Supplementary Materials

Mitomycin C versus Oxaliplatin for Hyperthermic Intraperitoneal Chemotherapy after Cytoreductive Surgery for Appendiceal Neoplasms: A Systematic Review and Meta-Analysis

Table S1. Search strategies and yields (PubMed, Europe PMC, ClinicalTrials.gov and citation searching: 29 September 2026; Scopus, Web of Science and SpringerLink: 1 October 2026).

Source	Strategy	Records
PubMed/MEDLINE S1 (both agents)	("Appendiceal Neoplasms"[Mesh] OR "Pseudomyxoma Peritonei"[Mesh] OR appendiceal[tiab] OR appendix[tiab] OR appendicular[tiab] OR pseudomyxoma[tiab] OR LAMN[tiab] OR HAMN[tiab]) AND ("Hyperthermic Intraperitoneal Chemotherapy"[Mesh] OR HIPEC[tiab] OR hyperthermic[tiab] OR "intraperitoneal chemotherapy"[tiab] OR "intraperitoneal chemoperfusion"[tiab] OR "Cytoreduction Surgical Procedures"[Mesh] OR cytoreduct*[tiab]) AND ("Mitomycin"[Mesh] OR mitomycin*[tiab] OR MMC[tiab]) AND ("Oxaliplatin"[Mesh] OR oxaliplatin[tiab] OR L-OHP[tiab]) AND ("2005/01/01"[dp] : "2026/09/29"[dp])	40
PubMed/MEDLINE S2 (either agent)	("Appendiceal Neoplasms"[Mesh] OR "Pseudomyxoma Peritonei"[Mesh] OR appendiceal[tiab] OR appendix[tiab] OR appendicular[tiab] OR pseudomyxoma[tiab] OR LAMN[tiab] OR HAMN[tiab]) AND ("Hyperthermic Intraperitoneal Chemotherapy"[Mesh] OR HIPEC[tiab] OR hyperthermic[tiab] OR "intraperitoneal chemotherapy"[tiab] OR "intraperitoneal chemoperfusion"[tiab] OR "Cytoreduction Surgical Procedures"[Mesh] OR cytoreduct*[tiab]) AND (("Mitomycin"[Mesh] OR mitomycin*[tiab] OR MMC[tiab]) OR ("Oxaliplatin"[Mesh] OR oxaliplatin[tiab] OR L-OHP[tiab])) AND ("2005/01/01"[dp] : "2026/09/29"[dp])	239
PubMed/MEDLINE S3 (regimen terms)	("Appendiceal Neoplasms"[Mesh] OR "Pseudomyxoma Peritonei"[Mesh] OR appendiceal[tiab] OR appendix[tiab] OR appendicular[tiab] OR pseudomyxoma[tiab] OR LAMN[tiab] OR HAMN[tiab]) AND ("Hyperthermic Intraperitoneal Chemotherapy"[Mesh] OR HIPEC[tiab] OR hyperthermic[tiab] OR "intraperitoneal chemotherapy"[tiab] OR "intraperitoneal chemoperfusion"[tiab] OR "Cytoreduction Surgical Procedures"[Mesh] OR cytoreduct*[tiab]) AND (regimen*[tiab] OR "chemotherapeutic agent*"[tiab] OR "perfusion agent*"[tiab] OR "HIPEC agent*"[tiab] OR "HIPEC drug*"[tiab]) AND ("2005/01/01"[dp] : "2026/09/29"[dp])	98
PubMed/MEDLINE, unique S1–S3	De-duplicated by PMID	296
Europe PMC (title/abstract)	(TITLE/ABSTRACT: appendiceal OR appendix OR appendicular OR pseudomyxoma) AND (HIPEC OR hyperthermic OR "intraperitoneal chemotherapy" OR cytoreduct*) AND (mitomycin* OR MMC OR oxaliplatin) AND PUB_YEAR:[2005 TO 2026]	149 (147 duplicates of PubMed; 2 preprints, ineligible)
Europe PMC (full text, both agents)	Same terms without field restriction	753 (titles screened for regimen comparisons; no additional eligible study)
ClinicalTrials.gov	Condition: appendiceal OR pseudomyxoma; Intervention: HIPEC OR hyperthermic OR mitomycin OR oxaliplatin	58 (NCT01580410 = included trial)
Scopus	TITLE-ABS-KEY((appendi* OR "pseudomyxoma peritonei") AND (hipec OR "hyperthermic intraperitoneal" OR "intraperitoneal chemotherapy" OR "intraperitoneal chemoperfusion") AND oxaliplatin AND mitomycin*)	322 (70 duplicates of PubMed records; 252 screened; 1 full text assessed, excluded)
Web of Science Core Collection	TS=((appendi* OR "pseudomyxoma peritonei") AND (HIPEC OR "hyperthermic intraperitoneal" OR "intraperitoneal chemotherapy" OR "intraperitoneal chemoperfusion") AND oxaliplatin AND mitomycin*)	56 (36 duplicates of PubMed, 1 of Scopus; 19 screened; 2 full texts assessed: 1 included, 1 excluded)
SpringerLink (supplementary)	(appendiceal OR appendix OR "pseudomyxoma peritonei") AND (HIPEC OR "hyperthermic intraperitoneal") AND oxaliplatin AND mitomycin; "pseudomyxoma peritonei" AND oxaliplatin AND mitomycin (articles, sorted by relevance)	≈220 screened online; no additional eligible study (Mangieri 2023 already identified)

Source	Strategy	Records
Citation searching	References and citing articles (PubMed) of PMIDs 39531120, 29331663, 31720933, 39008204, 42805016, 36484904, 33502455	205 new records; none eligible

Table S2a. Extracted time-to-event data (oxaliplatin vs mitomycin C).

outcome	set	study	design	n_ox	n_mmc	logHR	seLogHR	HR	source	adjusted
DFS	primary	Levine 2025 (RCT)	RCT	60	61	0.022076	0.265059	1.0223	IPD reconstructed (Guyot) from Fig 3 + numbers at risk; PMC11698756	no (randomised)
DFS	primary	Marques 2026	Retrospective cohort	35	104	0.996949	0.377322	2.7100	Abstract/Results: multivariable Cox, recurrence, HR 2.71 (1.26-5.53)	yes (multivariable Cox)
DFS	primary	Santullo 2021	Retrospective cohort	13	34	-0.385262	0.739521	0.6803	Table 5, univariate Cox PFS, MMC vs OX HR 1.47 (0.345-6.263), inverted	no
DFS	primary	Nassabein 2022 (PMCA)	Retrospective cohort	14	22	-0.622188	0.584454	0.5368	IPD reconstructed from Fig 4A (step heights + censor ticks); PMC9188801	no
DFS	sensitivity (probable overlap with RCT)	Mangieri 2023 (HG appendiceal)	Retrospective cohort	11	96	0.127371	0.351283	1.1358	IPD reconstructed from Fig 2 (DFS appendiceal; OX step heights exact n=11; MMC n from step height ~96; no numbers at risk); reconstructed log-rank p 0.715 vs 0.725 in figure	no
OS	primary	Levine 2025 (RCT)	RCT	60	61	0.045769	0.289663	1.0468	IPD reconstructed (Guyot) from Fig 2 + numbers at risk; PMC11698756	no (randomised)
OS	primary	Nassabein 2022 (PMCA)	Retrospective cohort	14	22	-1.059576	1.099626	0.3466	IPD reconstructed from Fig 4B; PMC9188801	no
OS	sensitivity (probable overlap with RCT)	Mangieri 2023 (HG appendiceal)	Retrospective cohort	19	140	0.210017	0.260238	1.2337	IPD reconstructed from Fig 2 (OS appendiceal; OX 19 = 61.3% of 31, MMC 140 = 159-19); reconstructed log-rank p 0.416 vs 0.412 in figure	no

Table S2b. Extracted binary outcome data.

analysis	study	e_ox	n_ox	e_mmc	n_mmc	population	source
MajorMorbidity	Levine 2018 (RCT)	20	60	19	61	appendiceal	Levine 2018 Table 2 (sum of III, IIIa, IIIb, IV, IVa, IVb, V)
MajorMorbidity	Benzaquen 2021 (appendiceal, derived)	13	32	5	10	appendiceal (derived)	Table 4: all minus colorectal (OX 22-9 / 76-44; MMC 10-5 / 42-32); OX includes 1 unknown-origin patient
MajorMorbidity_mixed	Levine 2018 (RCT)	20	60	19	61	appendiceal	as above
MajorMorbidity_mixed	Benzaquen 2021 (all)	22	76	10	42	mixed	Table 4: 22/53 and 10/25 of patients with complications
MajorMorbidity_mixed	Sticca 2025	54	234	13	48	mixed	Table 3
MajorMorbidity_mixed	McConnell 2013	35	113	38	85	mixed (appendix 60.6%, colorectal 33.3%, other 6.0%)	J Surg Oncol 2013;107:591, Table II (HIPEC group: 38/85 vs 35/113)
Mortality90	Levine 2018 (RCT)	3	60	2	61	appendiceal	Results text: 90-day mortality 3.3% MMC vs 5% OX
Mortality90_mixed	Levine 2018 (RCT)	3	60	2	61	appendiceal	Results text: 90-day mortality 3.3% MMC vs 5% OX
Mortality90_mixed	Benzaquen 2021 (all)	0	76	1	42	mixed	Table 5 + text (one MMC death within 90 d)
Mortality90_mixed	Sticca 2025	3	234	1	48	mixed	Table 3
Thrombocytopenia34	Levine 2018 (RCT)	1	60	2	61	appendiceal	Results: grade 3-4 thrombocytopenia 1 OX, 2 MMC

analysis	study	e_ox	n_ox	e_mmc	n_mmc	population	source
Thrombocytopenia34_mixed	Levine 2018 (RCT)	1	60	2	61	appendiceal	Results: grade 3-4 thrombocytopenia 1 OX, 2 MMC
Thrombocytopenia34_mixed	Votanopoulos 2013	6	55	4	134	mixed	Table 1 grade 3+4 platelet toxicity
Leukopenia	Horvath 2016	0	10	10	32	appendiceal (PMP)	Table 1
Neutropenia_mixed	Votanopoulos 2013	8	55	6	134	mixed	Table 1
Neutropenia_mixed	Sticca 2025 (high-dose MMC)	10	234	13	48	mixed	Table 2

Table S2c. Extracted single-arm proportions (all appendiceal patients).

analysis	study	x	n	definition
CC01	Levine 2025 (RCT)	70	121	R0/R1 (Table 1: 13+20 MMC, 14+23 OX)
CC01	Marques 2026	133	139	CC0-1
CC01	Santullo 2021	47	50	CC0-1
CC0	Marques 2026	105	139	CC0 75.7% of 139 (=105.2 -> 105)
CC0	Santullo 2021	37	50	CC0
CC0	Horvath 2016	24	42	CC0 (21 MMC + 3 OX; HIPEC only after CC0-1)
MajorMorbidity	Levine 2018 (RCT)	39	121	CD>=III (Table 2)
MajorMorbidity	Marques 2026	39	139	CD III-IV 28.1% of 139 (=39.06 -> 39)
MajorMorbidity	Santullo 2021	5	50	CD III-IV
MajorMorbidity	Benzaquen 2021 (appendiceal, derived)	18	42	CD III-IV, derived
Mortality30	Levine 2018 (RCT)	4	121	30-day: 1 MMC (1.6%) + 3 OX (5%); text also states 3 deaths in each group (inconsistent)
Mortality30	Marques 2026	5	139	30-day 3.6%
Mortality30	Santullo 2021	1	50	30-day

Notes on source inconsistencies identified during extraction: (1) Levine 2025: R0/R1 reported as 54% (MMC) and 51% (OX) in the text, but Table 1 counts give 33/61 (54.1%) and 37/60 (61.7%); high-grade disease 17 (OX) in Table 1 vs 15 in the 2018 report vs n = 12 in the 2025 subgroup text. (2) Levine 2018: Clavien–Dindo ≥ III reported as 32.7% for MMC but Table 2 counts give 19/61 (31.1%); 30-day mortality reported both as "3 deaths in each group" and as 1.6% vs 5%. (3) Marques 2026: the CI 1.26–5.53 is reported for three different hazard ratios; the abstract assigns it to oxaliplatin (HR 2.71). (4) Santullo 2021: several OS hazard ratios in Table 6 are incompatible with their confidence intervals; only the PFS HR for HIPEC drug (consistent on the log scale) was used. (5) Nassabein 2022: OS p value reported as 0.33 and 0.55 for the same comparison. (6) Votanopoulos 2013: MMC group size 132 (text) vs 134 (table). (7) Horvath 2016: 42 patients in Methods and Table 1, 40 in Results. (8) Mangieri 2023: the hazard ratios given in the Results text for the appendiceal subgroup (OS 0.42, 95% CI 0.09–1.93; DFS 2.25, 0.41–12.26) correspond approximately to odds ratios of the 5-year survival rates (e.g., OS 10.9% vs 21.9%: OR 0.44; DFS 18.2% vs 8.9%: OR 2.28) and are labelled as odds ratios in the main analysis; log-rank p values for the appendiceal subgroup are 0.99 (OS) and 0.46 (DFS) in Table 5 but 0.412 and 0.725 on Figure 2; Clavien–Dindo ≥ III rate of 20.3% for 302 MMC patients does not correspond to an integer count (61/302 = 20.2%, 62/302 = 20.5%); the study period is not reported. The appendiceal arms (19 OX = 61.3% of 31; 140 MMC = 159 − 19) were confirmed by the step heights of the oxaliplatin curve (1/19 for OS; 1/11 for DFS). (9) McConnell 2013: complication rates by individual complication (e.g., venous thrombosis 8.7% vs 1.7%) do not correspond to integer counts of the group sizes and were not extracted.

Table S3. Risk-of-bias judgements and rationale.

Study / tool	Domain judgements	Overall	Rationale
Levine (RCT), RoB 2	D1 Some concerns; D2 Low; D3 Low; D4 Some concerns (DFS unblinded); D5 Some concerns	Some concerns	Sequence generation/allocation concealment not described; timing of randomisation reported inconsistently; survival secondary endpoint; HR not reported; text–table inconsistencies.

Study / tool	Domain judgements	Overall	Rationale
Marques 2026, ROBINS-I	Confounding serious; selection moderate; classification low; deviations low; missing data moderate; measurement moderate; reporting moderate	Serious	Era-based allocation (MMC unavailable after 2015); multivariable adjustment; repeated CI for different HRs.
Santullo 2021, ROBINS-I	Confounding serious; others low–moderate	Serious	Chronological switch; unadjusted; few events; implausible OS estimates.
Nassabein 2022, ROBINS-I	Confounding serious; others low–moderate	Serious	Agent selected by disease type, prior chemotherapy and performance status; unadjusted.
Benzaquen 2021, ROBINS-I	Confounding serious; others low–moderate	Serious	Agent determined by centre and surgeon; appendiceal subgroup derived.
Horvath 2016, ROBINS-I	Confounding serious; deviations moderate; others low–moderate	Serious	Co-intervention (IV 5-FU) in OX arm; small; unadjusted.
Votanopoulos 2013, ROBINS-I	Confounding serious; others low–moderate	Serious	Mixed population; OX patients mainly from phase I trial.
Sticca 2025, ROBINS-I	Confounding serious; others low–moderate	Serious	Era-based allocation, concurrent ERAS implementation; mixed population.
Mangieri 2023, ROBINS-I	Confounding serious; selection serious; classification low; deviations low; missing data moderate; measurement moderate; reporting serious	Serious	Agent by institutional preference; only patients exposed to neoadjuvant oxaliplatin; DFS excludes incomplete cytoreduction and 90-day deaths; unadjusted subgroup; mislabelled effect measures and discordant p values; probable overlap with the RCT (sensitivity analysis only).
McConnell 2013, ROBINS-I	Confounding serious; selection low; classification low; deviations serious (co-intervention); missing data low; measurement moderate; reporting moderate	Serious	Consecutive eras; MMC combined with EPIC 5-FU and OX with IV 5-FU; mixed population; univariable comparison by agent.

Table S4. Sensitivity and leave-one-out analyses (hazard ratio, oxaliplatin vs mitomycin C).

Analysis	Method	k	HR (95% CI)	I^2	τ^2	95% PI
DFS, all studies	REML	4	1.12 (0.55–2.29)	60%	0.31	0.06–19.62
DFS, all studies	REML + HKSJ	4	1.12 (0.36–3.48)	60%	0.31	0.06–19.62
DFS, all studies	DerSimonian–Laird	4	1.13 (0.56–2.25)	60%	0.28	0.07–17.68
DFS, all studies	Leave-one-out (REML), omitting Levine 2025 (RCT)	3	1.11 (0.37–3.32)	70%		
DFS, all studies	Leave-one-out (REML), omitting Marques 2026	3	0.89 (0.57–1.40)	0%		
DFS, all studies	Leave-one-out (REML), omitting Santullo 2021	3	1.22 (0.52–2.86)	71%		
DFS, all studies	Leave-one-out (REML), omitting Nassabein 2022 (PMCA)	3	1.36 (0.63–2.93)	63%		
DFS, excluding Marques 2026	REML	3	0.89 (0.57–1.40)	0%	0.00	0.05–16.43
DFS, excluding Marques 2026	REML + HKSJ	3	0.89 (0.42–1.88)	0%	0.00	0.05–16.43
DFS, excluding Marques 2026	DerSimonian–Laird	3	0.89 (0.57–1.40)	0%	0.00	0.05–16.43
DFS, excluding Marques 2026	Leave-one-out (REML), omitting Levine 2025 (RCT)	2	0.59 (0.24–1.44)	0%		
DFS, excluding Marques 2026	Leave-one-out (REML), omitting Santullo 2021	2	0.91 (0.57–1.47)	1%		
DFS, excluding Marques 2026	Leave-one-out (REML), omitting Nassabein 2022 (PMCA)	2	0.98 (0.60–1.59)	0%		
DFS, observational studies only	REML	3	1.11 (0.37–3.32)	70%	0.62	0.00–244504.50
DFS, observational studies only	REML + HKSJ	3	1.11 (0.11–10.81)	70%	0.62	0.00–244504.50
DFS, observational studies only	DerSimonian–Laird	3	1.10 (0.35–3.46)	70%	0.71	0.00–510919.03
DFS, observational studies only	Leave-one-out (REML), omitting Marques 2026	2	0.59 (0.24–1.44)	0%		
DFS, observational studies only	Leave-one-out (REML), omitting Santullo 2021	2	1.28 (0.26–6.24)	82%		

Analysis	Method	k	HR (95% CI)	I^2	τ^2	95% PI
DFS, observational studies only	Leave-one-out (REML), omitting Nassabein 2022 (PMCA)	2	1.57 (0.42–5.91)	64%		
DFS, adding Mangieri 2023	REML	5	1.15 (0.69–1.92)	47%	0.16	0.26–5.19
DFS, adding Mangieri 2023	REML + HKSJ	5	1.15 (0.56–2.39)	47%	0.16	0.26–5.19
DFS, adding Mangieri 2023	DerSimonian–Laird	5	1.16 (0.70–1.90)	47%	0.14	0.27–4.95
DFS, adding Mangieri 2023	Leave-one-out (REML), omitting Levine 2025 (RCT)	4	1.16 (0.56–2.41)	57%		
DFS, adding Mangieri 2023	Leave-one-out (REML), omitting Marques 2026	4	0.96 (0.66–1.40)	0%		
DFS, adding Mangieri 2023	Leave-one-out (REML), omitting Santullo 2021	4	1.22 (0.69–2.13)	57%		
DFS, adding Mangieri 2023	Leave-one-out (REML), omitting Nassabein 2022 (PMCA)	4	1.30 (0.78–2.18)	46%		
DFS, adding Mangieri 2023	Leave-one-out (REML), omitting Mangieri 2023 (HG appendiceal)	4	1.12 (0.55–2.29)	60%		
OS	REML	2	0.97 (0.56–1.69)	0%	0.00	n/a
OS	REML + HKSJ	2	0.97 (0.03–30.99)	0%	0.00	n/a
OS	DerSimonian–Laird	2	0.97 (0.56–1.69)	0%	0.00	n/a
OS, adding Mangieri 2023	REML	3	1.11 (0.76–1.61)	0%	0.00	0.10–12.47
OS, adding Mangieri 2023	REML + HKSJ	3	1.11 (0.57–2.16)	0%	0.00	0.10–12.47
OS, adding Mangieri 2023	DerSimonian–Laird	3	1.11 (0.76–1.61)	0%	0.00	0.10–12.47
OS, adding Mangieri 2023	Leave-one-out (REML), omitting Levine 2025 (RCT)	2	1.03 (0.43–2.47)	21%		
OS, adding Mangieri 2023	Leave-one-out (REML), omitting Nassabein 2022 (PMCA)	2	1.15 (0.78–1.68)	0%		
OS, adding Mangieri 2023	Leave-one-out (REML), omitting Mangieri 2023 (HG appendiceal)	2	0.97 (0.56–1.69)	0%		

HKSJ intervals with k = 2 are not informative. PI, prediction interval ($k \geq 3$).

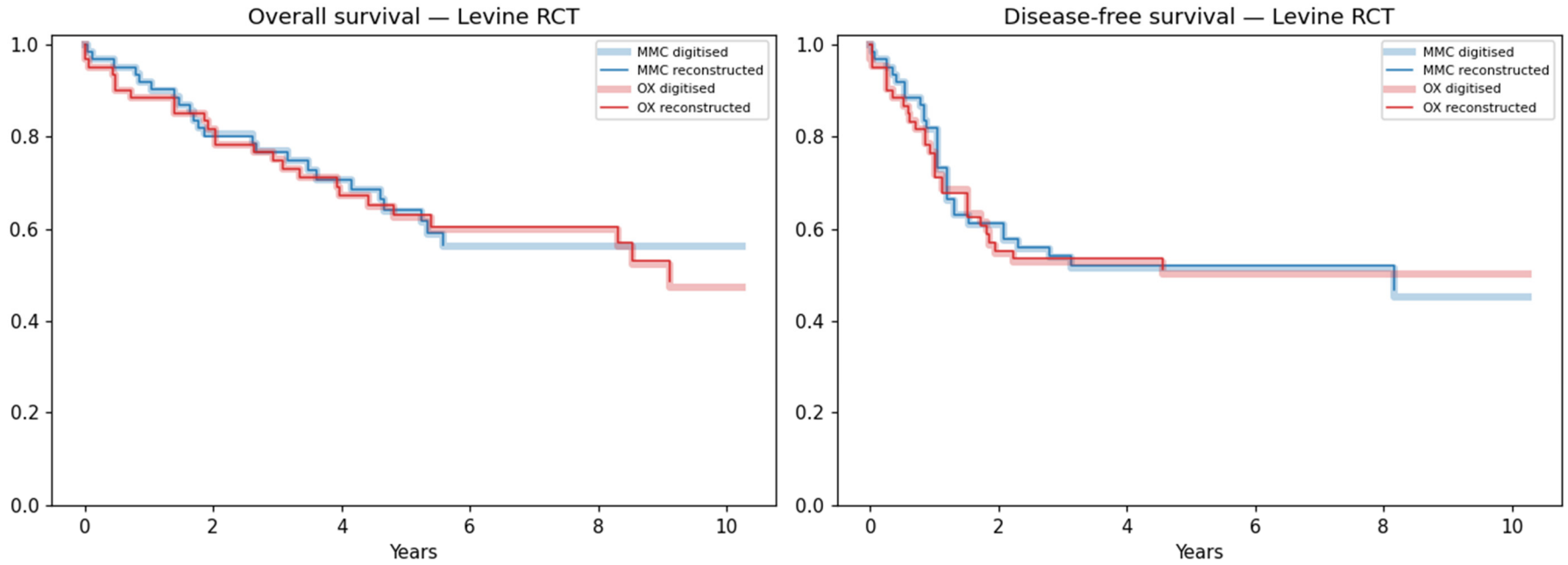


Figure S1. Validation of reconstructed individual patient data for the randomised trial (Levine 2025): digitised published curves (thick, transparent) and Kaplan–Meier curves of the reconstructed data (thin). Reconstructed numbers at risk equal the published values at 0, 2, 4, 6, 8 and 10 years; reconstructed log-rank p = 0.87 (OS; reported 0.83) and 0.93 (DFS; reported 0.95).

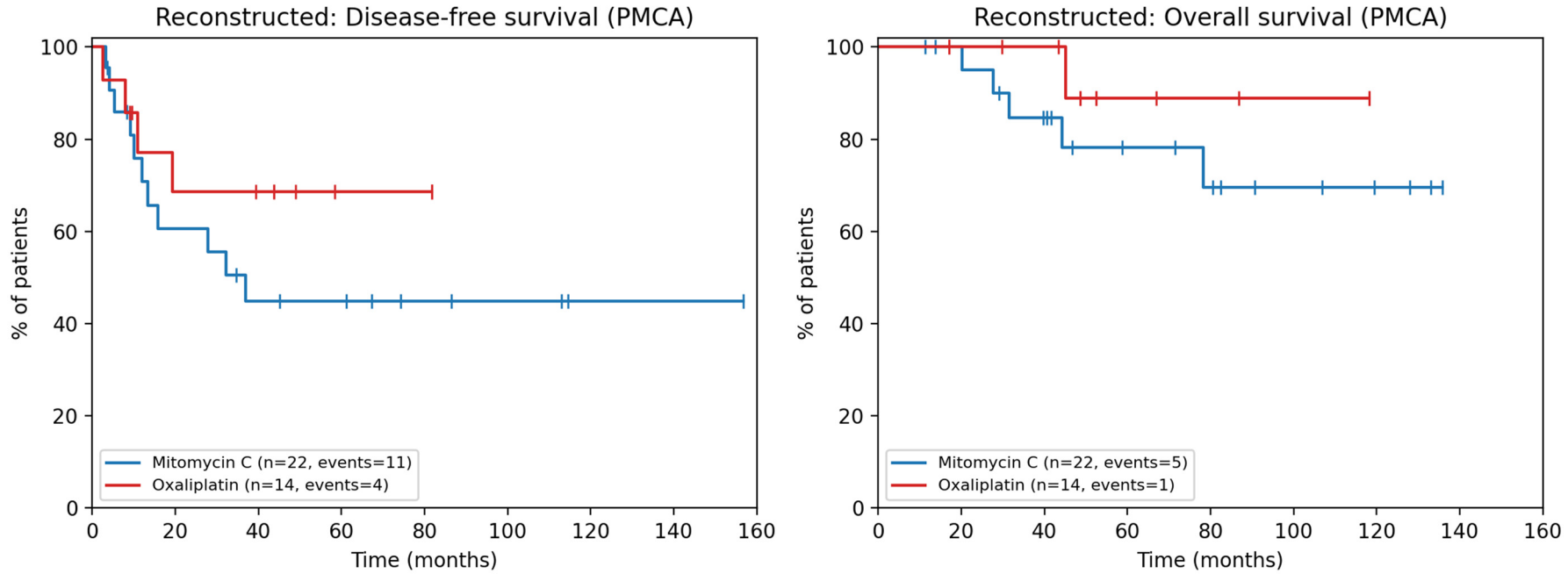


Figure S2. Reconstructed Kaplan–Meier curves for the PMCA subgroup of Nassabein 2022 (mitomycin C n = 22, oxaliplatin n = 14). Reconstructed log-rank p = 0.28 for DFS (reported 0.28) and 0.31 for OS (reported 0.33).

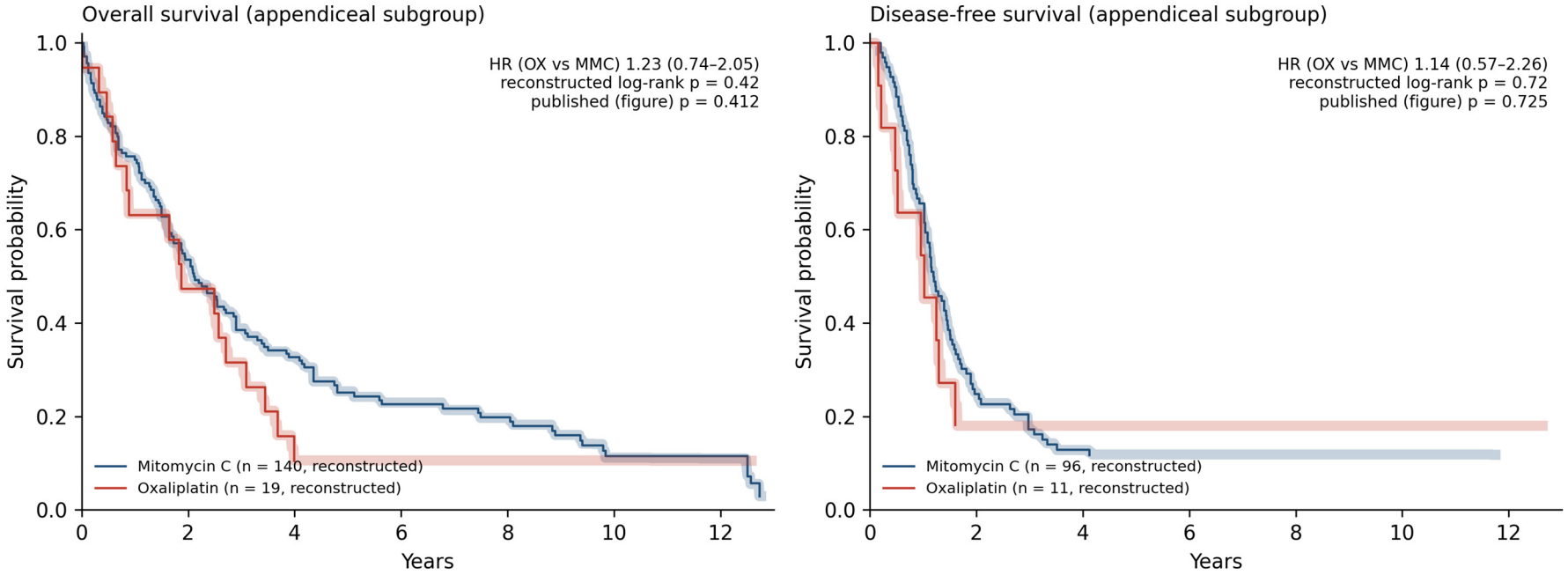


Figure S3. Reconstruction of the high-grade appendiceal subgroup of Mangieri 2023 (source Figure 2): digitised published curves (thick, transparent) and Kaplan–Meier curves of the reconstructed data (thin). Oxaliplatin arms reconstructed exactly from step heights (OS n = 19, DFS n = 11); mitomycin C denominators 140 (OS; 159 − 19) and 96 (DFS; from the single-event step height, not reported). Varying the DFS denominator between 90 and 110, or the OS denominator between 120 and 140, changed the HR by ≤ 0.02.

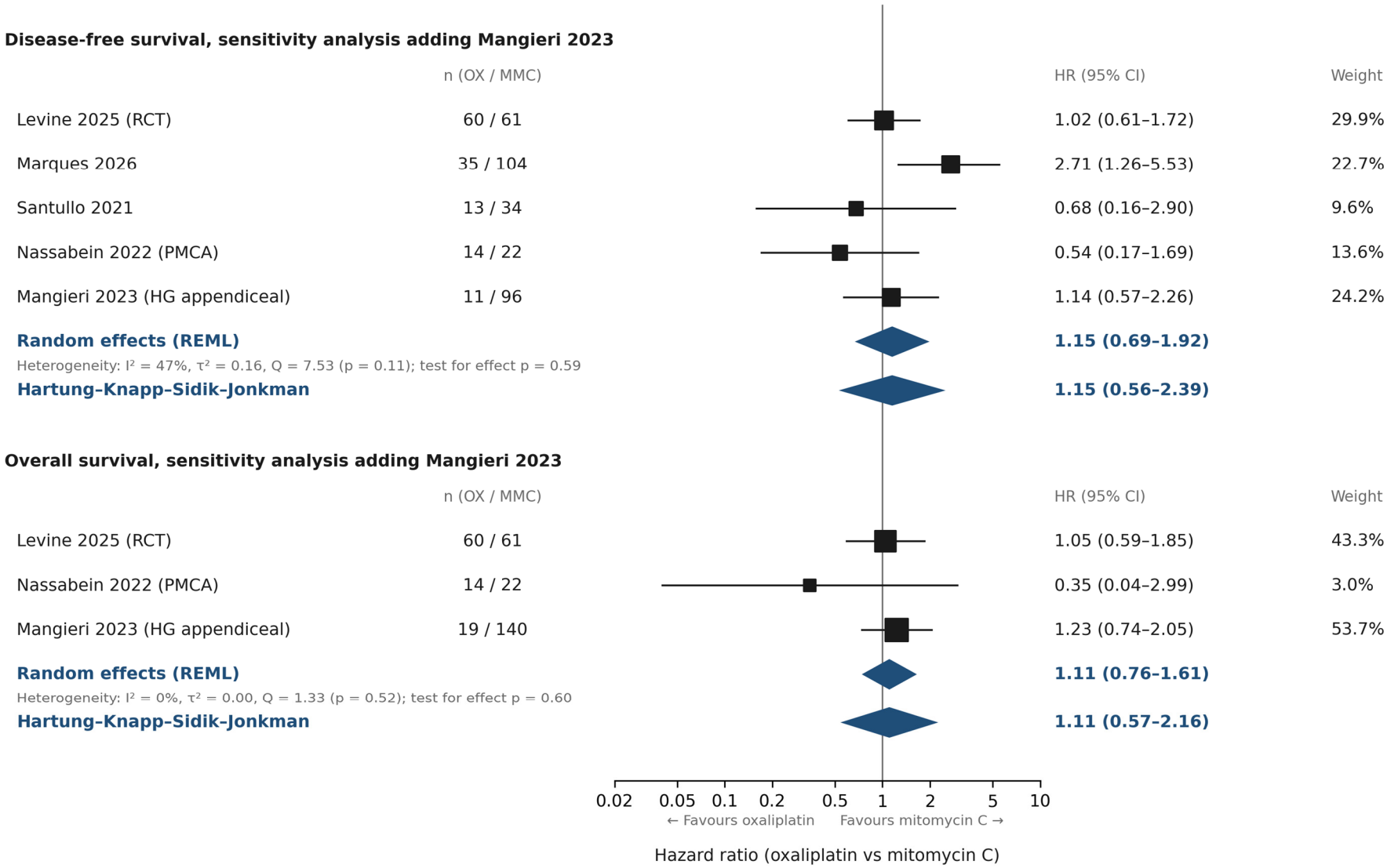


Figure S4. Sensitivity analysis adding Mangieri 2023 (probable overlap with the randomised trial) to the DFS and OS meta-analyses (random effects, REML).

Table S5. Reports assessed in full text and excluded, and reports that could not be retrieved.

Report	Source	Status	Reason
Kusamura 2021, JAMA Surg	PubMed	Excluded	Each HIPEC regimen compared only with CRS alone (no head-to-head MMC vs OX comparison); discussed as indirect evidence.

Report	Source	Status	Reason
Kirby 2014, Open Surg Oncol J	Scopus	Excluded	15 OX + IV 5-FU vs 15 MMC + EPIC 5-FU, matched; tumour origin of the patients compared not reported; outcomes not reported by primary site.
Yüksel 2022, Ann Ital Chir	Web of Science	Excluded	All 40 patients received the same regimen (MMC 20 mg/m² + carboplatin 450 mg/m²).
Hassan 2023, Eur J Surg Oncol	PubMed	Not retrieved	Full text not accessible through the authors' institution (open vs closed technique; morbidity by agent in mixed colorectal/appendiceal patients according to the abstract).
Lam 2015, Am J Surg	PubMed	Not retrieved	Full text not accessible; colorectal and high-grade appendiceal patients, MMC + EPIC vs OX alone; same institution and period as McConnell 2013 (included), hence probable overlap.

PRISMA 2020 checklist (item and location in manuscript).

Item	Location
1 Title	Title
2 Abstract	Abstract (structured)
3 Rationale	Introduction, paragraphs 1–2
4 Objectives	Introduction, paragraph 3
5 Eligibility criteria	Section 2.2
6 Information sources	Section 2.3; Table S1
7 Search strategy	Table S1
8 Selection process	Section 2.4
9 Data collection process	Sections 2.5–2.6
10 Data items	Sections 2.2, 2.5; Table S2
11 Risk of bias assessment	Section 2.7; Table S3
12 Effect measures	Sections 2.6, 2.8
13 Synthesis methods	Section 2.8
14 Reporting bias assessment	Section 2.8 (not performed, k < 10)
15 Certainty assessment	Section 2.9
16 Study selection	Section 3.1; Figure 1
17 Study characteristics	Section 3.2; Tables 1–2
18 Risk of bias in studies	Section 3.3; Figure 2; Table S3
19 Results of individual studies	Figures 3–6; Table S2
20 Results of syntheses	Sections 3.4–3.8; Table S4
21 Reporting biases	Not assessable (k < 10)
22 Certainty of evidence	Section 3.10; Table 4
23 Discussion	Section 4
24 Registration and protocol	Section 2.1 (not registered)
25 Support	Funding statement
26 Competing interests	Conflicts of Interest
27 Availability of data, code	Data Availability Statement; Tables S2; code files