Supplementary Materials

Selective Internal Radiation Therapy Using Y-90 Resin Microspheres for Metastatic Colorectal Cancer: An Updated Systematic Review and Network Meta-Analysis

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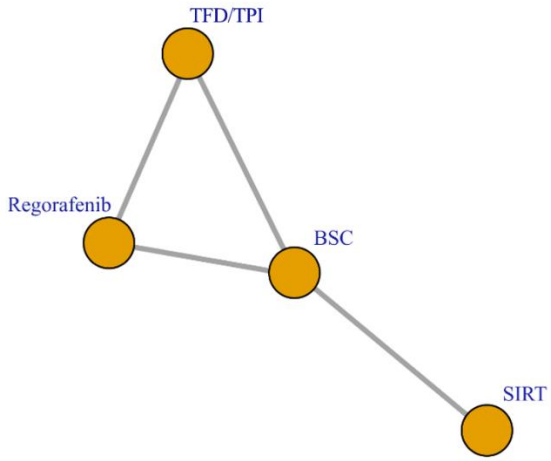
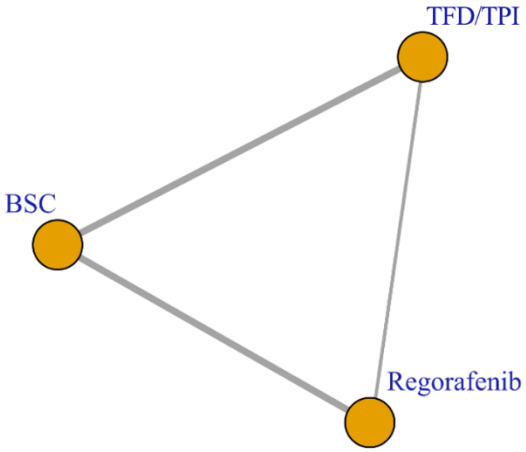
Figure S1 Network graph for A) overall survival and B) progression-free survival

A



B



Nodes represent patients receiving each treatment, and edges (connecting lines) represent the comparison between the treatments.

Table S1 Guidelines, recommendations, and reviews on the use of SIRT in mCRC by publication date

Author/group/guidelines[a]	Year	Summary of guidelines
NCCN; Colon Cancer Guidelines[13]	2023	SIRT with Y-90 microspheres is "an option in highly selected patients with chemotherapy-resistant/refractory disease and with predominant liver metastases" and as preoperative portal vein embolization “when hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume”.
NCCN; Rectal Cancer Guidelines[12]	2023	SIRT is "an option in highly selected patients with chemotherapy-resistant/refractory disease and with predominant liver metastases"
ESMO clinical practice guidelines on mCRC[15]	2023	The guideline identifies SIRT as an intraarterial treatment modality in treatment of colorectal metastases. The guideline states “TACE, TARE/SIRT and HAIC may be also considered as treatment options with non-curative intent [III, B]” “SIRT, HAIC and chemoembolization of CRLMs in earlier treatment lines may be interesting as ‘consolidation treatment’ but should be limited to clinical trials.”
ASCO; Guideline (Morris VK, Kennedy EB, Baxter NN, et al. Treatment of Metastatic Colorectal Cancer: ASCO Guideline. J Clin Oncol. 2023;41:678-700.)	2022	SIRT is not routinely recommended. MDT management is required for patients with mCRC who are considered candidates for SIRT.
French guidelines, an intergroup consensus on clinical practice involving mCRC (Phelip JM, Tougeron D, Léonard D, et al. Metastatic colorectal cancer (mCRC): French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SFR). Dig Liver Dis. 2019;51:1357-63.)	2022	Following first-line chemotherapy, guidelines recommend the use of SIR-Spheres Y-90 resin microspheres in the case of exclusive or predominant liver metastases (≤ 5 extrahepatic liver lesions) with maintained liver function (bilirubin ≤ 2N).
Manual de Oncologia Clínica do Brasil[14]	2021	The colon cancer recommendations were updated in 2021 and now recommend SIRT with Y-90 resin microspheres for patients with advanced stage unresectable disease (Stage IV) who are not suitable for surgery
NICE; Guidelines 151: Colorectal Cancer (NG151) (National Institute for Health and Care Excellence. Colorectal Cancer, 2020)	2020	For people who are intolerant or refractory to chemotherapy, SIRT should only be used with special arrangements for clinical governance, consent, and audit or research. In people who can receive

		chemotherapy, SIRT should only be used in the context of clinical trials
NICE; Guidance on intervention procedures 672: **Selective internal radiotherapy for colorectal metastases unresectable cells in the liver [IPG672]** (National Institute for Health and Care Excellence, 2020)	2020	For people who are intolerant or refractory to chemotherapy, SIRT should only be used under special conditions for clinical governance, consent and audit, or research. In people who can receive chemotherapy, SIRT should only be used in the context of clinical trials
Spanish consensus on liver metastases in CRC (Vera R, González-Flores E, Rubio C, et al. Multidisciplinary management of liver metastases in patients with colorectal cancer: a consensus of SEOM, AEC, SEOR, SERVEI, and SEMNIM. Clin Transl Oncol. 2020;22:647-62.)	2020	There is clinical evidence that the use of SIRT is safe and well tolerated and is indicated in third-line dominant liver disease following chemotherapy or in combination with chemotherapy.
German GGPO **S3 Guidelines** (German Guideline Program in Oncology (GGPO). Evidenced-based Guideline for Colorectal Cancer. Version 2.1. 2019.)	2019	SIRT with Y-90 resin microspheres can be used for disseminated liver metastases of CRC for patients where no other equal therapy is available.
NSH. Clinical commissioning policy for SIRT (NHS) (NHS. Clinical commissioning policy for Selective internal radiation therapy for chemotherapy refractory intolderant metastatic colorectal câncer (2018). https://www.england.nhs.uk/wp-content/uploads/2018/12/Selective-internal-radiation-therapy-for-chemotherapy-refractory-intolerant-metastatic-colorectal-cancer.pdf. Accessed 16 May 2023.)	2018	NHS England recommended the use of SIRT for patients with liver-limited, chemotherapy-refractory/intolerant metastatic colorectal cancer who met the inclusion criteria
Expert consensus statements and expert opinion		
US-based expert consensus on the role of yttrium-90 SIRT in liver-dominant mCRC[43]	2020	SIRT with Y-90 has the potential to play a major role in all phases of liver mCRC treatment, eg; in chemotherapy refractory or-intolerant patients, in patients who need a chemotherapy holiday, as a

		consolidation therapy as an adjunct to second-line or later, to facilitate downsizing.
Expert opinion (Bekaii-Saab T, Kim R, Kim TW, et al. Third- or later-line therapy for metastatic colorectal cancer: reviewing best practice. Clin Colorectal Cancer.2019;18:e117-29.)	2019	SIRT should be considered as an option in first line treatment for patients with liver-limited or -dominant metastatic disease
Wang et al. expert opinion (Wang DS, Louie JD, Sze DY. Evidence-based integration of yttrium-90 radioembolization in the contemporary management of hepatic metastases from colorectal cancer. Tech Vasc Interv Radiol. 2019;22:74-80.)	2019	In patients who have failed two or more lines of systemic chemotherapy, the authors found that SIRT with Y-90 resin microspheres "confers a significant survival benefit with low toxicity...", and point out that it is endorsed by the NCCN and ESMO in this setting. Y-90 resin microspheres have been recommended for use in patients-refractory or -intolerant to chemotherapy
Recommendations from a panel of Spanish experts on the use of SIRT in CRC in liver metastasis (Aranda E, Aparicio J, Bilbao JI, et al. Recommendations for SIR-Spheres Y-90 resin microspheres in chemotherapy-refractory/intolerant colorectal liver metastases. Future Oncol. 2017;13:2065-82.)	2017	The expert panel recommends the use of SIR Spheres Y-90 resin microspheres in chemotherapy-refractory and chemotherapy-intolerant patients

[a] Reference numbers according to the main article. References not cited in the main article are provided in full in parenthesis.
ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; mCRC, colorectal cancer metastatic; MOC, “Manual de Oncologia Clínica”; NCCN, National Comprehensive Cancer Network; NG, NICE guideline; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; SIRT, selective internal radiotherapy.

Table S2 Search terms

Database	ID	Search strategy	Hits
MEDLINE and EMBASE (through EMBASE)	#1	('colorectal cancer'/exp OR 'colorectal cancer') AND ([embase]/lim OR [medline]/lim)	400,691
	#2	('colorectal cancer':ab,ti OR 'colorectal carcinoma':ab,ti) AND ([embase]/lim OR [medline]/lim)	194,797
	#3	(#1 OR #2) AND ([embase]/lim OR [medline]/lim)	403,715
	#4	('tipiracil plus trifluridine'/exp OR 'regorafenib'/exp OR 'brachytherapy device'/exp) AND ([embase]/lim OR [medline]/lim)	9,331
	#5	('lonsurf':ab,ti OR 'tas 102':ab,ti OR 2022 'tas102':ab,ti OR 'tipiracil hydrochloride plus trifluridine':ab,ti OR 'trifluridine plus tipiracil':ab,ti OR 'trifluridine plus tipiracil hydrochloride':ab,ti OR 'regorafenib':ab,ti OR bay 73 4506':ab,ti OR 'bay 73-4506':ab,ti OR 'bay 734506':ab,ti OR 'bay73 4506':ab,ti OR 'bay73-4506':ab,ti OR 'bay734506':ab,ti OR 'resihance':ab,ti OR 'stivarga':ab,ti OR 'sir-sphere':ab,ti OR 'sir-spheres':ab,ti OR 'sirshere':ab,ti OR 'sirsphere':ab,ti OR ('yttrium-90':ab,ti AND 'resin microspheres':ab,ti)) AND ([embase]/lim OR [medline]/lim)	4,506
	#6	(#4 OR #5) AND ([embase]/lim OR [medline]/lim)	4,301
	#7	('clinical trial'/exp OR 'randomization'/de OR 'controlled study'/de OR 'comparative study'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'clinical trial' OR 'clinical trials' OR 'controlled clinical trial' OR 'controlled clinical trials' OR 'randomised controlled trial' OR 'randomized controlled trial' OR 'randomised controlled trials' OR 'randomized controlled trials' OR 'randomisation' OR 'randomization' OR rct OR 'random allocation' OR 'randomly allocated' OR 'allocated randomly' OR placebo* OR 'prospective study'/de OR (allocated NEAR/2 random) OR (random* NEAR/1 assign*) OR random* OR ((single OR double OR triple OR treble) NEAR/1 (blind* OR mask*))) NOT ('case study'/de OR 'case report' OR 'abstract report'/de OR 'letter'/de) AND ([embase]/lim OR [medline]/lim)	11,822,616
	#8	('cohort analysis'/exp OR 'longitudinal study'/exp OR 'prospective study'/exp OR 'follow up'/exp OR 'case control study'/exp OR ((case* NEXT/1 control*):ti,ab) OR cohort*:ab,ti OR ((('follow up' OR followup) NEXT/1 (study OR	4,646,242

		studies)):ab,ti) OR 'retrospective study'/exp) AND ([embase]/lim OR [medline]/lim)	
	#9	(#7 OR #8) AND ([embase]/lim OR [medline]/lim)	13,932,337
	#10	#3 AND #6 AND #9 AND ([embase]/lim OR [medline]/lim)	2,668
	#11	#10 AND (2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py)	**1,410**
The Cochrane	#1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	9,373
Library	#2	"colorectal cancer" OR "colorectal carcinoma" OR "colorectal neoplasm"	15,722
	#3	#1 OR #2	19,652
	#4	"lonsurf" OR "tas 102" OR "tas102" OR "tipiracil hydrochlorid plus trifluridine" OR "trifluridine plus tipiracil" OR "trifluridine plus tipiracil hydrochloride" OR "regorafenib" OR "bay 73 4506" OR "bay 73-4506" OR "bay 734506" OR "stivarga" OR "SIR-Sphere" OR "SIR-Spheres" OR "SIRShere"	816
	#5	#3 and #4 with Publication Year from 2018 to 2022, in Trials	**179**
Total			**1,589**

Table S3 Risk of bias for randomized controlled trials using the RoB 2.0 for overall survival

Study[a]	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall
Hendlisz et al.[33]	!	+	+	+	!	+
Yoshino et al.[38]	+	+	!	+	!	+
Grothey et al.[35]	+	+	+	+	+	+
Li et al.[36]	+	+	+	+	+	+
Mayer et al.[37]	+	+	+	+	+	+
Sanoff et al.[4]	+	+	+	+	+	+
Xu et al.[30]	!	+	+	+	+	+
Xu et al.[31]	!	!	+	+	+	+

[a] Reference numbers according to the main article.
Domain 1: Randomization process; Domain 2: Deviations from the intended interventions; Domain 3: Missing outcome data; Domain 4: Measurement of the outcome; Domain 5: Selection of the reported result. Green circle: Low risk of bias. Yellow circle: Some concerns.

Table S4 Risk of bias for randomized controlled trials using the RoB 2.0 for progression-free survival

Study[a]	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall
Yoshino et al.[38]	+	+	!	+	!	+
Grothey et al.[35]	+	+	+	+	+	+
Li et al.[36]	+	+	+	+	+	+
Mayer et al.[37]	+	+	+	+	+	+
Sanoff et al.[4]	+	+	+	+	+	+
Xu et al.[30]	!	+	+	+	+	+
Xu et al.[31]	!	!	+	+	+	+

[a] Reference numbers according to the main article.
Domain 1: Randomization process; Domain 2: Deviations from the intended interventions; Domain 3: Missing outcome data; Domain 4: Measurement of the outcome; Domain 5: Selection of the reported result.

Table S5 Risk of bias for non-randomized trials using the ROBINS-I tool

Study[a]	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Overall
Bester et al.[34]	Critical	Serious	Low	Low	Low	Serious	Moderate	Critical
Seidensticker et al.[32]	Serious	Serious	Low	Low	Moderate	Serious	Moderate	Serious
Moriwaki et al.[26]	Moderate	Serious	Low	Low	Moderate	Serious	Moderate	Serious
Nakashima et al.[27]	Serious	Serious	Low	Low	Moderate	Serious	Moderate	Serious
Patel et al.[28]	Serious	Serious	Low	Low	Moderate	Serious	Moderate	Serious
Vitale et al.[29]	Critical	Serious	Low	Low	Moderate	Serious	Moderate	Critical
Hsieh et al.[25]	Serious	Serious	Low	Low	Moderate	Serious	Moderate	Serious

[a] Reference numbers according to the main article.
Domain 1: Bias due to confounding; Domain 2: Bias in selection of participants into the study; Domain 3: Bias in classification of interventions; Domain 4: Bias due to deviations from intended interventions; Domain 5: Bias due to missing data; Domain 6: Bias in measurement of outcomes; Domain 7: Bias in selection of the reported result.

Table S6 Assessment of the certainty of the evidence (GRADE) for the pairwise comparison between SIRT and BSC for mCRC

SIRT compared to BSC for mCRC

Outcomes	No. of participants (studies) Follow-up	Certainty of evidence (GRADE)	Relative effect (95% CI)
Overall survival	44 (1 RCT)	⨁⨁⨁◯ Moderate[a]	**HR 0.48 (0.27, 0.87)**[c]
	311 (2 observational studies)	⨁⨁⨁◯ Moderate[b]	

[a] Single study with a small sample size. [b] Some issues regarding patient selection and no mention of adjustments for confounders. Even though blindness is not mandatory for some outcomes, patients and investigators knew the intervention and it brings some level of bias. [c] The findings from the RCT and the observational studies were grouped for the statistical analysis.
BSC, best supportive care; HR, hazard ratio; mCRC, metastatic colorectal cancer; RCT, randomized controlled trial.

Table S7 Assessment of the certainty of the evidence (GRADE) for the pairwise comparison between TFD/TPI and Regorafenib for mCRC

TFD/TPI compared to Regorafenib for mCRC			
Outcomes	**№ of participants (studies) Follow-up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**
Overall survival	6,040 (3 observational studies)	⨁⨁⨁◯ Moderate[a]	**HR 0.79 (0.6, 1.06)**
Progression-free survival	550 (1 observational study)	⨁⨁◯◯ Low[a,b]	**HR 0.97 (0.65, 1.44)**

[a] Some issues regarding patient selection and no mention of adjustments for confounders. Even though blindness is not mandatory for some outcomes, patients and investigators knew the intervention and it brings some level of bias. [b] Single study.
HR, hazard ratio; mCRC, metastatic colorectal cancer; TFD/TPI, trifluridine–tipiracil.

Table S8 Assessment of the certainty of the evidence (GRADE) for the pairwise comparison between TFD/TPI and BSC for mCRC

TFD/TPI compared to BSC for mCRC			
Outcomes	**№ of participants (studies) Follow-up**	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**
Overall survival	1,375 (3 RCTs)	⨁⨁⨁⨁ High	**HR 0.62 (0.46, 0.83)**
Progression-free survival	1375 (3 RCTs)	⨁⨁⨁⨁ High	**HR 0.44 (0.31, 0.62)**

BSC, best supportive care; HR, hazard ratio; mCRC, metastatic colorectal cancer; RCT, randomized controlled trial; TFD/TPI, trifluridine–tipiracil.

Table S9 Assessment of the certainty of the evidence (GRADE) for the pairwise comparison between Regorafenib and BSC for mCRC

Regorafenib compared to BSC for mCRC

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)
Overall survival	1,317 (4 RCTs)	⊕⊕⊕⊕ High	**HR 0.78 (0.57, 1.05)**
Progression-free survival	1,317 (4 RCTs)	⊕⊕⊕⊕ High	**HR 0.46 (0.33, 0.63)**

BSC, best supportive care; HR, hazard ratio; mCRC, metastatic colorectal cancer; RCT, randomized controlled trial.

Table S10 Demographic and clinical characteristics of study samples

	No. patients	Median age (years)	Male (%)	ECOG PS 0 (%)	ECOG PS 1 (%)	ECOG PS 2 (%)	KRAS mutation (%)	EHD (%)	Multiple metastatic organs (%)
TFD/TPI vs. REG									
Moriwaki et al [26]							49[f]		
TFD/TPI	327	64	60	39	54	7		NR	77
REG	223	64	57	43	54	3	49[f]	NR	73
Nakashima et al [27]									
TFD/TPI	3,777	68	60	NR	NR	NR	NR	NR	28
REG	1,501	66	62	NR	NR	NR	NR	NR	30
Patel et al [28]									
TFD/TPI	126	55	45.2	27.0	46.8	4.0	53.3	NR	NR
REG	95	57	54.7	25.3	32.6	3.2	52.5	NR	NR
Vitale et al [29]							48[f]		
TFD/TPI	76	NR	NR	50	49	1		NR	NR
REG	64	NR	NR	45	50	5	62[f]	NR	NR
Hsieh et al [25]							64[f]		
TFD/TPI	50	64	52	NR	NR	NR		NR	NR
REG	75	64	59	NR	NR	NR	60[f]	NR	NR
TFD/TPI vs. placebo									
Yoshino et al [38]									
TFD/TPI	112	63	57	64	33	3	45	NR	78
Placebo	57	62	49	61	37	2	52	NR	81
Mayer et al [37]									
TFD/TPI	534	63	61	56	44	NR	51	NR	NR
Placebo	266	63	62	55	45	NR	51	NR	NR
Xu et al [31]	271	58	63	24	76	NR	37	NR	39[c]
TFD/TPI									

Placebo	135	56	62	22	78	NR	37	NR	39[c]
REG vs. placebo									
Grothey et al [35]									
REG	505	61	62	52	48	NR	54	NR	NR
Placebo	255	61	60	57	43	NR	62	NR	NR
Li et al [36]									
REG	136	58	63	26	74	NR	34	NR	79
Placebo	68	56	49	22	78	NR	26	NR	78
Sanoff et al [4]							45[f]		
REG	120	62	57	43	57	NR		NR	NR
Placebo	61	62	52	38	62	NR	61[f]	NR	NR
Xu et al [31]									
REG	112	58	66	28	72	NR	35	NR	83
Placebo	60	55	45	22	78	NR	27	NR	78
SIRT vs. BSC									
Hendlisz et al [33]									
SIRT	21	62	48	71	24	5	NR	0[e]	0[e]
BSC	23	62	78	74	22	4	NR	0[e]	0[e]
Bester et al [34]									
SIRT	224	67[a]	63	85	NR	NR	NR	38	NR
BSC	51[b]	66[b]	69[b]	NR	NR	NR	NR	33[b]	NR
Seidensticker et al [32]									
SIRT	29	62[a]	76	NR	NR	80[d]	NR	48.3	NR
BSC	29	61[a]	79	NR	NR	80[d]	NR	48.3	NR

[a] Mean age; [b] Also included patients with other primary tumours; [c] ≥3 metastatic sites; [d] Karnofsky index, not ECOG OS; [e] Extrahepatic disease listed as exclusion criteria; [f] RAS mutation, not KRAS.

BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; EHD, extrahepatic disease aside from the primary site; KRAS, Kirsten rat sarcoma; NR, not reported; REG, regorafenib; SIRT, selective internal radiation therapy; TFD/TPI, trifluridine–tipiracil.

Table S11 Summary of prior systemic therapies

	Prior chemotherapy regimens (%)										%				
TFD/TPI vs REG	**Any**	**1**	**1-2**	**2**	**3**	**≥ 3**	**4**	**≥ 4**	**5**	**6**	**Irino**	**Oxa**	**Bevac**	**Cetuximab**	**REG**
Moriwaki et al [26]															
TFD/TPI	NR	NR	NR	NR	NR	50	NR	NR	NR	NR	NR	NR	NR	NR	NR
REG	NR	NR	NR	NR	NR	48	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nakashima et al [27]															
TFD/TPI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	76	72	74	11	NR
REG	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	76	66	72	15	NR
Patel et al [28]															
TFD/TPI	NR	6.3	NR	31	28.6	NR	20.6	NR	13.5	NR	NR	NR	NR	NR	NR
REG	NR	4.2	NR	30.5	23.2	NR	23.2	NR	18.9	NR	NR	NR	NR	NR	NR
Vitale et al [29]															
TFD/TPI	NR	NR	NR	55	37	NR	NR	8	NR	NR	97	95	NR	NR	NR
REG	NR	NR	NR	50	39	NR	NR	11	NR	NR	98	92	NR	NR	NR
Hsieh et al [25]															
TFD/TPI	NR	NR	NR	40	44	NR	16	NR	NR	NR	NR	NR	NR	NR	NR
REG	NR	NR	NR	33	53	NR	14	NR	NR	NR	NR	NR	NR	NR	NR
TFD/TPI vs placebo															
Yoshino et al [38]															
TFD/TPI	NR	NR	NR	15	NR	85	NR	NR	NR	NR	100	100	78	63	NR
Placebo	NR	NR	NR	23	NR	77	NR	NR	NR	NR	100	100	82	63	NR
Mayer et al [37]															
TFD/TPI	NR	NR	NR	18	22	NR	NR	60	NR	NR	100	100	100	NR	17
Placebo	NR	NR	NR	17	20	NR	NR	63	NR	NR	100	100	>99	NR	20
Xu et al [30]															
TFD/TPI	45	NR	NR	23	27	NR	NR	50	NR	NR	NR	NR	19	NR	NR
Placebo	51	NR	NR	19	27	NR	NR	55	NR	NR	NR	NR	20	NR	NR

REG vs placebo															
Grothey et al [35]															
REG	NR	NR	27	NR	25	NR	NR	49	NR	NR	NR	NR	100	NR	NR
Placebo	NR	NR	25	NR	28	NR	NR	47	NR	NR	NR	NR	100	NR	NR
Li et al [36]															
REG	NR	NR	NR	23	24	NR	NR	54	NR	NR	NR	NR	41	NR	NR
Placebo	NR	NR	NR	21	28	NR	NR	51	NR	NR	NR	NR	37	NR	NR
Sanoff et al [4]															
REG	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	63	9	NR
Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	67	7	NR
Xu et al [31]															
REG	63	NR	NR	25	18	NR	NR	57	NR	NR	NR	NR	23	20[a]	NR
Placebo	65	NR	NR	18	25	NR	NR	57	NR	NR	NR	NR	22	20[a]	NR
SIRT vs BSC															
Hendlisz et al [33]															
SIRT	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	62	19	NR	NR	NR
BSC	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	87	9	NR	NR	NR
Bester et al [34]															
SIRT	86[b]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
BSC	92	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Seidensticker et al [32]															
SIRT	NR	0	NR	28	31	NR	35	NR	3	3	90	90	52	52	NR
BSC	NR	0	NR	24	38	NR	24	NR	10	3	100	90	48	66	NR

[a] Anti-VEGF and anti-EGFR; [b] Also included patients with other primary tumours.
Bevac, bevacizumab; BSC, best supportive care; EGFR, epidermal growth factor receptor; Irino, irinotecan; NR, not reported; Oxa, oxaliplatin; REG, regorafenib; SIRT, selective internal radiation therapy; TFD/TPI, trifluridine–tipiracil; VEGF, vascular endothelial growth factor.

Table S12 Outcomes from the individual studies

Outcome	Hendlisz 2010		Bester 2012		Seidenstick er 2012	Yoshino 2012		Grothey 2013		Li 2015		Mayer 2015		Moriwaki 2018			Sanoff 2018		Xu 2018		Xu 2020		Vitale 2021	Nakashima 2020		Patel 2021		Hsieh 2022	
	Treatment (n)																												
	SIRT (21)	BSC (22)	SIRT (224)	BSC (29)	SIRT (29)	BSC (29)	TFD/TPI (113)	BSC (57)	REG (505)	BSC (253)	REG (136)	BSC (68)	TFD/TPI (533)	BSC (265)	REG (223)	TFD/TPI (327)	REG (120)	BSC (61)	TFD/TPI (271)	BSC (135)	REG (112)	BSC (60)	REG (93)	TFD/TPI (100)	TFD/TPI (3777)	REG (1501)	TFD/TPI (126)	REG (95)	TFD/TPI (50)	REG (75)
Median OS (months)	10.0	7.3	12.0	6.3	8.3	3.5	9.0	6.6	6.4	5.0	8.8	6.3	7.1	5.3	7.9	7.4	13.8	11.7	7.8	7.1	8.4	6.2	6.8	7.6	10.2	6.4	7.5	7.1	6.5	4.9
Median PFS (months)	-	-	-	-	5.5	2.1	2.0	1.0	1.9	1.7	3.2	1.7	2.0	1.7	2.1	2.1	6.1	5.3	2	1.8	2.0	1.7	2.5	3.0	-	-	-	-	2	1.8
RR (%)	9.5	0	-	-	41.4	-	41	39	1.0	0.4	4	0	1.6	0.4	0	1	34	21	1.1	0	4	0	0	0	-	-	52.5[a]	34.2[a]	15	9

[a] rwORR, real-world overall response rate. BSC, best supportive care; OS, overall survival; PFS, progression free survival; RR, response rate; REG, regorafenib; SIRT, selective internal radiation therapy; TFD/TPI, trifluridine–tipiracil.

Table S13 Grade 3 or higher relative adverse events reported by the individual studies (grey indicates SIRT results)

	Hendlisz 2010		Bester 2012		Seidenstücker 2012		Yoshino 2012		Grothey 2013		Li 2015		Mayer 2015		Moriwaki 2018		Sanoff 2018		Xu 2018		Xu 2020		Vitale 2021	
	Treatment (n)																							
Adverse event	**SIRT (21)**	**BSC (22)**	**SIRT (224)**	**BSC (29)**	**SIRT (29)**	**BSC (29)**	**TFD/TPI (113)**	**BSC (57)**	**REG (505)**	**BSC (253)**	**REG (136)**	**BSC (68)**	**TFD/TPI (533)**	**BSC (265)**	**REG (223)**	**TFD/TPI (327)**	**REG (120)**	**BSC (61)**	**TFD/TPI (271)**	**BSC (135)**	**REG (112)**	**BSC (60)**	**REG (93)**	**TFD/TPI (100)**
Abdominal pain									0.2	0.0	0.7	0.0	2.4	3.8					0.4	0.0	0.9	0.0		
Acute kidney injury											0.0	1.5									0.0	1.7		
Alanine aminotransferase increase											6.6	0.0	1.9	3.8					1.1	3.0	6.2	0.0		
Alkaline phosphatase increase											0.0	1.5	8.0	10.7					4.1	3.7	0.9	1.7		
Allergy	0.0	4.5																						
Anaemia							16.8	5.3	2.8	0.0	1.5	0.0	18.2	3.0	4.9	10.7	4.2	6.6	17.7	5.9	1.8	0.0	0.0	6.0
Anorexia	0.0	4.5		3.4			4.4	3.5	3.2	2.8	0.7	0.0			4.5	5.5	5.0	0.0			0.9	0.0		
Aspartate aminotransferase increased											5.9	0.0	4.4	6.1					3.7	5.2	5.4	0.0		
Atrial fibrillation											0.0	1.5									0.0	1.7		
Bilirubin increased											6.6	1.5	8.6	11.8					7.0	7.4	4.5	1.7	1.1	0.0
Bone marrow failure																			1.1	0.0				
Cardiac ischemia													0.2	0.4										
Conduction disorder											0.0	1.5												
Decreased appetite													3.6	4.9					0.7	0.0				
Dehydration																	5.8	3.3						
Diarrhoea							6.2	0.0	7.1	0.8	0.7	1.5	3.0	0.4			15.0	4.9	0.7	0.7	1.8	1.7	2.2	1.0
Dyspnoea	0.0	4.5		3.4					0.2	0.0									0.0	0.7				
Peripheral oedema																				0.7				
Fatigue	0.0	22.7		17.2			6.2	3.5	9.5	5.1	2.9	1.5	4.0	6.0	3.1	2.4	10.8	6.6	1.5	0.0	2.7	1.7	16.1	6.0
Febrile neutropenia							4.4	0.0					3.8	0.0	0.0	2.8	9.2	3.3					0.0	5.0
Fever									0.8	0.0			1.3	0.4							0.9	0.0		
Flank pain											0.7	0.0												
GGT increased											0.7	0.0									1.8	0.0		
Hand-foot skin reaction	4.8	0.0							17	0.4	16	0			19.7	0.0					18.8	0.0	26.9	0.0
Headache									0.6	0.0														

Heart failure									0.0	1.5									0.0	1.7				
Hepatic function abnormal																	0.4	0.0						
Hoarseness							0.2	0.0	0.7	0.0									0.0	0.0				
Hypercalcemia																	0.0	0.7						
Hyperglycaemia																	2.6	2.2						
Hyperkalaemia																	0.4	0.0						
Hypertension							7.1	0.8	11.0	2.9			5.8	0.0	8.3	1.6	0.4	0.0	13.4	3.3	1.1	0.0		
Hypoalbuminemia									0.7	0.0							3.0	0.0						
Hypocalcaemia																	1.1	0.7						
Hypokalaemia									0.7	0.0					5.8	1.6	0.7	0.7	0.9	0.0				
Hyponatremia																	4.4	4.4						
Hypophosphatemia							3.8	0.4	6.6	0.0					14.2	0.0			7.1	0.0				
Increase in creatinine level											0.9	0.8					1.1	0.0						
Laparotomy abnormality: hyperbilirubinemia							2.0	0.8																
Leukopenia						28.3	0.0			2.2	0.0	21.4	0.0			9.2	11.5	20.7	0.0	2.7	0.0			
Lipase increased									4.4	1.5					8.3	4.9			4.5	1.7				
Liver dysfunctions					10.3[a]								12.1	0.3			0.0	0.7						
Lymphocytosis																	0.4	0.0						
Lymphopenia						9.7	3.5										14.4	2.2						
Maculopapular rash									4.4	0.0									4.5	0.0				
Mucositis								3.0	0.0						9.2	9.8					3.2	0.0		
Myalgia								0.4	0.4	0.7	0.0								0.9	0.0				
Nausea						4.4	0.0	0.4	0.0			1.9	1.1				0.7	0.0			0.0	1.0		
Neutropenia						50.4	0.0			2.2	0.0	37.9	0.0	2.7	32.7	40.8	29.5	33.2	0.0	2.7	0.0	2.2	16.0	
Oesophageal varices haemorrhage										0.7	0.0													
Pain																					1.1	0.0		
Palmar-plantar erythrodysesthesia																5.0	1.6							
Palpitations																		0.4	0.0					
Pharyngitis										0.7	0.0													
Pneumonia																		0.0	0.7					
Proteinuria								1.4	0.4	1.5	1.5									1.8	1.7			
Pulmonary	0.0	4.5		3.4																				
Rash								5.7	0.0													2.2	0.0	
Rectal haemorrhage																								

Sensory neuropathy								0.4	0.0																	
Serum amylase increased										0.0	1.5											0.0	1.7			
Skin disorders														3.6	0.3							0.9	0.0			
Small intestinal obstruction																				1.1	0.0					
Stomatitis	0.0	4.5		3.4								0.4	0.0							0.4	0.0					
Syncope																				0.4	0.0					
Thrombocytopenia							4.4	0.0	2.8	0.4	2.9	0.0	5.1	0.4	6.3	3.4	4.2	0.0	3.0	1.5	2.7	0.0	0.0	2.0		
Thromboembolism																	5.0	1.6								
Upper respiratory tract infection																			0.4	0.0						
Vaginal fistula											0.7	0.0									0.9	0.0				
Visceral arterial ischemia											0.7	0.0									0.9	0.0				
Vomiting							3.5	0.0	0.6	0.0			2.1	0.4					0.7	0.0						
Wound infection											0.7	0.0									0.9	0.0				
Total adverse events (n)	1	6	0	5	1	0	11	4	21	10	28	12	19	15	9	8	16	13	31	17	26	11	9	7		

[a] Radioembolization induced liver disease (REILD).

BSC, best supportive care; REG, regorafenib; SIRT, selective internal radiation therapy; TFD/TPI, trifluridine–tipiracil.