.

There were consistent reports of increased adverse events in patients who received RFA, SIRT and DEBIRI with chemotherapy. Of particular note was neutropenia, diarrhoea,
fatigue, abdominal pain, haematologic toxicities and gastrointestinal events. In using DEBIRI or HAI alone, fewer adverse events were reported. Significance was either not known or varied.

**Grade C**

**Quality of Life**

Health-related Quality of Life (QoL) was assessed for patients who were treated with RFA in addition to systemic chemotherapy using the EORTC QoLQ-C30 Questionnaire. At 8 weeks follow up, there was a difference of approximately 10 points in mean global QoL. After 4.4 years median follow up, it was 27 points. It is not clear how this compared to systemic chemotherapy patients as results were descriptive with no endpoints reported and no significance reported either.

For patients who received SIRT in addition to systemic chemotherapy, only Van Hazel (2004) has reported QoL outcomes. The SIRFLOX trial will be releasing this in future with other studies. At 3 months follow up, QoL was measured using a validated 23 point FLIC questionnaire. Clinicians also assessed the patients’ wellbeing using the Spitzer index. No endpoints were reported however no significance was found to any differences between the groups. It was reported that changes in the quality of life was almost identical in the two arms (p=0.96) as was with the physician rated quality of life (p=0.098). Since patients were still receiving chemotherapy during this period, this may be biasing towards a lack of effect.

QoL was not reported for patients who received DEBIRI in addition to systemic chemotherapy. However in Fiorentini’s (2012) study, QoL was measured using the Edmonton Symptom Assessment System and Edmonton scale for patients who received DEBIRI alone. Physical functioning of DEBIRI patients were reportedly better than those of systemic chemotherapy only patients at 1 months (p=0.038), 3 months (p=0.025) and at 8 months (p=0.025). The time to decline in QoL at 12 months follow up took significantly longer in DEBIRI alone patients (p=0.0002) at 8 months (95% CI 3 – 13 months) compared to systemic chemotherapy patients which was reported at 3 months (95% CI 2- 4 months).

In patients who were treated with HAI alone, QoL physical functioning was assessed using the Rand 26-item Health Status Profile (Kemeny 2006). HAI patients showed significantly higher rates of physical functioning at 3 months (p=0.038), 6 months (p=0.024) and among late dropouts at 12 months (p=0.001). At 18 months follow up,
overall physical functioning of HAI patients were better than those of systemic chemotherapy patients, 62% and 58% respectively. Significance was not reported. QoL social functioning was measured with the Medical Outcomes Study Sexual Functioning Scale and general health perception were measured with the Memorial Symptom Assessment Scale. The endpoints were not reported however there was reportedly no difference between the two arms in these measures.

Liver directed therapies provided little to no benefit for quality of life in colorectal cancer patients with unresectable liver disease although this is not clear since most results were reported descriptively with the significance either not known or not reported. Furthermore, the varying QoL measure scales are not comparable. However, Fiorentini (2012) and Kemeny (2006) appear to agree that DEBIRI and HAI alone have shown an improved physical functioning.

Grade C

3. Clinical impact See body of evidence tables in report - p value (95% CI), size of effect rating and relevance of evidence (Indicate in the space below if the study results varied according to some unknown factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)

Tumour Response
Significance was either not known or not reported for many of the outcomes across the studies. Significance also varied greatly within and between studies.

Van hazel (2004) showed a significant advantage given to SIRT patients in both the first integrated and best confirmed tumour response at 36 months follow up. Greater complete and partial responses were reported, less remained stable and none progressed (p<0.001). While the improved overall tumour response rate at 60 months follow up in the SIRFLOX trial was not significant (p=0.113), the complete response was close to significance with 4.5% in SIRT patients reporting tumour response and 1.5% in non-SIRT patients (p=0.054). The liver response rate had strong significance to an improved objective response rate with 78.7% reported in SIRT patients and 68.8% reported in non-SIRT patients (p=0.042). There was also strong evidence for an improvement in the liver complete response due to the addition of SIRT with 6% reported in SIRT patients and 1.9% reported in non-SIRT patients (p=0.02).

Likewise, there was an improved best overall hepatic response after a median follow up of 24.8 months in Hendlisz (2010) trial although the evidence was weaker. This was seen in the partial response with 10% reported in SIRT patients and none occurring in non-SIRT patients (p=0.22, 95% CI -0.10 – 0.32). There was strong evidence to suggest however

A Very large
B Substantial
C Moderate
D Slight/Restricted
that more SIRT patients were with stable disease than non-SIRT patients \((p=0.001)\). While fewer SIRT patients who had progressive disease, significance of this was not reported.

Martin (2015) described a significant benefit for the overall response rate of patients who received DEBIRI in addition to systemic chemotherapy at 2 months \((p=0.01)\), 4 months \((p=0.03)\) and 6 months follow up \((p=0.05)\). This advantage was seen when using RECIST v1.1 and Choi’s Criteria. At 2 months \((p=0.01)\) and 12 months follow up, there was a significantly higher overall response rate in the DEBIRI arm using Choi’s criteria. However there was poorer evidence for the advantages of DEBIRI at 4 months \((p=0.09)\) and 6 months \((p=0.12)\) with Choi’s Criteria. Significance was not reported for the other outcomes in this study.

Fiorentini (2012) did not report significance effects for patients who received DEBIRI alone in comparison to systemic chemotherapy. However, DEBIRI appeared to provide a benefit to treated patients, showing a higher tumour response rate at 50 months follow up, less stable disease and fewer with progressive tumours in comparison to patients who did not receive DEBIRI.

There was strong evidence for improved overall tumour response rate in patients who received HAI relative to those who did not (Kemeny 2006) at 6 years follow up \((p=0.012)\). This was reported in 47% of HAI patients and 24% of systemic chemotherapy patients. This advantage was observed in the complete and partial response of HAI patients and there were fewer patients who remained with stable disease although the significance of these was not reported.

Patients treated with RFA in addition to systemic chemotherapy did not report on tumour response.

Overall, the evidence suggests some benefit to tumour response rate with the use of DEBIRI, HAI or the addition of SIRT for colorectal cancer patients with unresectable liver disease.

**Grade C**

**Progression Free Survival**

RFA in addition to systemic chemotherapy showed a significant benefit for the median
progression free survival of patients after 4.4 years median follow up (Ruers 2012). With an HR of 0.63 (95% CI 0.42 – 0.95), RFA patients reported 16.8 months and non-RFA patients reported 9.9 months (p=0.025). The rate of progression free survival was 27.6% in RFA patients and 10.6% in non-RFA patients (p=0.025).

SIRT in addition to systemic chemotherapy gave a strong advantage to the PFS of patients. In the SIRFLOX trial, the median PFS at 60 months follow up was similar between the two arms with poor significance (p=0.43). For SIRT patients, 10.7 months was reported and for non-SIRT patients, 10.2 months was reported with an HR of 0.93 (95% CI 0.77 – 1.12). However SIRT patients reported a significantly longer median PFS in the liver (p=0.002). SIRT patients reported 20.5 months while non-SIRT patients reported 12.6 months with an HR of 0.69 (95% CI 0.55 – 0.90). There was strong evidence for this benefit found by Hendlisz (2010) and Van Hazel (2004). The median time to progression and time to liver progression at 26 months were significantly longer in SIRT patients compared to non-SIRT patients with the HR equal to 0.51 (95% CI 0.28-0.94, p=0.03) and 0.38 (95% CI 0.20 – 0.72, p=0.003) respectively. This remained the same for the censored median TTLP (p=0.002) with the HR at 0.35 (95% CI 0.18 – 0.69). Again, Van Hazel (2004) reported significantly longer median time to disease progression at 36 months for SIRT patients (p<0.0005) at 18.6 months compared to 3.6 months for non-SIRT patients.

DEBIRI in addition to systemic chemotherapy provided a weak benefit to median liver PFS of DEBIRI patients after 24 months follow up (Martin 2015). DEBIRI patients reported 17 months and non-DEBIRI patients reported 12 months (p=0.05). While the liver non-target liver only median PFS was longer for DEBIRI patients, this had poor significance (p=0.68). Any benefit provided for liver target median PFS was not reported however this was said to be non-significant in any case. The median PFS overall and overall extra-hepatic median PFS was shorter in DEBIRI patients but these were not significant (p=0.18 and p=0.35 respectively).

For patients who received DEBIRI only, there was significantly longer PFS and longer median time to hepatic progression after 50 months median follow up. PFS and median TTHP for DEBIRI patients were reported both at 7 months while non-DEBIRI patients reported 5 (p=0.006) and 4 months (p=0.006) respectively. Median time to extra-hepatic progression was also longer for those who received DEBIRI although this had very poor significance (p=0.64).

Patients who received HAI (Kemeny 2006) showed a significant benefit in median time to hepatic progression after 3 years follow up (p=0.034). However there was also strong evidence to suggest a shorter median time to extra-hepatic progression in HAI patients.
Median time to progression was also shorter although this did not have much significance (p=0.95).

The strength of evidence for liver directed therapies to extend progression free survival varied from poor to strong across the studies. However, most studies reported a benefit overall.

**Grade C**

**Overall Survival**

There was weak significance to improvements in the overall survival of patients who received RFA in addition to systemic chemotherapy (Ruers 2012). After 4.4 years median follow up, the median overall survival for RFA patients were 45.3 months in comparison to 40.5 months for systemic chemotherapy patients (HR=0.74, 95% CI 0.46 – 1.19).

Fiorentini (2012) reported strong significance to an extended overall median survival of patients who received DEBIRI only (p=0.031). This was reflected at 24, 30 and 50 months survival rates although the significance of these was not reported.

Across the studies which looked at SIRT in addition to systemic chemotherapy, an improved overall survival was reported although significance varied in strength. This had strong significance in Van Hazel’s (2004) trial (p=0.025, HR=0.33, 95% CI 0.12 – 0.91) but became weaker when censored (p=0.07, HR=0.39, 95% CI 0.14 – 1.13). Hendlisz (2010) also reported little significance to the advantage observed in median overall survival (p=0.8, HR=0.92, 95% CI 0.47 – 1.78).

In Kemeny’s (2006) trial, HAI significantly extended the overall survival of patients at 6 years follow up (p=0.034).

While the liver directed therapies RFA, SIRT with chemotherapy and HAI or DEBIRI alone have been reported to extend the overall survival of colorectal cancer patients with unresectable liver disease, significance varied.

**Grade C**

**Resection Rate**
In the SIRFLOX trial (Van Hazel 2016), there was little significance between the two arms in terms of liver resection rate (p=0.857). Patients receiving SIRT in addition to systemic chemotherapy reported minimal improvement at 14.2% compared to 13.7% of non-SIRT patients. In Martin (2015)'s trial, there was a substantially higher resection rate in patients who received DEBIRI in addition to systemic chemotherapy, however this bordered on what was considered statistically significant (p=0.05). There is inconclusive evidence to suggest a definitive benefit given by liver directed therapies in improving resection rate in colorectal cancer patients with incurable liver metastases.

**Grade D**

**Adverse Events and Toxicity**

In the SIRFLOX trial (Van Hazel 2016), there was strong significance to higher incidences of neutropenia, febrile neutropenia, thrombocytopenia, fatigue and abdominal pain in SIRT patients. There were also incidences of gastric or duodenal ulcers and ascites, likely to be SIRT associated (p=0.001, p=0.005 respectively). Van Hazel (2016) also reported strong evidence for higher rates of serious adverse events in SIRT patients (p=0.005) and haematologic toxicities (p<0.05) although the endpoints were not reported. Total adverse events ≥ Grade 3, pulmonary embolism, treatment related Grade 5 adverse events, nausea and/or vomiting as well as total grade 5 adverse events were all reported higher in SIRT patients although these were not significant findings. Only diarrhoea and peripheral neuropathy were fewer in SIRT patients but again, these had poor significance (p=0.535 and p=0.586 respectively).

While significance was not reported, Hendlisz (2010) also reported higher rates of adverse events in SIRT patients including gastrointestinal, neurology, pain and toxicities such as ascites, thrombocytopenia and stomach ulcers. Adverse events reported less frequently in SIRT patients were constitutional, dermatology related, pulmonary, cardiac arrhythmia and allergies with significance not reported. While there were fewer Grade 3 or 5 toxicities reported in SIRT patients compared to non-SIRT patients, this was not significant (p=0.1). Likewise, Van Hazel (2004) reported higher rates of the same adverse events in SIRT patients. Treatment related deaths was reported in 9% of SIRT patients with none from the control arm and Grade 3 and 4 Toxicities were reported in 13% of SIRT patients with 5% from the control arm. Significance was not reported for any adverse events in Van Hazel (2004)'s study.

RFA in addition to systemic chemotherapy were observed with higher incidences of Grade 3-4 Tolerance to systemic treatment although the impact of these can’t be determined as
DEBIRI in addition to systemic chemotherapy was significantly associated with greater incidences of serious adverse events \((p=0.03)\). There were greater incidences of chemotherapy related adverse events too but this held weaker significance \((p=0.08)\). This pattern was seen across total adverse incidence and specific adverse events but held no statistical significance. No further significance or size of effect was reported for the remaining adverse events. However, there was a consistent trend of higher incidences in patients who received DEBIRI in addition to their standard chemotherapy.

For DEBIRI and HAI on their own, there were significantly fewer reports of adverse events. DEBIRI patients reported significantly fewer neutropenia grade \(\geq 3\) \((p<0.0001)\) and mucositis \((p=0.0002)\). They also reported less diarrhoea although this was not significant \((p=0.73)\). DEBIRI patients also reported higher liver enzyme elevations \((p<0.0001)\) and bilirubin elevation \((p<0.00002)\). While liver relapse was reported less frequently, there were more reports of extra-hepatic relapse in DEBIRI patients. The significance of this was not reported. HAI patients reported less adverse events than their systemic chemotherapy counterparts \((\text{Kemeny 2006})\). While there was weak significance for rates of diarrhoea \((p=0.075)\), this was highly significant in terms of fewer reports of neutropenia grade \(\geq 3\) \((p<0.0001)\) and stomatitis \((p=0.00002)\). However, there were also significantly greater reports of bilirubin elevation \(\geq 3\text{mg/dL}\) in HAI patients \((p=0.006)\).

Liver directed therapies in combination with systemic chemotherapy generally observed higher incidences of adverse events in treated patients. In particular, there were often more reports of neutropenia, diarrhoea, fatigue, abdominal pain, haematologic toxicities and gastrointestinal events but significance of these were either not known or varied. Generally fewer adverse events were associated with the use of HAI or DEBIRI alone but again the significance of these varied.

### Grade C

#### Quality of Life

Significant advantage was reported only for the physical functioning of patients who had received DEBIRI or HAI alone. Otherwise, there was also strong evidence for a faster decline in quality of life at 12 months follow up \((p=0.002)\) for DEBIRI patients. Furthermore, the social functioning, emotional and general health perception measures for HAI patients had reportedly little difference to those who received standard
Chemotherapy and were not statistically significant.

Of what was reported, there was little to no significant benefit given by the addition of RFA or SIRT for quality of life outcomes. Most were reported descriptively with significance either not known or not reported.

For patients receiving RFA in addition to systemic chemotherapy, an improvement in quality of life was observed although the significance of this was not reported. For patients who received SIRT in addition to systemic chemotherapy, there were reportedly no differences between the two arms in terms of quality of life (p=0.96) and the physician rated quality of life (p=0.98).

Grade D

4. Generalisability (How well does the body of evidence match the population and clinical settings being targeted by the Guideline?) For study population characteristics see table of study characteristics in report

All studies were trialled across several developed countries including Australia. SIR-Spheres are also an Australian invention which makes it a treatment of local interest with SIRT studies commonly being trialled in Australian hospitals. Transarterial chemoembolization, radiofrequency and hepatic arterial technologies are present in Australia. Hepatic arterial technologies may be less widely available. Findings from these studies are likely to be directly generalisable to clinical settings in Australia where technology is available. All systemic chemotherapies utilised in the trials are also used in Australia: FOLFOX with or without bevacizumab, FULV and FOLFIRI.

While extent of extrahepatic disease, overall liver tumour and synchronous or metachronous characteristics varied across the trials, all patients included were histologically confirmed with either colon, rectal or colorectal cancer with proven unresectable liver metastases.

Grade B

1. - https://www.bowelcanceraustralia.org/sirtex

<table>
<thead>
<tr>
<th></th>
<th>Evidence directly generalisable to target population</th>
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<tbody>
<tr>
<td>A</td>
<td>Evidence directly generalisable to target population with some caveats</td>
</tr>
<tr>
<td>B</td>
<td>Evidence not directly generalisable to the target population but could be sensibly applied</td>
</tr>
<tr>
<td>C</td>
<td>Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply</td>
</tr>
</tbody>
</table>
5. **Applicability** *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*

Liver directed therapies for colorectal cancer patients in Australia appear to heavily favour SIRT which suggest that expertise to perform SIRT exists\(^1\). In 2011, its stage of development was nearly established in Australia but with limited use across the country’s hospitals\(^2\).

Radiofrequency ablation is also a known procedure in Australia although used more often in the treatment of non-colorectal diseases\(^3,4\); It is not as clear whether this is the same for Transarterial chemoembolization such as DEBIRI and hepatic arterial infusions. These may be rarely used in public hospitals and limited to private clinics.

Cost effectiveness studies have not been taken for HAI, RFA or DEBIRI in colorectal cancer patients with incurable liver metastases within Australia. These therapies are not publically funded and are yet to be covered by Medicare\(^2\). However, SIR-Spheres are reportedly fully funded by health funds\(^2\). SIRT has also been noted to be cost effective considering the population’s otherwise poor prognosis\(^5\).

**Grade C**

1. [https://www.bowelcanceraustralia.org/selective-internal-radiation-therapy](https://www.bowelcanceraustralia.org/selective-internal-radiation-therapy)

<table>
<thead>
<tr>
<th></th>
<th>Evidence directly applicable to Australian healthcare context</th>
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<tbody>
<tr>
<td>A</td>
<td>Evidence applicable to Australian healthcare context with few caveats</td>
</tr>
<tr>
<td>B</td>
<td>Evidence probably applicable to Australian healthcare context with some caveats</td>
</tr>
<tr>
<td>C</td>
<td>Evidence not applicable to Australian healthcare context</td>
</tr>
</tbody>
</table>

**Other factors** *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation).*
Significance and size of effects were often not reported which made it difficult to determine the true impact of the treatment on many outcomes. Quality of life outcomes were also often reported descriptively and measured on various scales that could not be comparable between studies. Many of the studies are of high bias and patient characteristics are not homogenous across them.

### EVIDENCE STATEMENT MATRIX

*Please summarise the development group’s synthesis of the evidence relating to the key question, taking all the above factors into account.*

<table>
<thead>
<tr>
<th>Component</th>
<th>Rating</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence base</td>
<td>D</td>
<td>One Level II study at low risk of bias. Two Level II studies at high risk of bias. Four Level II studies at unclear risk of bias.</td>
</tr>
<tr>
<td>2. Consistency</td>
<td>B</td>
<td>Grade B - Tumour Response Rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade B - Progression Free Survival</td>
</tr>
<tr>
<td></td>
<td>A</td>
<td>Grade A – Overall survival</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Grade C – Resection Rate</td>
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<td></td>
<td>B</td>
<td>Grade B – Adverse Events</td>
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<td></td>
<td>C</td>
<td>Grade C – Quality of Life</td>
</tr>
<tr>
<td>3. Clinical impact</td>
<td>C</td>
<td>Grade C - Tumour Response Rate</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>Grade C - Progression Free Survival</td>
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<td>Grade D – Quality of Life</td>
</tr>
<tr>
<td>4. Generalisability</td>
<td>B</td>
<td>Evidence directly generableisable to the target population with some caveats</td>
</tr>
<tr>
<td>5. Applicability</td>
<td>C</td>
<td>Evidence probably applicable to Australian healthcare context with some caveats</td>
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</tbody>
</table>
Evidence statements:

- Overall, the evidence suggests some benefit to tumour response rate with the use of DEBIRI (TACE), HAI, or the addition of SIRT for colorectal cancer patients with non-resectable liver limited disease, but the clinical relevance of these endpoints remain unclear.
- There is limited evidence that liver directed therapies prolong progression free survival. Some phase II studies suggest benefit for RFA and DEBIRI, and for SIRT in chemotherapy refractory disease, but there are no phase III studies showing improved PFS for liver directed therapies.
- Liver directed therapies with RFA and DEBIRI have been shown to improve overall survival in single phase II studies, however there are no phase III studies demonstrating improved overall survival with liver directed therapies.
- Overall, liver-directed therapies provide little or no benefit in improving quality of life in metastatic colorectal cancer patients with non-resectable liver limited disease.
- There is inconclusive evidence to suggest a definitive benefit given by liver directed therapies in improving resection rate in colorectal cancer patients with incurable liver metastases.
- Liver-directed therapies, in combination with systemic chemotherapy, were generally associated with higher incidences of adverse events in treated patients.

RECOMMENDATION

What recommendation(s) does the guideline development group draw from this evidence? Use action statements where possible.

GRADE OF RECOMMENDATION: D

For patients with non-resectable liver metastases of colorectal cancer, liver-directed therapies (selective internal radiation treatment, radiofrequency ablation, hepatic arterial infusion of chemotherapy agents or transarterial chemoembolisation) can be considered in centres with expertise in the specific technique after multidisciplinary team discussion, or in the context of a clinical trial.

PRACTICE POINT OR CONSENSUS-BASED RECOMMENDATION

If there is no good quality evidence available but there is consensus among Guideline committee members, a consensus-based recommendation or practice point can be given.

Consensus-based recommendation:

In patients with non-resectable liver metastases only (or limited extra-hepatic disease) liver directed techniques can be considered by the MDT based on local experience, patient preference and tumour characteristics. Treating clinicians should have an in-depth discussion with every patient regarding technical complexity, potential outcomes and complications in addition to other therapies available for that patient.
Practice point:

- All patients with metastatic colorectal cancer should be discussed at a multidisciplinary team meeting with clinicians who have expertise in management of metastatic colorectal cancer.

- For patients who could be considered surgical candidates if their metastases were smaller, we suggest initial systemic chemotherapy followed by re-evaluation for surgery.

- Wherever possible, patients considering liver-directed therapies should be enrolled into clinical trials examining these treatments in comparison to standard therapies.

- SIRT in combination with systemic chemotherapy can be used to prolong the time to liver progression but not improve colorectal cancer survival with most evidence currently in the chemo-refractory patients. At present there is insufficient data to recommend SIRT in the first line setting for patients with non-resectable mCRC.
Table 2: Unresolved issues

<table>
<thead>
<tr>
<th>UNRESOLVED ISSUES</th>
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<tbody>
<tr>
<td>If needed, keep note of specific issues that arise when each recommendation is formulated and that require follow-up.</td>
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</table>

Table 3: Implementation of recommendation

<table>
<thead>
<tr>
<th>IMPLEMENTATION OF RECOMMENDATION</th>
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<tbody>
<tr>
<td>Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines.</td>
</tr>
</tbody>
</table>

| Will this recommendation result in changes in usual care? | NO |
| Are there any resource implications associated with implementing this recommendation? | NO |

The present recommendations would have little effect on current resourcing because they would only affect referral centres with the necessary expertise and infrastructure required to perform liver ablative therapies. Only highly selected group of mCRC would be suitable for such therapies based on current evidence.
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
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<tbody>
<tr>
<td>Will the implementation of this recommendation require changes in the way care is currently organised?</td>
<td>NO</td>
</tr>
<tr>
<td>Are the guideline development group aware of any barriers to the implementation of this recommendation?</td>
<td>NO</td>
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</tbody>
</table>