JAMA Oncology | Review | WOMEN'S HEALTH

Chemotherapy and Surgical Outcomes for Ovarian Metastases From Colorectal Cancer
A Narrative Review

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IMPORTANCE Colorectal cancer is the third most common and deadly cancer among women worldwide. Although ovarian metastases from colon cancer are relatively uncommon, they remain clinically significant due to their association with poor prognosis and the longstanding suspicion that the ovaries may function as a chemotherapy-resistant sanctuary site. This review examines the evidence for this phenomenon and potential role of surgical resection of metastatic disease.

OBSERVATIONS Twenty-four retrospective studies comprising 2705 patients with ovarian metastases from colorectal cancer were evaluated. Ovarian metastases demonstrated lower objective chemotherapy response rates than extraovarian metastases, had substantially lower mean shrinkage, and frequently exhibited discordant growth during treatment. The most favorable outcomes associated with improved survival were observed in patients who had complete surgical resection of ovarian metastases and microscopically negative margins.

CONCLUSIONS Collectively, the literature supports the ovary functioning as a relative sanctuary site in metastatic colorectal cancer, suggesting that systemic therapy alone should not be regarded as adequate. Instead, systemic therapy assumes a complementary role in reducing overall tumor burden and improving candidacy for resection. Therefore, optimal management should aim for clearance of all macroscopic disease, with negative surgical margins pursued when feasible. Metastasectomy should be performed within the context of comprehensive disease control, including resection of the primary tumor.

JAMA Oncol. doi:10.1001/jamaoncol.2026.3634
Published online September 24, 2026.

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Colorectal cancer (CRC) is the third most common and deadly cancer among women worldwide, with approximately 856 822 new cases and 404 144 deaths annually.[1] In recent decades, the incidence has stabilized or declined in many countries with high Human Development Index scores. Within these same countries, a consistent upward trend has been observed among younger adults (age ≤50 years), suggesting a shift toward populations historically considered to be lower risk and therefore less likely to receive routine screening.[2-5] In contrast, while the incidence remains 3-fold to 4-fold lower in countries with low Human Development Index scores overall, several nations undergoing major development are experiencing steadily rising occurrence rates.[1] This likely reflects changes in diet, lifestyle, and environmental exposures.[6-9]

CRC frequently spreads to distant organs and is the most common nongynecologic cancer to metastasize to the ovaries.[10] Although ovarian metastases from CRC (OM-CRC) are uncommon and occur less frequently than other colorectal metastases, such as liver metastases, which develop in 50% of patients, they are not rare.[11] Ovarian metastases (OMs) are identified in approximately 0.8% to 7.4% of female patients with CRC during surgery or follow-up and 5.0% to 9.7% of postmortem examinations.[12]

Radiologically, OM-CRC typically presents as solid cystic adnexal masses that closely resemble primary ovarian cancers.[13,14] They may also be mistaken for benign tumors associated with Meigs syndrome when ascites and pleural effusion are present, particularly when the primary tumor is occult.[15] Consequently, misdiagnosis is not uncommon, with 4% to 29% of patients with OM-CRC initially treated for presumed primary ovarian cancers.[16] Although several imaging approaches have been proposed to differentiate OM-CRC from primary ovarian tumors, these techniques remain experimental.[17-19] Therefore, the true incidence of OM-CRC may be under or overestimated.

Clinically, OM-CRC lacks unique symptoms at presentation, most commonly manifesting as abdominal pain, distension, or a palpable pelvic mass.[20-22] The diagnosis of a primary ovarian cancer vs CRC relies primarily on pathological evaluation using immunohistochemistry. Ovarian cancer expresses cytokeratin 7, carbohydrate antigen 125, SRY-box transcription factor (SOX) 17, and paired box gene 8, whereas cytokeratin 20, caudal-type homeobox transcription factor 2, special AT-rich sequence-binding protein 2, and dipeptidase 1 identify colorectal cancers.[12,23-25]

Despite progress in managing advanced CRC with molecularly targeted therapies, OM-CRC continues to be associated with poor

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prognosis.[26-30] Potential explanations for reduced survival include an overall advanced disease stage at presentation, inherent tumor aggressiveness, or that the ovaries function as a chemotherapy-resistant sanctuary site, like metastases in the central nervous system.[31] Given the lack of standardized treatment guidelines for OM-CRC and ongoing uncertainty regarding the sensitivity of colorectal metastases within the ovaries to systemic therapy, this review examines the evidence for sanctuary site behavior and role of surgical intervention.

Methods

A literature search used the PubMed electronic database from January 2000 through July 2025 to identify studies that evaluated either the response of OM-CRC to systemic therapy or outcomes following surgical management. The following search terms were used: *colorectal cancer OR CRC OR colorectal carcinoma OR colon cancer OR rectal cancer AND ovarian metastasis OR ovarian metastases OR ovary metastasis AND resection OR metastasectomy OR oophorectomy OR chemotherapy*. The search was limited to the title and abstract fields, and the results were filtered to only include studies published in English and those involving human participants. Additional records were identified manually.

Studies were included if they met the following criteria: (1) patients were confirmed to have OM-CRC and (2) treatment outcomes associated with systemic therapy and/or surgical intervention were reported. Case reports, editorials, literature reviews, conference abstracts, and preclinical and qualitative studies were excluded. Screening was performed in 3 phases (title, abstract, and full-text review), applying inclusion and exclusion criteria at each stage.

Inclusion was limited to studies that provided data suitable for comparative evaluation. For systemic therapy studies, this included site-specific *Response Evaluation Criteria in Solid Tumors* (RECIST), version 1.1, data and/or discordant growth rates.[32] Ovarian discordant growth was defined as the progression of OM despite stable or responding extraovarian metastases (EOMs) during systemic therapy. For the analyses of resection, studies were included if they reported Kaplan-Meier survival estimates and/or Cox proportional hazards model analyses that evaluated overall survival (OS), disease-specific survival (DSS), or progression-free survival (PFS). Following full-text review, studies were categorized into 4 non–mutually exclusive groups: (1) the ovaries' responsiveness to systemic therapy; (2) ovarian metastasectomy; (3) resection more broadly, including the ovaries; and (4) the extent of cytoreductive surgery (CRS).

Finally, analyses that stratified outcomes by residual tumor classification (R), completeness of the cytoreduction score, or any other relevant dichotomous metrics were categorized as evaluating the extent of CRS, regardless of whether resection was specific to the ovaries or involved broader metastatic disease.[33] Accordingly, such analyses were evaluated together, reflecting the association of residual disease burden.

The Newcastle-Ottawa Scale (NOS)[34] was used to assess the quality of all included studies. Several studies evaluated the radiographic response to chemotherapy rather than survival outcomes. Certain NOS items, particularly follow-up duration, were less applicable to these studies and may underestimate their quality.

Results

Study and Patient Demographic Characteristics

Of 102 publications identified, 26 (25.6%) were subject to full-text review. Twenty four retrospective studies met the inclusion criteria.[16,20-22,35-54] In total, these studies included 2705 patients with OM-CRC and originated from 10 countries, with the largest proportion from China (n = 6), the US (n = 5), and Japan (n = 5).

Baseline clinicopathological characteristics are summarized in **Table 1**. The median (range) patient age was approximately 50.0 (30.0-64.0) years, and most women were premenopausal. Primary tumors most commonly arose from the colon, and OM frequently presented synchronously. Bilateral ovarian involvement was common, and EOM were present in most patients. Histology was reported with varying specificity. While several studies reported only conventional adenocarcinoma, others included mixed adenocarcinoma with mucinous, signet-ring, or neuroendocrine features, and a minority enrolled patients with no histological restrictions (Table 1). Despite this heterogeneity, adenocarcinoma was the predominant histological type across all included studies. Table 1 also summarizes the calculated NOS risk of bias scale for each study. Thirteen studies (54.2%) scored 5 to 6 (fair quality), and 11 studies (45.8%) scored 7 to 8 (good quality).

Ovarian Sanctuary Site Behavior

Eight studies comprising 352 patients were included in the analysis of systemic therapy response and ovarian sanctuary site behavior.[21,37,42-45,47,52] **Table 2** summarizes the systemic therapy response for these patients with OM-CRC. Five studies reported site-specific RECIST, version 1.1, data for OM and EOM (in 1 case, non–OM-CRC), from which objective response rates (ORRs) and progressive disease rates (PDRs) were extracted.[21,42,43,45,52] Across the 5 studies, ORRs were consistently lower for OM, despite treatments ranging from cytotoxic drugs alone to combination regimens with molecularly targeted agents. Three studies reported statistically significant differences, with ORRs of 36.7%, 23.5%, and 18.2%, respectively, for OM compared with 70.0%, 63.6%, and 33.3%, respectively, for EOM ($P = .02$, $P = .01$, and $P < .001$, respectively).[42,43,45] The remaining 2 studies, which did not provide statistical analyses, recorded ORRs of 0.0% and 5.0%, respectively, for OM vs 34.8% and 40%, respectively, for EOM.[21,52]

PDRs varied across studies. Three reported higher rates for OM than EOM (23.3% vs 10.0%, 87.0% vs 35.0%, and 50.0% vs 20.0%, respectively),[21,45,52] while 2 noted slightly higher rates for EOM than OM (11.8% vs 13.6% and 21.2% vs 27.3%, respectively),[42,43] although in all 5 cases statistical analyses were either not provided or did not reach statistical significance.

Three studies documented discordant growth of the ovary during treatment.[37,44,47] Two reported comparable rates (19.0% and 28.6%),[37,47] whereas 1 observed a substantially higher rate of 81.0%.[44] One study assessed median tumor size change following first-line therapy, reporting a significant difference between OM and EOM (−17.5% vs −36.5%; $P = .01$).[42]

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Table 1. Study and Demographic Characteristics of Patients With Ovarian Metastases From Colorectal Cancer

Source	Country	Patients, No.	Mean age, y	%							Follow-up mo	NOS risk of bias scale[a]
				Premenopausal	Bilateral	Synchronous	Metachronous	EOM	Colon	Rectum		
Thornblade et al,[35] 2021	US	1272	56.6	NA	NA	59.4	40.6	77.8	92.5	7.5	21	6
Nomura et al,[36] 2023	Japan	22	64.5	NA	NA	22.7	77.3	90.9	86.4	13.6	20.9	7
Ursem et al,[37] 2020	US	108	60	NA	61.1	63.9	36.1	88	NA	NA	NA	6
Zhou et al,[38] 2020	China	46	48.5	71.7	58.7	73.9	26.1	69.6	63	37	14	7
Al-Busaidi et al,[39] 2019[b]	New Zealand	31	55	NA	45.2	71	29	80.6	75.9	24.1	23	7
Fujiwara et al,[40] 2010[b]	Japan	22	54.9	NA	27.3	36.4	63.6	50	77.3	22.7	45.3	6
Chung et al,[41] 2009	Korea	34	49	NA	47.1	79.4	20.6	76.5	73.5	26.5	NA	7
Seline et al,[42] 2018	Japan	37	NA	NA	NA	NA	NA	94.6	NA	NA	69.2	6
Lee et al,[43] 2010	Korea	130	51	54.6	52.4	46.9	53.1	76.9	86.2	13.8	60.8	7
Ganesh et al,[44] 2017	US	195	50	NA	45	NA	NA	76	NA	NA	NA	6
Tong et al,[45] 2022	China	50	39.5	NA	40	56.7	43.3	NA	93.3	6.7	NA	6
Li et al,[46] 2021[c]	China	162	49	51.9	53.1	53.7	46.3	NA	71.6	28.4	NA	8
Ayhan et al,[20] 2005	Turkey	33	49.1	51.5	NA	NA	NA	NA	NA	NA	NA	5
Li et al,[16] 2020[c]	China	68	46.4	54.4	39.7	47.1	52.9	82.4	76.5	23.5	NA	8
Garrett et al,[47] 2012	US	110	49	NA	NA	64.5	35.5	NA	93.3	6.7	49	6
Xu et al,[48] 2021	China	93	50.7	59.1	NA	58.1	41.9	60.2	72	28	17	6
McCormick et al,[22] 2007	US	39	51.5	NA	NA	70	30	70	NA	NA	13	8
Xu et al,[50] 2017[b]	China	57	49.3	56.1	63.2	36.82	63.2	50.9	80.7	19.3	42	7
Rayson et al,[51] 2000	Canada	NA	54.4	NA	31.6	28.9	71.1	NA	100	0	31	6
Goéré et al,[21] 2008	France	23	52	NA	34.8	21.8	78.2	100	NA	NA	54	7
Taylor et al,[52] 1995	UK	51	49	50	76.4	35.3	64.7	90.1	49	51[d]	28	6
Hamasaki et al,[53] 2022	Japan	38	50	73.7	36.8	23.7	76.3	81.6	81.6	18.4	59.6	7
Kammar et al,[54] 2017	India	25	42	60	84	84	16	72	96	4	10	5
Yu et al,[55] 2023	China	52	46	55.8	46.2	42.3	57.7	96.2	61.5	38.5	NA	5

Abbreviations: EOM, extraovarian metastasis, NA, information not available; NOS, Newcastle-Ottawa risk of bias scale.

[a] NOS:[34] 0-4 = poor quality; 5-6 = fair quality; 7-9 = good quality.

[b] Synchronous defined as diagnosis of ovarian metastases within 3 months of colorectal cancer diagnosis.

[c] Synchronous defined as diagnosis of ovarian metastases within 1 year of colorectal cancer diagnosis.

[d] Other sites: stomach, small intestine, and pancreas.

One study analyzed genomic features of OM-CRC using the Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets.[44] No recurrent ovary-specific variants were identified when comparing OM with EOM or primary tumors. When comparing tumors from patients with OM-CRC with those with non–OM-CRC, the former exhibited significantly higher frequencies of *KRAS* (65.8% vs 46.5%; *P* = .02), *SMAD4* (39.5% vs 18.5%; *P* = .002), and *NTRK1* (10.5% vs 3.8%; *P* = .05) variants. *SMAD4* variants were associated with markedly reduced OS in multivariate analysis, corresponding to a 27.7-fold increase in the hazard of death (hazard ratio [HR], 27.69; 95% CI, 4.98-154.02; *P* < .001). In a comparison of tumors exhibiting discordant growth of OM vs those responding concordantly with EOM, SOX9 alterations were present in 50.0% of concordant cases but only 7.8% in discordant ones, suggesting a potential protective effect.[44]

Associations of Ovarian Metastasectomy With Survival

Eight studies comprising 1927 patients evaluated the association between resection of OM and survival.[35-37,43,45-48] **Table 3** summarizes the survival outcomes for patients with isolated resection of ovarian metastases from CRC. Seven studies performed univariate analyses.[35,36,43,45-48] Of the 7 studies that analyzed OS, 6 demonstrated significantly longer survival among patients who underwent OM resection,[35,36,43,45,47,48] while the remaining 1 did not report a *P* value.[37] The largest study, which included 1272 patients,

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Table 2. Systemic Therapy Response in Patients With Ovarian Metastases (OMs) From Colorectal Cancer

Source	Patients, No.[a]	Regimens	ORR		P value	PDR		P value	Discordant OM growth, %
			OM	EOM		OM	EOM		
Ganesh et al,[44] 2017	123	NA	NA	NA	NA	NA	NA	NA	81
Ursem et al,[37] 2020	52	NA	NA	NA	NA	NA	NA	NA	19
Tong et al,[45] 2022[b]	50	Modified FOLFOX6 + bev, FOLFIRI + bev, FOLFIRI + cmab	36.7	70.0	.02	23.3	10.0	.23	NA
Sekine et al,[42] 2018	37	FU + bev, FU + OX/IRI, 5-FU + OX/IRI + bev/cmab/pmab[c]	23.5	63.6	.01	11.8	13.6	NS	NA
Lee et al,[43] 2010	33	FOLFOX, FOLFIRI, XELIRI, XELOX with or without bev/cmab	18.2	33.3	<.001	21.2	27.3	NS	NA
Goéré et al,[21] 2008	23	OX, IRI, FU[c]	0	34.8	NA	87.0	34.8	NA	NA
Taylor et al,[52] 1995	20	FU[c]	5.0	40.0	NA	50.0	20.0	NA	NA
Garrett et al,[47] 2012	14	Palliative chemotherapy	NA	NA	NA	NA	NA	NA	28.6

Abbreviations: bev, bevacizumab; cmab, cetuximab; EOM, extraovarian metastasis; FOLFIRI, leucovorin, FU, IRI; FOLFOX, leucovorin, FU, and OX; FU, fluorouracil; IRI, irinotecan; NA, information not available; NS, not significant; ORR, objective response rate; OX, oxaliplatin; PDR, progressive disease rate; pmab, panitumumab; XELIRI, capecitabine, irinotecan; XELOX, capecitabine, oxaliplatin.

[a] Patients who received chemotherapy.

[b] Study reported a comparison of OM with non-OM colorectal cancer, not EOM.

[c] List is not exhaustive.

Table 3. Survival Outcomes in Patients With Colorectal Cancer Undergoing Resection of Ovarian Metastases (OMs)

Source	OM resection, yes/no, No.	End point	Survival mo,[a] yes/no	P value	Multivariate HR (95% CI)	P value
Thornblade et al,[35] 2021	574/182[b]	OS	24.0/18.0	.01	NA	NA
	41/475[c]	OS	25.0/7.0	<.001	0.42 (0.33-0.54)	<.001
Nomura et al,[36] 2023	12/10	OS	NA[d]	.003	0.23 (0.07-0.82)	.02
Ursem et al,[37] 2020	83/25	OS	36.7/25.0	NA	0.57 (0.27-1.22)	.15
Lee et al,[43] 2010	83/47	OS	28.1/21.2	.02-.04	NA	NA
	83/47	PFS	15.6/6.1	<.001	NA	NA
Garrett et al,[47] 2012	54/17[b]	OS	39.4/18.2	<.001	NA	NA
	32/7[c]	OS	50.0/12.0	<.001	NA	NA
Xu et al,[48] 2021	76/17	OS	NA[d]	<.001	0.29 (0.12-0.67)	.002
Tong et al,[45] 2022	14/16	OS	21.0/15.0	<.001	NA	NA
	14/16	PFS	9.0/6.0	<.001	NA	NA
Li et al,[46] 2021	152/10	DSS	25.0/32.0	.51	0.65 (0.26-1.65)	.37

Abbreviations: DSS, disease-specific survival; HR, hazard ratio; NA, not available; OS, overall survival; PFS, progression-free survival.

[a] Yes or no to resection of OMs.

[b] Synchronous disease.

[c] Metachronous disease.

[d] No data on months were given, although OM resection was reported as associated with significantly longer survival than no resection.

of whom 615 (42%) underwent surgery, observed a significant survival benefit associated with ovarian metastasectomy irrespective of whether the metastases were synchronous or metachronous.[35] One study assessed disease-specific survival and found lower survival in the OM resection group (25.0 vs 32.0 months), although this difference was not statistically significant.[46] PFS was also reported in 2 studies and was significantly prolonged in patients who underwent OM resection.[43,45]

Five studies evaluated the independent association between resection of OM and survival using multivariate Cox proportional hazards models.[35-37,46,48] Of the 4 studies that assessed OS, 2 demonstrated a statistically significant survival benefit, corresponding to 77.0% (HR, 0.23; 95% CI, 0.07-0.82; $P = .02$) and 71.0% (HR, 0.29; 95% CI, 0.12-0.67; $P = .002$) reductions in the hazard of death.[36,48] One study found a significant association between resection of OM and greater OS among patients with metachronous OM (HR, 0.42; 95% CI, 0.33-0.54; $P < .001$), although a similar analysis for patients with synchronous disease was not provided, despite both showing significant benefits in their respective univariate analyses.[35] The remaining study noted an association between OM resection and improved OS (HR, 0.57; 95% CI, 0.27-1.22; $P = .15$), but this finding did not reach statistical significance.[37] Only 1 study analyzed disease-specific survival, reporting a nonsignificant decrease in mortality risk (HR, 0.65; 95% CI, 0.26-1.65; $P = .37$) despite finding a nonsignificant trend in a univariate analysis that favored no OM resection.[46] One study performed a matched survival analysis, finding that OS and disease-free survival did not differ significantly between patients with solitary OM-CRC and those with nonmetastatic CRC when OM and primary tumors were resected.[48]

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Table 4. Survival Outcomes in Patients With Colorectal Cancer Undergoing Surgical Resection vs No Resection of Intra-Abdominal Plus Ovarian Metastases

Source	Resection,[a] yes/no	End point	Survival mo, yes/no[b]	*P* value
Chen et al,[49] 2021	63/4	OS	22.0/7.0	.04
Kammar et al,[54] 2017	15/10	OS	23.0/28.0	.38
Sekina et al,[42] 2018	13/24	OS	43.1/17.0	.002
	13/24	PFS	5.5/8.4	.93

Abbreviations: OS, overall survival; PFS, progression-free survival.

[a] All patients received chemotherapy, so this comparison reflects surgery and chemotherapy vs chemotherapy alone.

[b] Yes of no to resection of ovarian metastases.

Table 5. Extent of Cytoreduction and Survival Outcomes in Patients With Ovarian Metastases From Colorectal Cancer

Source	Extent of surgery,[a] patients, No.	End point	Survival mo, patients, No.	*P* value	Multivariate HR (95% CI)	*P* value
Zhou et al,[38] 2020	R0: 19; R1/2: 27	OS	R0: 20.0; R1/2: 7.0	.001	0.19 (0.05-0.73)	.02
Al-Busaidi et al,[39] 2019	R0: 14; R1/2: 17	OS	R0: 30.5; R1/2: 23.5	.04	NA	NS
Fujiwara et al,[40] 2010	R0: 15; R1/2: 7	OS	R0: 60.5; R1/2:13.5	<.001	NA	NA
Chung et al,[41] 2009	C: 11[a]; P: 23	OS	C: 36.0; P: 15.0	.001	NA	NA
Li et al, et al,[16] 2202	R0: 29; R1/2: 28	DSS	R0: 33.0; R1/2: 20.0	<.001	0.059 (0.01-0.33)	.001
Rayson et al,[51] 2000	C: 19; P: 19	DSS[b]	C: 31.0; P: 14.0	.01	NA	NA
Hamasaki et al,[53] 2022	R0: 8; R1/2: 30	OS[c]	R0: NR; R1/2: 26.0	<.001	NA	NA
Kammar et al,[54] 2017	R0: 8; R1/2: 7	OS	R0: 22.0; R1/2: 12.0	NS	NA	NA
Ayhan et al,[20] 2005	O: 19; SO: 14	OS[c]	O: 77.0; SO: 36.0	.04	NA	NA
Chen et al,[49] 2021	R0: 37; R1/2: 17	OS	NA	<.001	0.26 (0.13-0.53)	<.001
McCormick et al,[22] 2007	O: 26; SO: 9	OS	O: 35.0; SO: 7.0	<.001	NA	NA
McCormick et al,[22] 2007	O: 26; SO: 9	PFS	O: 11.0; SO: 2.5	<.001	NA	NA
Xu et al,[50] 2017	C: 42; P: 15	OS	C: 39.0; P: 13.0	<.001	0.14 (NA)	.001
Ganesh et al,[44] 2017	R0/1: 114; R2: 81	OS	R0/1: 38.3; R2: 12.0	<.001	0.43 (0.29-0.62)	<.001
Ganesh et al,[44] 2017	R0/1: 114; R2: 81	PFS	R0/1: 15.5; R2: 5.9	<.001	0.55 (0.38-0.81)	.002
Tong et al,[45] 2022	R0: 10[d]	OS	R0: 23.0; R1: 17.0	<.001	NA	NA

Abbreviations: C, complete cytoreduction; DSS, disease-free survival; HR, hazard ratio; NA, information not available; NS, not significant; O, optimal cytoreduction; OS, overall survival; P, palliative cytoreduction; PFS, progression-free survival; SO, suboptimal cytoreduction.

[a] C and P were defined by the study as R0 and R1/2, respectively.

[b] End point was not clearly stated, but was interpreted as DSS.

[c] End point was interpreted as OS.

[d] Study did not specify the number of R1 patients.

Table 4 summarizes the findings of 3 studies comprising 129 patients that evaluated the association between resection of all intra-abdominal metastatic disease, including OM, and survival.[42,49,54] All studies performed univariate analyses. Two studies demonstrated significantly improved OS among patients who underwent resection compared with those who did not .[42,49] In contrast, 1 study observed lower OS in the resection group; however, this difference did not reach statistical significance.[54] In 2 of the 3 studies, all patients received chemotherapy.[42,54] These comparisons reflect surgery and chemotherapy vs chemotherapy alone. PFS was also reported in 1 study and favored patients who did not undergo resection, although this finding was not statistically significant.[42]

Associations of the Extent of Cytoreduction With Survival

While cytoreductive surgery overall is established with clear therapeutic benefits, 14 studies comprising more than 665 patients evaluated the association of the extent of CRS and resection of OM in particular with survival outcomes.[16,20,22,38-41,44,45,49-51,53,54] Table 5 summarizes the survival outcomes by extent of cytoreduction for these patients. All studies performed univariate analyses. Of the 12 studies that analyzed OS, all demonstrated improved survival with greater extent of CRS. Ultimately, 11 analyses reached statistical significance,[20,22,38-41,44,45,49,50,53] while the remaining 1 did not.[54] Two studies assessed disease-specific survival, both of which reported significantly greater survival with more complete CRS.[16,51] PFS was also reported in 2 studies and was significantly prolonged in patients with more extensive cytoreduction.[22,44]

Six studies conducted multivariate analyses using Cox proportional hazards models to assess the independent association between the extent of CRS and survival outcomes.[16,38,39,44,49,50] Of the 5 studies that assessed OS, 4 reported a significant association between more complete cytoreduction and prolonged survival.[38,44,49,50] In the remaining study, no significant association was observed.[39] One study evaluated disease-specific survival and found a substantial decrease in mortality risk (HR, 0.06; 95% CI, 0.01-0.33; *P* = .001) that corresponded to a 94.0% reduction in the hazard of death, an approximately 17-fold decrease.[16] PFS was also reported in 1 study that demonstrated a significant benefit with more complete CRS (HR, 0.55; 95% CI, 0.38-0.81; *P* = .002).[44]

Eight studies performed analyses that were stratified by residual tumor classification following CRS.[16,38-40,44,45,53,54] Across these studies, a clear gradient in survival was observed, with more complete debulking consistently associated with better outcomes. Patients rendered free of macroscopic disease (R0/1) demonstrated superior survival compared with those with gross residual

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disease (R2).[44] This benefit was further accentuated among patients who experienced complete microscopic clearance, with R0 resection conferring additional survival advantage vs R1.[45]

Discussion

Key Findings

This review identified several consistent trends in the literature. OMs exhibited significantly lower ORRs than EOM/non–OM-CRC to chemotherapy. There are limited data on the effect of molecularly targeted agents. Discordant growth of the ovary was frequently observed, ranging from 19% to 81%, and OMs experienced substantially less mean shrinkage than EOM. These findings support the ovarian sanctuary site hypothesis.

Second, genomic analysis revealed a higher frequency of *SMAD4* variants in tumors from patients with OM-CRC, which was associated with poorer survival outcomes. Similarly, chemotherapy response in the ovaries was associated with SOX9 status. Discordant responses were associated with the wild-type form, whereas variants were associated with concordant responses.

Third, resection of OM consistently conferred a significant survival advantage, as summarized in Table 5. However, the findings could have been associated with many other factors, and the prognostic effect of resection more broadly was less absolute, likely reflecting the limited number of patients included and absence of multivariate analyses, although it still demonstrated a therapeutic benefit.

Analysis and Clinical Implications

Across the included studies, resection consistently emerged as the strongest determinant of improved survival, although its benefit was neither uniform nor absolute. Instead, outcomes varied according to disease distribution and the completeness of cytoreduction.

Resection of the primary tumor is a prerequisite for survival benefit. Ovarian metastasectomy alone was not associated with improved survival when the primary tumor remained unresected.[16,32]

Moreover, several studies found no significant survival benefit from OM resection in patients with EOM[35,43] except when metastases were confined to the liver.[37] EOMs were independently associated with poorer survival, demonstrating a clear prognostic gradient in which increasing extent and distribution corresponded to progressively worse outcomes.[48,50] Conversely, metastases limited to the pelvis were associated with improved survival.[41,51] Following resection, these patients experienced survival comparable with those with solitary OM,[51] although another study demonstrated that solitary OM still conferred a statistically significant survival advantage.[22]

A matched survival analysis of a single institution (NOS score, 6) found that patients with solitary OM-CRC who underwent resection of OM and the primary tumor experienced OS and disease-free survival that were comparable with patients with nonmetastatic CRC who were undergoing primary tumor resection. This is hypothesis generating that complete cytoreduction may not only be associated with improved survival, but also with a reduced adverse prognostic effect of metastatic disease.[48]

Additionally, EOMs were the primary factor limiting the feasibility of metastasectomy.[48] The median study-level EOM prevalence was 76.9% (range, 50%-100%). However, analyses of CRS stratified by residual tumor burden demonstrated a median study-level R0 rate of 50.9% (range, 21.1%-71.4%), indicating that microscopic clearance remains achievable for many patients despite the frequent presence of EOM. Nevertheless, R0/1 resection was more commonly experienced among patients without EOM, as expected.[44]

Survival outcomes were closely associated with the completeness of resection. R0/1 status was associated with significantly improved survival, including among patients with EOM.[44] Similarly, improved outcomes were observed in patients with EOM when OMs and EOMs were resected.[48] In contrast, another study reported that R1/2 resections (which were considered palliative in that analysis) failed to outperform chemotherapy alone, even when combined with chemotherapy, emphasizing the adverse association of residual disease.[16] This finding may reflect the inclusion of R2 cases, potentially masking the more modest benefits of R1 resection. Supporting this interpretation, surgery remained associated with improved survival even after excluding R0 cases,[42] and R0/1 status was independently associated with greater OS and PFS.[44] Rather than representing an all-or-nothing phenomenon, surgical benefit appears to diminish progressively as residual disease increases.

Within this context, chemotherapy assumes a complementary role. Despite the relative resistance of OM, systemic therapy remained independently associated with improved survival and should not be regarded as ineffective in OM-CRC.[16,39,50] However, the current evidence does not support its use as a primarily curative intervention when used in isolation, as systemic therapy alone is insufficient to control OM in most patients. Instead, its principal value lies in managing extraovarian disease. Contemporary trials in metastatic CRC have demonstrated that adding molecularly targeted agents (particularly bevacizumab and cetuximab) is associated with improved survival, with OS frequently reaching or exceeding 30 months.[26-29] Within this review, these drugs also increased ovarian ORRs, potentially expanding their clinical use; however, the relative ratio of OM to EOM responses remained largely unchanged, highlighting the persistent nature of ovarian resistance.[42,43,45] By reducing overall disease burden, systemic therapy may increase surgical eligibility by simplifying operative complexity, improving resectability, and facilitating cleaner margins.

These findings support a treatment paradigm in which comprehensive cytoreduction, including primary and metastatic disease, offers the greatest survival advantage, with R0 status prioritized whenever feasible. Chemotherapy can be used to reduce systemic disease burden, facilitate resection, and, in select cases, achieve sufficient disease control without surgery. This integrated approach is important for patients with EOM, for whom systemic therapy may reduce overall disease burden sufficiently to permit successful cytoreduction.

Future Directions

Large-scale, focused studies are needed to identify the mechanisms underlying ovarian sanctuary site behavior and more precisely define the patient subgroups most likely to benefit from resection. Several clinically relevant interventions were addressed in this review, including prophylactic oophorectomy, postoperative systemic therapy, and CRS-positive hyperthermic intraperito-

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neal chemotherapy. As *KRAS* alterations are more commonly seen in OM, targeted therapies tailored to these differences should be investigated.

Prophylactic oophorectomy warrants evaluation as a potential risk-reducing strategy in carefully selected patients, with consideration of age, menopausal status, and long-term endocrine consequences, given that many patients with OM-CRC are young, premenopausal women. Postoperative systemic therapy and hyperthermic intraperitoneal chemotherapy should be investigated as adjuncts to CRS.

Emerging prognostic and stratification tools represent a potentially promising avenue for refining treatment selection. Li et al[46] developed a nomogram to estimate 1-year, 2-year, and 5-year OS, while Chen et al[49] proposed a clinical risk score to estimate postoperative survival, although both require clinical validation. Advanced stratification approaches, including computed tomography–based radiomics and genomic markers, such as SOX9, may help distinguish patients for whom systemic therapy is sufficient and aggressive cytoreduction could be safely avoided.[44,55]

Strengths and Limitations

The primary strength of this review was its balance between methodological rigor and analytic flexibility. The use of formal search and screening procedures ensured transparency and reproducibility, while the absence of restrictive statistical inclusion criteria allowed the incorporation of a broader range of relevant studies than would be possible in a meta-analysis, an important consideration given the limited literature on this topic. This approach fills a distinct and previously unaddressed niche by contextualizing surgical and systemic treatment strategies together. Including studies from multiple geographic regions enhanced the generalizability of this review's conclusions.

Several limitations should be acknowledged. First, all included studies were retrospective, introducing a potential source of bias and limiting the ability to make causal inferences. Second, the total number of studies was relatively small. Third, heterogeneity across the studies was non-negligible, including differences in patient selection, treatments administered, and histological types. Fourth, median follow-up periods were either unreported or relatively short in many studies, reducing confidence in long-term outcomes.

Conclusions

While OM-CRC demonstrated reduced sensitivity to systemic therapy, which manifested as reduced ORRs, significantly lower mean tumor shrinkage, and frequent discordant growth, modern regimens, such as FOLFOX or FOLFIRI with bevacizumab or cetuximab, remain highly effective against EOM and play an essential role in reducing overall tumor burden, which directly affects the feasibility of resection. Cytoreduction should aim for clearance of all macroscopic disease (R0/1), with R0 pursued when appropriate. Likewise, metastasectomy should be performed within the context of broader disease removal, including the primary tumor. Systemic therapy should not be regarded as curative, but rather as a vital component of a broader treatment strategy. Optimal outcomes require a multimodal approach in which surgery and systemic therapy are complementary, producing a survival benefit greater than that achievable with either strategy alone.

ARTICLE INFORMATION

Accepted for Publication: July 26, 2026.

Published Online: September 24, 2026. doi:10.1001/jamaoncol.2026.3634

Conflict of Interest Disclosures: None reported.

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