Supplemental digital content 2.pdf - Summary of the characteristics of all included studies on treatment for metastatic uveal melanoma

Intervention	Study	Publication year	Study design	Number of uveal melanoma patients	Number of first-line treatments (%)	Number of surgically treated patients (%)	Median time from metastasis to treatment months, (range)	OS definition	Median OS, published Kaplan-Meier estimate months, (95% CI)	Median OS, digitised Kaplan-Meier estimate months, (95% CI)	Region(s)
Conventional chemotherapy (CHT)											
Dacarbazine	Carling [1]	2015	Retrospective CCS	14	NR	NR	2.5 (0.6-4.7)	Treatment	4.6	4.5 (1.4-13.7)	🇳🇴
Gemcitabine + treosulfan	Corrie [2]	2005	Prospective NRCS phase I	5	4 (80%)	0 (0%)	NR	NR	12.2	12.2 (4.6-ND)	🇬🇧
Docosahexaenoic acid-paclitaxel	Homsi [3]	2010	Prospective NRCS phase II, open label	22	13 (59%) NC	NR	NR	Enrollment	9.8	9.8 (5.6-15.4)	🇺🇸
Fotemustine	Leyvraz [4]	2014	Prospective randomised trial EORTC multicentre	85	85 (100%)	0 (0%)	NR	Enrollment	13.8 (10.2-17.2)	13.8 (10.3-15.5)	🇨🇭 🇫🇷 🇧🇪 🇵🇱 🇮🇹 🇬🇧 🇩🇪
Gemcitabine + treosulfan	Pföhler [5]	2003	Retrospective case series	14	1 (7%)	0 (0%)	NR	Enrollment	14 (12-31)	13.8 (4.1-ND)	🇬🇧 🇩🇪
Temozolomide + bevacizumab	Piperno-Neumann [6]	2016	Prospective trial phase II	35	35 (100%)	0 (0%)	NR	Treatment	10 (8-15)	10.0 (6.9-11.9)	🇫🇷
Multiple[*]	Pons [7]	2011	Retrospective CCS	25	0 (0%)	0 (0%)	NR	NR	10.83 (5.35-16.30)	10.5 (5.6-21.1)	🇵🇹 🇪🇸
Gemcitabine + treosulfan + cisplatin	Schmittel [8]	2005	Prospective NRCS phase II	19	19 (100%) NC	NR	NR	Treatment	7.7 (1.9-13.8)	7.7 (1.8-13.9)	🇩🇪
Gemcitabine + treosulfan 2500 or 3000 mg/m^2	Schmittel [9]	2005	Prospective NRCS phase II	14	12 (86%) NC	NR	NR	Treatment	6.0 (4-8)	5.9 (2.4-8.0)	🇩🇪
Gemcitabine + treosulfan 3500 or 4000 mg/m^2				19	16 (84%) NC	NR	NR	Treatment	9.0 (0-18)	8.9 (4.4-24.9)	
Gemcitabine + treosulfan	Terheyden [10]	2004	Prospective NRCS phase II	20	8 (40%)	0 (0%)	NR	Treatment	NR	17.0 (9.0-31.0)	🇩🇪

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[*] Thirteen patients received dacarbacine, five received temozolomide with or without interferon, five received fotemustine, two received carboplatin/dacarbacine/interferon-alpha/interleukin-2. Because of multiple different therapies the patients were included in the conventional chemotherapy group but could they could not be organised under a specific chemotherapy agent.

Chemoimmunotherapy (CIT)											
Fotemustine IA/IV + IL2+ IFN-alpha2	Becker [11]	2002	Prospective NRCS	48	NR	NR	NR	Treatment	12 (11.4-12.8)[*]	14.1 (11.7-19.6)	🇩🇪
BOLD + IFN-alpha2b	Kivelä [12]	2003	Prospective nonrandomised trial phase II EORTC multicentre	24	24 (100%)	0 (0%)	NR	Treatment	10.6 (6.9-16.4)	10.4 (5.9-14.6)	🇫🇮 🇸🇪 🇩🇪 🇳🇱 🇧🇪 🇬🇧
BOLD + leucocyte IFN	Pyrhönen [13]	2002	Prospective nonrandomised trial phase II	22	18 (82%)	0 (0%)	NR	Treatment	12 (8-22)	12.4 (8.2-22.2)	🇫🇮
Thalidomide + IFN-alpha2b	Solti [14]	2007	Prospective NRCS pilot study	6	0 (0%)	NR	NR	Treatment	NR	3.7 (0.9-ND)	🇺🇸
Fotemustine IV + IL2 + IFN-alpha2b	Terheyden [15]	1998	Retrospective case series	3	3 (100%)	0 (0%)	2 (2-4)	Treatment	NR	41.0 (10.0-ND)	🇩🇪
Dacarbazine + IFN-alpha2a + bevacizumab	Vihinen [16]	2010	Prospective trial phase II	4	4 (100%)	0 (0%)	NR	Treatment	NR	10.8 (6.5-ND)	🇫🇮
Hepatic intra-arterial chemotherapy (HIA)											
Carboplatin	Cantore [17]	1994	Prospective NRCS phase II	8	5 (63%)	NR	NR	Treatment	15[†]	12.0 (7.0-20.0)	🇮🇹
Fotemustine	Egerer [18]	2001	Prospective NRCS pilot study	7	5 (71%)	0 (0%)	2 (1-10)	Treatment	18[‡]	20.0 (3.0-ND)	🇩🇪
Fotemustine or carboplatin	Farolfi [19]	2011	Retrospective case series	18	NR[§]	NR	NR	Treatment	21 (8-39)	21.2 (7.4-ND)	🇮🇹
Melphalan Melphalan and additional agents[**]	Heusner [20]	2011	Retrospective CCS	38 23	43 (70%) NC	NR NR	3.3 (0.5-2), mean	Treatment	10.3 (5.01-15.59) 8.7 (8.07-9.32)	10.2 (4.6-16.4) 8.5 (5.5-13.3)	🇩🇪
Fotemustine	Leyvraz [4]	2014	Prospective randomised trial EORTC multicentre	86	86 (100%)	0 (0%)	NR	Enrollment	14.6 (10.2-15.4)	14.6 (10.2-17.2)	🇨🇭 🇫🇷 🇧🇪 🇮🇹 🇬🇧 🇩🇪 🇵🇱
Fotemustine	Leyvraz [21]	1997	Prospective NRCS	31	31 (100%) NC	NR	NR	Diagnosis	14	11.8 (6.7-18.6)	🇨🇭

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[*] The Kaplan-Meier graph did not have steps and possibly because of resultant difficulty in digitizing the median survivals differ.

[†] Median survival is 12 months when calculated from Table 1; the reported median survival of 15 months appears to correspond to mean survival [(7+8+8+12+16+18+20+29)/8=15 months].

[‡] The reported median survival of 18 months appears to be arithmetically calculated and not a Kaplan-Meier estimate.

[§] Reported for all patients, not specifically for uveal melanoma patients.

[**] Dacarbazine, doxorubicin, fotemustine, gemcitabine, MMC.

Cisplatin + vinblastine + dacarbazine	Melichar [22]	2009	Retrospective case series	10	7 (70%)	0 (0%)	1.4 (0.5-9.5)	Treatment	16	16.0 (5.0-19.0)	🇨🇿
Fotemustine or dacarbazine + cisplatin, after biopsy[*]	Salmon [23]	1998	Prospective nonrandomised comparative case series	16	16 (100%)	0 (0%)	NR	NR	NR	6.2 (1.0-10.1)	🇫🇷
Fotemustine	Siegel [24]	2007	Retrospective case series	18	NR	0 (0%)	2 (6-63)	Treatment	22	22.0 (6.1-31.8)	🇩🇪
Fotemustine[†]	Peters [25]	2006	Retrospective case series	101	101 (100%) NC	39 (39%) [‡]	1.9 (0.1-45)	Diagnosis	15 (12.1-17.6)	14.9 (13.3-19.1)	🇨🇭 🇮🇹 🇮🇱 🇩🇪 🇧🇪 🇫🇷
Transarterial chemoembolisation (TACE)											
Cisplatin w/wo polyvinyl sponge[§]	Agarwala [26]	2004	Prospective randomised trial phase I/II	19	13 (68%)	0 (0%)	NR	NR	8.5	8.4 (2.9-16.0)	🇺🇸
Irinotecan-eluting beads	Carling [1]	2015	Retrospective CCS	14	11 (79%)	1 (7%)	4.1 (1.2-12.7)	Treatment	9.4	9.4 (2.7-14.2)	🇳🇴
Cisplatin + doxorubicin + MMC + gelatin sponge	Dayani [27]	2009	Retrospective case series	21	17 (81%)	1 (5%)	NR	Treatment	NR	5.1 (3.3-8.2)	🇺🇸
Fotemustine + polyvinyl alcohol particles	Edelhauser [28]	2012	Retrospective case series	21	2 (10%)	0 (0%)	NR	Diagnosis	NR	28.8 (9.9-ND)	🇦🇹
Irinotecan-eluting beads	Fiorentini [29]	2009	Prospective trial phase II	10	0 (0%)	0 (0%)	44 (24-84)	Treatment	NR	ND[**]	🇮🇹
BCNU + gelatin sponge	Gonsalves [30]	2015	Retrospective case series	50[††]	50 (100%)	0 (0%)	NR	Treatment	7.1	7.1 (4.3-8.0)	🇺🇸
Cisplatin[‡‡] + gelatin sponge or polyvinyl alcohol particles	Gupta [31]	2010	Retrospective case series	125	82 (66%)	NR	7 (1-122), mean	Treatment	6.7 (4.9-8.5)	6.8 (4.8-8.9)	🇺🇸
Cisplatin or carboplatin + polyvinyl alcohol particles	Huppert [32]	2010	Prospective NRCS pilot study	14	8 (57%)	1 (7%)	4.5 (1-38)	Treatment	11.5	12.0 (9.0-22.0)	🇩🇪
Cisplatin + polyvinyl sponge	Mavligit [33]	1988	Retrospective case series	30	19 (63%)	0 (0%)	NR	Diagnosis	11 (9-18)	11.1 (8.0-18.0)	🇺🇸
BCNU + gelatin sponge	Patel [34]	2005	Prospective trial phase II	30	24 (80%)	0 (0%)	NR	Treatment	5.2	5.0 (2.9-9.8)	🇺🇸

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[*] Patients received at least two months fotemustine or dacarbazine and cisplatin after biopsy.

[†] In addition, 38 patients underwent debulking surgery at the time of catheter placement. In the Kaplan-Meier plot 100 patients were depicted.

[‡] As prior treatment, 39 patients had undergone surgery; the prior treatment of 11 patients was unknown.

[§] Of 19 patients, ten were treated with TACE.

[**] Median overall survival was not reached, i.e. cumulative survival plot did not fall below 50%.

[††] Fifty patients met the inclusion criteria but 49 patients are included in the Kaplan-Meier analysis.

[‡‡] Two patients additionally received paclitaxel and one patient doxorubicin + MMC.

Fotemustine or cisplatin + starch microspheres	Schuster [35]	2010	Retrospective case series	25	0 (0%)	NR	9 (2-24)	Treatment	6 (5-7)	5.8 (4.9-10.8)	🇩🇪
Cisplatin + gelatin sponge	Shibayama [36]	2017	Retrospective case series	29	27 (93%)	1 (3%)	NR	Treatment	23	23.0 (13.0-27.0)	🇯🇵
CPT-11 charged microbeads	Valpione [37]	2015	Retrospective CCS	58[*]	58 (100%)	0 (0%)	NR	Treatment	15.5[†]	16.5 (12.8-23.2)	🇮🇹
Bland embolisation + gelatin sponge	Valsecchi [38]	2015	Prospective randomised trial phase II	27	NR	NR	NR	Treatment	17.2 (11.9-22.4)	16.9 (10.9-22.1)	🇺🇸
MMC + iodised oil + microspheres	Vogl [39]	2007	Prospective NRCS pilot study	12	0 (0%)	4 (33%)	NR	Treatment	21	21.0 (8.3-26.0)	🇩🇪
Isolated hepatic perfusion (IHP)											
Melphalan	Alexander [40]	2003	Prospective trial phase I/II	29	22 (76%)	0 (0%)	NR	Enrollment	12.1	12.5 (6.0-ND)	🇺🇸
Melphalan w/wo TNF-alpha or cisplatin	Ben-Shabat [41]	2016	Retrospective case series	61	Majority	A few	NR	Treatment	22.4[‡]	23.9 (19.7- 26.0)	🇸🇪
Melphalan	de Leede [42]	2016	Retrospective case series	31	27 (87%)	0 (0%)	2.3 (0.9-13.3)	Treatment	10	10.0 (6.9-13.9)	🇳🇱
Melphalan	Forster [43]	2014	Retrospective case series	5	4 (80%)	0 (0%)	NR	Treatment	NR	14.2 (10.0-ND)	🇺🇸
Oxaliplatin + melphalan	van Iersel [44]	2014	Prospective trial phase I	3	2 (67%)	0 (0%)	NR	Treatment	NR	18.7 (7.8-ND)	🇳🇱
Melphalan	Vogl [45]	2017	Retrospective case series	18	7 (39)	5 (28)	NR	Treatment	9.6[§]	8.9 (4.4-23.5)	🇩🇪
Checkpoint inhibitor (CPI)											
Pembrolizumab or nivolumab or atezolizumab	Algazi [46]	2016	Retrospective case series	56	8 (14%)	0 (0%)	NR	Treatment	7.7 (0.7-14.6)	7.6 (4.9-14.9)	🇺🇸 🇪🇸
Ipilimumab	Danielli [47]	2012	Prospective NRCS	13	0 (0%)	NR	NR	Treatment	8.3	8.2 (3.7-15.9)	🇮🇹 🇬🇧
Tremelimumab	Joshua [48]	2015	Prospective trial phase II	11	NR[**]	3 (27%)	NR	Enrollment	12.8 (3.8-19.7)	12.8 (3.8-19.7)	🇨🇦
Pembrolizumab	Karydis [49]	2016	Retrospective case series	25	0 (0%)	3 (12%)	11.3 (3.7-65.1)	Treatment	NR	9.5 (5.0-14.1)	🇬🇧
Ipilimumab	Kelderman [50]	2013	Retrospective case series, WIN-O	22	0 (0%)	NR	NR	Treatment	5.2[††]	4.6 (2.3-10.8)	🇳🇱
Ipilimumab	Luke [51]	2013	Retrospective case series	39	0 (0%)	NR	NR	Treatment	9.6 (6.3-13.4)	9.7 (6.4-13.4)	🇺🇸 🇨🇭

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[*] In addition, 49 patients received intravenous fotemustine three weeks after TACE.

[†] In the Kaplan-Meier plot, some censored cases appear to be misaligned relative to the adjacent step and causing difficulty in digitizing.

[‡] The median differs either because of difficulty in digitizing the thick line with small steps in the published plot or because another method may have been used to calculate the median.

[§] A possible cause for the difference might be the dedicated statistical software used, because a very small difference in rounding would have shifted the step defining 0.5000 survival.

[**] Three patients had undergone surgery, three palliative radiation therapy, one TACE, three systemic chemotherapy.

[††] The reported median survival of 5.2 months appears to be arithmetically calculated and not a Kaplan-Meier estimate.

Ipilimumab	Maio [52]	2013	Prospective NRCS	83[*]	0 (0%)	NR	NR	NR	6.0 (4.3-7.7)	6.0 (4.6-8.4)	🇮🇹
Nivolumab or pembrolizumab	van der Kooij [53]	2017	Retrospective case series	17	8 (47%)	NR	NR	Treatment	8.8	8.7 (3.7-ND)	🇳🇱
Ipilimumab	Zimmer [54]	2015	Prospective trial phase II	53	8 (15%)	NR	NR	Treatment	6.8 (3.7-8.1)	6.8 (3.7-8.2)	🇩🇪
Protein kinase inhibitor (PKI)											
Sorafenib + carboplatin + paclitaxel	Bhatia [55]	2012	Prospective trial phase II	24	20 (83%)	NR	NR	Enrollment	11 (7-14)	10.5 (6.6-14.5)	🇺🇸
Cabozantinib	Daud [56]	2017	Prospective randomised discontinuation trial	23	NR[†]	NR	NR	Treatment	12.6	12.6 (4.6-19.9)	🇺🇸 🇮🇱 🇧🇪
Imatinib	Hofmann [57]	2009	Prospective NRCS	12	8 (67%)	NR	NR	Treatment	6.8[‡]	5.5 (2.6-8.7)	🇩🇪
Sunitinib	Mahipal [58]	2012	Prospective NRCS pilot study	20	3 (15%)	3 (15%)	NR	Treatment	8.2	8.0 (4.6-14.2)	🇺🇸
Sorafenib	Mouriaux [59]	2016	Prospective trial phase II	32	19 (59%)	0 (0%)	NR	Treatment	NR	7.8 (4.3-11.4)	🇫🇷 🇨🇦
Sorafenib + fotemustine	Niederkorn[60]	2014	Retrospective case series	8	2 (25%)	NR	NR	Treatment	15.9	15.9 (5.6-20.3)	🇦🇹
Imatinib mesylate	Penel[61]	2008	Prospective trial phase II	13	6 (46%)	0 (0%)	NR	Treatment	10.8	10.8 (1.2-ND)	🇫🇷
Selective internal radiation therapy (SIRT)											
SIRT, ^{90}Y resin microspheres	Eldredge-Hindy [62]	2016	Retrospective case series	50	13 (18%)[§]	NR	9.8	Treatment	NR	14.9 (9.7-17.2)	🇺🇸
SIRT, ^{90}Y resin microspheres	Klingenstein [63]	2013	Retrospective case series	13	2 (15%)	1 (8%)	5 (1-49)	Treatment	7	7.0 (2.0-15.0)	🇩🇪
SIRT, ^{90}Y glass microspheres	Schelhorn [64]	2015	Retrospective case series	8	0 (0%)	0 (0%)	17.1 (6.4-23.2)	Treatment	2.8	2.8 (0.8-13.0)	🇩🇪
Immunoembolisation (IE)											
Immunoembolisation with GM-CSF	Sato [65]	2008	Prospective trial phase I	34	28 (82%)	3 (9%)	NR	Treatment	14.4[**]	18.4 (11.2-22.8)	🇺🇸
Immunoembolisation with GM-CSF	Valsecchi [38]	2015	Prospective trial phase II	25	NR	NR	NR	Treatment	21.5 (18.5-24.8)	21.6 (17.5-30.1)	🇺🇸
Immunosuppressant (IS)											
Everolimus + pasireotide	Shoushtari [66]	2016	Prospective trial phase II	14	0 (0%)	NR	NR	Treatment	11	10.9 (5.4-17.6)	🇺🇸

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[*] One patient was lost in follow-up of 83 patients and in Kaplan-Meier plot 82 patients are depicted.

[†] Reported for all patients, not specifically for uveal melanoma patients.

[‡] The reported median survival of 6.8 months appears to correspond to mean survival [(1.59+2.62+3.60+4.57+4.57+5.55+5.67+6.59+6.65+8.66+10.73+ 20.73)/12=6.8 months, from the digitized Kaplan-Meier plot].

[§] Prior treatment reported for all 58 patients, and not specifically for the 50 patients who had a pretreatment positron emission tomography/computer tomography and were included in the Kaplan-Meier plot.

[**] The median overall survival is reported for 34 patients in intent-to-treat analysis whereas the Kaplan-Meier plot incudes 31 radiographically assessable patients.

Liver-directed thermotherapy (LDT)											
Stereotactic radiofrequency ablation	Bale [67]	2016	Retrospective case series	6	0 (0%)	0 (0%)	NR	Treatment	38[*]	36.2 (15.7-ND)	🇦🇹
Laser-induced thermotherapy	Eichler [68]	2014	Retrospective case series	18	NR[†]	NR	4 (22)	Diagnosis	29.2[‡]	29.2 (12.5-43.0)	🇩🇪
Vaccine											
Dendritic cell vaccine	Bol [69]	2014	Prospective NRCS	14	8 (57%)	3 (21%)	NR	Treatment	19.2	19.4 (6.8-38.1)	🇳🇱 🇩🇪
Surgery											
Resection	Aoyama [70]	2000	Retrospective case series	12	8 (67%)	0 (0%)	NR	Treatment	NR	27 (23-ND)	🇺🇸
Resection[§]	Frenkel [71]	2009	Retrospective CCS								🇮🇱
R0				14	NR	0 (0%)	NR	Diagnosis	NR	65.2 (11.2-ND)	
R1/R2				23	NR	0 (0%)	NR	Diagnosis	NR	16.3 (7.6-25.3)	
Resection[**]	Gomez [72]	2014	Retrospective CCS	18	NR	NR	NR	Treatment	27[††]	28.9 (20.0-ND)	🇬🇧
Resection	Hsueh [73]	2004	Retrospectice CCS	24	NR[‡‡]	NR	NR	Diagnosis	38[††]	35.7 (21.2-ND)	🇺🇸
Resection + fotemustine IA or cisplatin IA	Kodjikian [74] / Rivoire [75]	2005	Retrospective CCS								🇫🇷
R0				14	14 (100%)	0 (0%)	NR	Treatment	25[***]	35.3 (15.0-ND)	
R2[§§]				14	14 (100%)	0 (0%)	NR	Treatment	16	16.3 (11.0-17.6)	
	Mariani [76]	2016	Retrospective CCS								🇫🇷
Resection				57	57 (100%)	0 (0%)	NR	Treatment	27	26.9 (20.8-34.8)	
Resection + RFA				13	13 (100%)	0 (0%)	NR	Treatment	28	27.8 (16.9-ND)	

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[*] In the original publication median survival was reported as 38 months; according to personal communication this was calculated by the actuarial method and is 36.3 months by the Kaplan-Meier method.

[†] The authors state: “Limitations of our study are the small number of patients and the inhomogenous population concerning various treatments prior the LITT like immunochemotherapy and TACE”.

[‡] Personal communication.

[§] The authors state: “Some patients received chemotherapy intravenously or through an intra-arterial hepatic port, and some received adjuvant immunotherapy”.

[**] One RFA.

[††] The reported median survival appears to be arithmetically calculated and not a Kaplan-Meier estimate.

[‡‡] Of 112 treatments, 13 were first-line, but the numbers are not reported separately for the 24 patients who underwent surgery; in addition, some resections were combined with immunotherapy, systemic chemotherapy, and hepatic perfusion.

[§§] Three patients received no chemotherapy.

[***] The reported median survival appears to be arithmetically calculated and not a Kaplan-Meier estimate.

Resection[*]	Mariani [77]	2009	Retrospective comparative case series								🇫🇷
R0				76	76 (100%)	0 (0%)	NR	Treatment	27	27.0 (18.2-32.0)	
R1				22	22 (100%)	0 (0%)	NR	Treatment	17[†]	16.0 (7.1-30.1)	
R2				157	157 (100%)	0 (0%)	NR	Treatment	11	11.1 (9.0-12.0)	
Resection + fotemustine IA or dacarbazine IA + cisplatin IA	Salmon [23]	1998	Prospective nonrandomised comparative case series								🇫🇷
Curative resection				19	19 (100%)	0 (0%)	NR	NR	22	30.1 (17.1-ND)[‡]	
Tumour reduction				34	34 (100%)	0 (0%)	NR	NR	NR	8.1 (5.3-10.1)	
Resection, partial[§]	Yang [78]	2013	Retrospective case series	5	NR	NR	NR	Treatment	11.5 (7.5-15.8)	11.5 (8.5-ND)	🇨🇳

Abbreviations

BCNU, bis-chloroethylnitrosourea; BOLD, includes bleomycin, vincristine, lomustine, and dacarbazine; CCS, comparative case series; CHT, conventional chemotherapy; CI, confidence interval; CIT, chemoimmunotherapy; CPI, checkpoint inhibitor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HIA, hepatic intra-arterial chemotherapy; IA, intra-arterial; IFN, interferon; IHP, isolated hepatic perfusion; IL2, interleukin 2; IV, intravenous; LDT, liver-directed thermotherapy; LITT, laser-induced thermotherapy; MMC, mitomycin; NC, no prior chemotherapy nor systemic treatment; ND, not defined; NR, not reported; NRCS, nonrandomised controlled case series; OS, overall survival; PKI, protein kinase inhibitor; R0, microscopically complete liver surgery; R1, microscopically incomplete liver surgery; R2, macroscopically incomplete liver surgery; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TNF, tumour necrosis factor.

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[*] The authors state: “Postoperative chemotherapy was mandated in every patient during the first years of our experience, but since 2005 has been reserved for randomised patients in the intra-arterial arm of the European trial”; in addition, eight patients underwent RFA during laparotomy to attain R0 resection.

[†] A possible cause for the difference might be the dedicated statistical software used, because a very small difference in rounding of decimals would have shifted the step defining 0.5000 survival.

[‡] A possible cause for the difference might be the dedicated statistical software used, because a very small difference in rounding of decimals would have shifted the step defining 0.5000 survival; the adjacent steps in the plot are 22.2 and 30.1 months, and from the Kaplan-Meier plot it is clear that the median survival indeed is about 22 months, and 22.2 was used in our analysis.

[§] Of the five patients, two received adjuvant therapy with TACE with or without immunotherapy.

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