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Impact of RAS, BRAF mutations and microsatellite status in peritoneal metastases from colorectal cancer treated with cytoreduction + HIPEC: scoping review

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ABSTRACT

Background: Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has shown survival benefits in select patients with peritoneal metastases (PM) from colorectal cancer (CRC). Molecular alterations, particularly RAS/BRAF mutations and Microsatellite Instability (MSI), play crucial roles in prognostic stratification and treatment planning, influencing both disease-free survival (DFS) and overall survival (OS). This scoping review evaluates the prognostic role of MSI and RAS/BRAF mutations in patients with PM-CRC treated with CRS-HIPEC.

Design: A literature search was conducted across several databases to identify papers published between 2000 and September 2024. We selected 18 publications that considered DFS and OS as primary or secondary outcomes in patients with RAS/BRAF mutations and MSI following CRS-HIPEC treatment. Studies involving appendiceal cancer, peritoneal disease from non-CRC, pediatric patients, or subjects not treated with CRS-HIPEC were excluded.

Results: Most studies suggest that RAS and BRAF mutations have a negative influence on survival outcomes. While inconsistencies exist, RAS mutations are generally associated with worse DFS. Specific KRAS subtypes such as KRASMUT2 or KRAS G12V and the BRAF V600 variant correlate with poorer prognosis. MSI status appears to attenuate the adverse effects of RAS/BRAF mutations on survival, although conflicting data persist.

Conclusion: RAS and BRAF mutations correlate with poorer outcomes in PM-CRC, underscoring the need for mutation-informed strategies to refine HIPEC and systemic therapies. Recognizing subtypes may improve patient selection for CRS-HIPEC, optimizing both local disease control and long-term survival. Future research should incorporate these molecular profiles to enhance therapeutic decision-making and better address this challenging condition.

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Colorectal cancer; peritoneal metastasis; cytoreductive surgery; HIPEC; RAS/BRAF mutations; microsatellite instability

Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide [1], with up to 25% of patients presenting with metastases at diagnosis (stage IV disease) [2–4]. The liver, lungs, and abdominal peritoneum are the most common metastatic sites [5].

Synchronous peritoneal metastases (PM) are detected in 5–15% of patients at initial diagnosis, while metachronous PM can develop 1–3 years after curative resection of the primary tumor [3]. These metastases are seen in 4–12% of colon cancer patients and 2–19% of rectal cancer patients [6,7].

The development of peritoneal metastases is linked to poor prognosis, with median survival around 9–12 months without treatment [4] and up to 16 months with systemic therapy [8]. Cytoreductive surgery (CRS) combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is a potentially curative approach for select patients [9,10], showing improved overall survival up to 40–43 months and a lower recurrence rate of PM [11,12] compared to systemic treatment alone or palliative care [13]. However, outcomes vary widely and are influenced by factors such as tumor-sidedness and genetic characteristics.

Recent studies highlight the importance of molecular markers, including RAS, BRAF, and Microsatellite Instability (MSI), in determining tumor behavior, prognosis, and therapy response in CRC.

The assessment of RAS and BRAF mutational status is crucial for determining whether a patient is suitable for anti-EGFR treatment, while the evaluation of MSI status is key in distinguishing between sporadic and Lynch syndrome-related tumors [14].

Despite their established role in systemic CRC treatment, the impact of KRAS, BRAF, and MSI on outcomes in peritoneal metastases treated with CRS and HIPEC remains under-investigated.

This scoping review aims to summarize the current literature on these biomarkers in PM-CRC patients undergoing CRS and HIPEC, providing a comprehensive overview of current knowledge and identifying gaps that warrant further investigation.

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Methods

Study inclusion and data charting

This scoping review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [15]. A comprehensive literature search was conducted in August and September 2024 across PubMed, Cochrane Library, Web of Science, Scopus, OpenAIRE, Google Scholar, and ClinicalTrials.gov, with no language restriction. Articles which reported on the mutational status of RAS and/or BRAF and/or MSI in adult patients with peritoneal metastasis from colorectal cancer who underwent cytoreductive surgery and HIPEC were included. The following MeSH terms were used and adapted accordingly to the advanced search tool for each database, including term variants: 'Proto-Oncogene Proteins p21(ras)', 'Proto-Oncogene Proteins B-raf', 'Microsatellite instability', 'Colorectal neoplasms', 'Peritoneal neoplasms', 'Cytoreduction Surgical Procedures', 'Hyperthermic intraperitoneal chemotherapy'.

There was no restriction on the timing of peritoneal metastasis, meaning that studies considering either synchronous or metachronous PM were included. Exclusions included pediatric patients, non-CRC peritoneal metastasis, patients treated without CRS+HIPEC, those receiving palliative care or early post-operative intraperitoneal chemotherapy (EPIC) and articles lacking full text or published before 2000.

A data charting form was independently developed by one reviewer to determine which variables to extract and subsequently discussed among three reviewers and continuously updated through an iterative process.

Results

After duplicate removal, 113 studies were identified. The initial screening, based on titles and abstracts, was conducted by three reviewers, resulting in 31 studies selected for full-text appraisal. Suitability for inclusion was determined based on the previously established selection criteria. Ultimately, 18 studies were included in the data charting process (Figure 1).

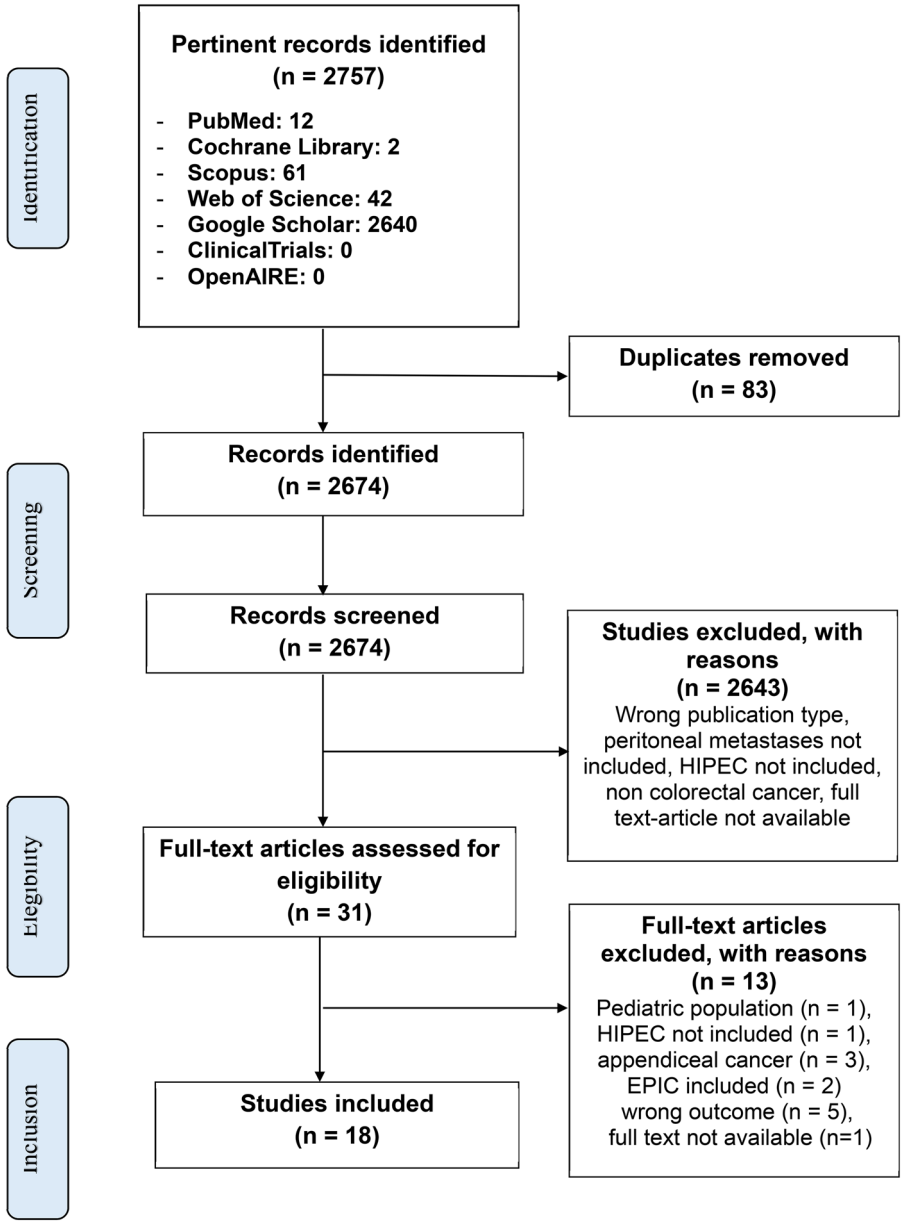

Figure 1. Screening flow chart.

All studies, published post-2017, reflect a recent focus on molecular status in CRS-HIPEC outcomes. The dataset comprised 14 retrospective studies (10 single-center, 4 multicenter), 2 single-center prospective cohort studies, a literature review, and a systematic review with meta-analysis. In all the cited studies, OS was measured in months from the date of diagnosis, while DFS was calculated as the number of months from CRS/HIPEC to the detection of peritoneal recurrence or distant metastasis, death, or the most recent follow-up. Relapse-free survival and progression-free survival were treated as equivalent to DFS (Table 1).

Impact of RAS mutation

Among the included articles, 9 reported a negative impact of RAS mutations on survival. In terms of overall survival, Shneider et al. [16] demonstrated a significantly shorter median survival of 21 months (CI: 31–46) for mRAS patients compared to 52 months (CI: 40–65) for RAS wild-type patients ($p = 0.036$). The same study showed that disease-free survival was reduced by 4 months in mKRAS patients ($p = 0.007$) and by 3 months in mNRAS patients ($p = 0.032$) compared to wild-type patients.

Arjona-Sanchez et al. [17] identified mRAS (HR 2.024; $p = 0.045$) and the Peritoneal Surface Disease Severity Score (PSDSS) [18] stage (Stage III vs. Stage I: HR: 2.90; $p = 0.009$) as the only factors impacting survival after CRS + HIPEC in their univariate analysis. The impact of RAS mutations is highlighted by comparing 5-year OS between RAS wild-type and mRAS patients across PSDSS stages (I, II, III, and IV): 61.8%, 39.9%, 24.4%, and 0% vs. 28.4%, 26.4%, 27.1%, and 0% ($p > 0.5$).

Hamed et al. [19], identified RAS/BRAF mutation as an independent prognostic factor for poorer OS (HR 1.6) in their univariate analysis and noted a worse outcome in patients with left-sided colon cancer (HR 1.97, $p = 0.02$).

In the retrospective study by Morgan et al. [20], while no significant differences in OS were observed, mRAS was identified as a prognostic factor for worse DFS, with a median of 5.4 months compared to 12.5 months in wild-type patients [HR 2.32 (95% CI:1.12–4.80; $p = 0.02$)].

Several studies, including those by Tonello et al. [21] and Allievi et al. [22] reported a reduction in both DFS and OS. Allievi et al. also found an increased rate of systemic recurrence (51.2% in mKRAS vs. 38.4% in KRAS wild type; $p = 0.033$) but no increase in peritoneal recurrence (PR).

Conversely, Breuer et al. [23] also noted a reduction in survival but identified mRAS as a predictive factor for PR after CRS/HIPEC (OR = 2.42, 95% CI = 1.11–5.47; $p = 0.03$), without an effect on hematogenous recurrence.

Several studies have explored the impact of specific KRAS mutational subtypes. Tonello et al. [24] distinguished KRAS mutations into two tiers based on specific amino acid substitutions: $KRAS^{MUT1}$ (G12R, G13A, G13C, G13V, Q61H, K117N, A146V) and $KRAS^{MUT2}$ (G12A, G12C, G12D, G12S, G12V, G13D, A59E, A59V, A146T). Their analysis found that $KRAS^{MUT1}$ had a similar survival rate to KRAS wild-type patients, while $KRAS^{MUT2}$ was independently associated with poorer prognosis in the multivariate analysis.

Flood et al. [25] in their observational cohort study, identified 12 different subtypes of KRAS somatic variants in the study population, with G12D (39.7%) and G12V (19.1%) being

Table 1. Evidence table of included studies.

Included Studies (n = 16 of 18 reports)

Citation	Population description	Study Design	Genotypes/Gene Expression Assessed	Outcomes Assessed	Statistically Significant Results Related to Genotype/Gene Expression	Interpretation of Results/Key findings
Massalou 2017	84 patients with PM-CRC, non extra-abdominal metastatic disease underwent CRS+HIPEC	Prospectivemonocentric	mKRAS mBRAF MSS/MSI status	Mutational status impact on OS and DFS	**mKRAS vs wtKRAS:** longer median DFS (17.5 Vs 11.6 months, $p = 0.15$); **MSI vs MSS:** median survival (85 Vs 35.7 months, $p = 0.01$) and DFS (24.9 Vs 12.4 months)	KRAS/BRAF status does not affect OS nor DFS; MSI status is associated with better median survival.
Schneider 2018	524 patients with PM-CRC underwent CRS+HIPEC	Retrospective multicentric (6 European tertiary centers)	mKRAS mNRAS mBRAF	Mutational status impact on OS and DFS,	**mRAS vs wt RAS:** median OS[a] 38 (CI: 31–46) vs 52 (CI: 40–65)months [$p = 0.036$]; Reduced median DFS by 4 months in mKRAS ($p = 0.007$) and 3 months for mNRAS ($P = 0.032$) **mBRAF vs wt BRAF:** median OS 21 (CI: 9–26) vs 52(CI: 40–65) months [$p < 0.001$] + reduced median DFS by 7 months	Mutations of KRAS, and in particular BRAF, are negative prognostic factors

(*Continued*)

Table 1. Continued.

Included Studies (n = 16 of 18 reports)						
Citation	Population description	Study Design	Genotypes/Gene Expression Assessed	Outcomes Assessed	Statistically Significant Results Related to Genotype/ Gene Expression	Interpretation of Results/Key findings
Arjona-Sanchez 2019	77 patients with PM-CRC underwent CRS + HIPEC	Retrospective monocentric	mRAS	Mutational status impact on OS and DFS; Updated RAS-PSDSS score by including RAS mutational status	*Univariate analysis:OS* **mRAS** [HR]: 2.024; $p = 0.045$) **PSDSS stage** (Stage III vs. Stage I: HR: 2.90; $p = 0.009$) **wtRAS Vs mRAS 5-year OS for PSDSS stages I, II, III and IV:** 61.8%, 39.9%, 24.4%, and 0% Vs 28.4%, 26.4%, 27.1%, and 0% ($p > 0.5$)	Only RAS mutational status and PSDSS stage were shown to be independent factors for OS.
Morgan 2019	47 patients with PM-CRC underwent CRS + HIPEC	Retrospective monocentric	mRAS mBRAF MSS/MSI status	Mutational status impact on OS and DFS	**DFS wtRAS Vs mRAS**: 12,5 months vs 5,4 months HR of 2.32 (95% CI:1.12–4.80; $p = 0.02$)	RAS mutation is a risk factor of worse DFS, no difference in OS
Shubin 2020	45 patients with PM-CRC (only synchronous) underwent CRS + HIPEC	Retrospective monocentric	mKRAS mNRAS mBRAF MSS/MSI status	Effect of somatic mutations of KRAS/NRAS/ BRAF genes and MSI on OS/DFS	**mKRAS-NRAS DFS/OS** not relevant $p = 0.87$) **mBRAF DFS/OS** not relevant ($p = 0.85$)	Somatic mutations in the KRAS/NRAS/ BRAF genes are not prognostic factors influencing OS/DFS; The molecular status of the primary tumor may differ from the status of peritoneal metastases.
Breuer 2021	505 patients with PM-CRC underwent CRS + HIPEC	Retrospective multicentric	mKRAS mNRAS mBRAF MSS/MSI status	Mutational status impact on OS and DFS	**mRAS:** shorter DFS (HR = 2.30, 95% CI = 1.58 to 3.33; $p < .001$) **mRAS (KRAS or NRAS):** *peritoneal recurrence after CRS-HIPEC* [OR = 2.42, 95% CI = 1.11–5.47; $p = 0.03$]	mKRAS/NRAS-are associated with shorter DFS and OS; Positive nodal status and the presence of mRAS are predictive factors of peritoneal recurrence after CRS/HIPEC, but not for hematogenous recurrence
Bhullar 2021	195 patients with PM-CRC underwent CRS + HIPEC	Retrospective monocentric	mKRAS mNRAS mBRAF MSS/MSI status	Mutational status impact on OS and DFS	**wtRAS vs mRAS:** Median OS 38.3 (95% CI 30.4–46.3 months) Vs 34.7 months (95% CI 23.8–45.6 months), $p = 0.21$ *OS in multivariate analysis:* mRAS (HR: 1.682, 95% CI 0.995–2.843, $p = 0.052$) **BRAFwt vs mBRAF:** Median OS 32.1 (95% CI 19.7–44.5 months) vs 17.2 months (95% CI 1.0–33.4) $p = 0.109$	RAS mutation status did not affect the outcome. BRAF V600 mutation status showed a trend towards predicting poorer OS.
Solomon 2021	100 patients with PM-CRC underwent CRS + HIPEC	Retrospective monocentric	mKRAS mNRAS mBRAF MSS/MSI status	Mutational status impact on OS and DFS	**mBRAF vs. wtBRAF:** *DFS* 7 Vs. 16 months ($p = 0.008$) *OS* 44 Vs. 72 months ($p = 0.023$)	mBRAF status is a negative prognostic factor both in terms of OS and DFS, and led to early recurrence, with a median DFS estimated at 7 months. mKRAS has no association with early or peritoneal recurrence. mKRAS and MSI statuses did not have an impact on the outcomes.
Di Giorgio 2021	66 patients with PM-CRC underwent CRS + HIPEC	Retrospective monocentric	mRAS mBRAF BRAFV600E MSS/MSI status	Mutational status impact on OS and DFS	*Multivariate analysis* **BRAF V600E** OS: (HR: 4.55; 95% CI: 1.21– 17.21; $p = 0.025$)	BRAF V600E mutation is an independent predictor for worse OS

(*Continued*)

Table 1. Continued.

Included Studies (n = 16 of 18 reports)						
Citation	Population description	Study Design	Genotypes/Gene Expression Assessed	Outcomes Assessed	Statistically Significant Results Related to Genotype/ Gene Expression	Interpretation of Results/Key findings
Tonello 2022	437 patients with PM-CRC underwent CRS + HIPEC	Retrospective national multicentric	mKRAS mBRAF MSS/MSI status	Mutational status impact on OS and DFS	**5-year survival mKRAS vs. mBRAF (wt ref):** *KRAS* median OS 33.2 months (29.9–43.7) - median DFS 11.5 months (9.8–13.8) p= 0.0052 OS < 0.001 DFS vs *BRAF* median OS 21.5 months (18.9–NE) - median DFS 10.5 mo (7.0–13.9) p = 0.0171 OS < 0.001 DFS WT median OS 70.7 mo (41.0–NE) - DFS 17.6 mo (14.2–22.1) **MSI/all-WT vs MSS/mutated patients:** 5-year OS 70.6% vs 23.4% 5-year DFS 62.5% vs 3.6% (p = 0.00001) **Multivariable analysis, correlation with OS:** *mKRAS* (HR, 2.0; 95% CI, 1.3–2.9; p = 0.0001), *mBRAF* (HR, 3.3; 95% CI, 1.7–6.1; p = 0.0001) *MSI/WT patients* (HR, 0.4; 95% CI, 0.1–1.1; p = 0.08) *MSI/mutated or MSS/WT* (HR 0.5; 95% CI, 0.3–0.7; p = 0.0001) **Correlation with DFS:** mKRAS (HR, 1.8; 95% CI, 1.3–2.3; p = 0.0001), mBRAF (HR, 3.4; 95% CI, 2.1–5.4; p = 0.0001):	mKRAS/BRAF have a negative prognostic impact on OS/DFS; MSI status can mitigate the detrimental effect of mKRAS/BRAF and is associated with improved OS in both mKRAS/BRAF and WT patients; MSS/ mutated patients have the worst OS/ DFS.
S. G. Larsen 2022	180 patients with PM-CRC underwent CRS + HIPEC	Retrospective monocentric (Norwegian National Unit)	mKRAS mBRAF MSS/MSI status mBRAF + MSI	Mutationa status impact on OS and DFS Postoperative complication;	**mBRAF + MSS vs mBRAF + MSI:** 5-year OS 25.2% Vs 58.3% (p = 0.022), long rank test shows better DFS for MSI group (p = 0.022) **MSI associated with:** *synchronous PM-CRC* (50% Vs 17.9%, p = 0.047), and with *poorly differentiated tumours* (83.8% Vs 15.4%, p < 0.001).	OS and DFS after CRS-HIPEC was similar comparing mBRAF, mKRAS and double wt. The small subgroup with mBRAF + MSI had had the best outcomes, with median survival not reached and a 5-year OS exceeding 58.3%. mBRAF/MSI are independent negative prognostic factors in mCRC.

(*Continued*)

Table 1. Continued.

Included Studies (n = 16 of 18 reports)						
Citation	Population description	Study Design	Genotypes/Gene Expression Assessed	Outcomes Assessed	Statistically Significant Results Related to Genotype/ Gene Expression	Interpretation of Results/Key findings

Flood, 2022	174 patients with PM-CRC underwent CRS + HIPEC, (molecular datas available for 169)	Observational cohort monocentric	mKRAS
			mNRAS
			KRAS G12V
			mBRAF
			BRAFV600E
			MSS/MSI status
				Mutational status impact on OS and DFS	**mBRAF Vs mKRAS vs wt:**
					median OS 12 Vs 37 Vs 39 months, $p = 0.012$**;**
					median *DFS*: BRAF 8 months, KRAS 10 months, wt 14 months, $p = 0.006$.
					In multivariate analysis:
					worse OS (HR 2.29, $p = 0.026$);
					worse DFS (HR 1.8, $p = 0.047$);
					lower PRS[b] (HR 3.11, $p = 0.007$)
					mKRAS subgroup G12V variant vs other variants:
					DFS (median: G12V 9 months, Other variants 11 months, $p = 0.016$);
					In multivariate analysis:
					Worse DFS (HR 2.63, $p = 0.016$)
					MSI status vs MSS status:
					median OS (MSI 27 months, MSS 29 months, $p = 0.025$)
						mBRAF is a negative, independent prognostic factor for OS/DFS/PRS; BRAF V600E and KRASG12V mutations as strong prognostic determinants of DFS.

Hamed 2023	250 patients with PM-CRC underwent CRS + HIPEC	Retrospective monocentric	mKRAS mNRAS mBRAF MSS/MSI status	Effects of primary tumor site and Mutational status impact on OS and DFS	**RAS/BRAF mutation:** *Univariate analysis* worse OS in left sided cancer (HR 1.97; $p = 0.02$); combined mutations of BRAF/PIK3CA predicted worse OS (HR 4.9; $p = 0.02$); Independent prognostic factors for worse OS mRAS (HR 1.6), and mBRAF (HR 1.7); **MSI status:** better OS in patients with mRAS/BRAF (HR 0.3; $p = 0.01$); reduction in mortality risk following CRS-HIPEC (HR at 1 year 0.4, HR at 2 years 0.3)	Rectal origin, mRAS and mBRAF are each associated with poorer survival after CRS+HIPEC for PM-CRC. MSI status is correlated to superior survival with an independent time-varying effect, with reduction in mortality risk after 1 year following CRS-HIPEC.
Wu 2023	142 patients with PM-CRC underwent CRS + HIPEC (only synchronous)	Retrospective monocentric	mKRAS mBRAF	Mutational status impact on OS and DFS; Prevalence of KRASmut in conjunction with BRAFmut Create a nomogram to predict 1- and 2-year OS	**mBRAF vs wtBRAF:** worse median OS (8.4 Vs. 34.4 months) $p < 0.001$; worse median DFS (4.2 Vs. 10.2 months) $p < 0.001$	mBRAF is an independent prognostic risk factor for patients with synchronous PM, with worse OS and DFS than wtBRAF patients; no significant difference between mKRAS vs wtKRAS OS and PFS
Allievi 2024	555 patients with PM-CRC underwent CRS + HIPEC	Retrospective monocentric	mKRAS mNRAS mBRAF MSS/MSI status [mBRAF + MRR status excluded from multivariable analysis]	Mutational status impact on OS and DFS	**mKRAS vs wtKRAS:** *5-year OS* (55.8% Vs 70.7%) *5-year DFS* (27.9% Vs 37.6%) *Sistemic Recurrence* (51.2% Vs. 38.4%; $p = 0.033$) *Univariate analysis:* **MSI** *better OS* (HR 0.73, 95% CI 0.01–0.52; $p = 0.009$), *DFS* (HR 0.25, 95% CI 0.10–0.61; $p = 0.002$), *LR* (OR 0.33, 95% CI 0.11–0.98; $p = 0.048$), and *SR* (OR 0.12, 95% CI 0.03–0.54; $p = 0.005$) *Multivariate analysis:* **mKRAS** *decreased OS* (HR 1.82, 95% CI 1.25–2.65; $p = 0.002$), *DFS* (HR 1.55, 95% CI 1.13–2.12; $p = 0.007$), *and SR*[d] (OR 1.89, 95% CI 1.11–3.21; $p = 0.019$)	Patients with mKRAS are a high-risk cohort, with increased probability of SR and reduced survival, but not local recurrence. MSI status was shown to have a positive prognostic role.

(*Continued*)

Table 1. Continued.

Included Studies (n = 16 of 18 reports)						
Citation	Population description	Study Design	Genotypes/Gene Expression Assessed	Outcomes Assessed	Statistically Significant Results Related to Genotype/ Gene Expression	Interpretation of Results/Key findings
Tonello 2024	362 patients with PM-CRC underwent CRS + HIPEC (172 patients with mKRAS)	Retrospective national multicentric	$KRAS^{MUT1}$ (G12R, G13A, G13C, G13V, Q61H, K117N, A146V) $KRAS^{MUT2}$ (G12A, G12C, G12D, G12S, G12V, G13D, A59E, A59V, A146T)	Mutational status impact on OS and DFS	**$KRAS^{MUT1}$ Vs $KRAS^{MUT2}$ Vs $KRAS^{WT}$:** *Median OS* > 120 (95% CI not estimable) Vs 31.2 (95% CI 27.6–37.9 months) Vs 57.3 months (95% CI 42.3–95.0 months; $p < 0.0001$) Multivariate analysis **$KRAS^{MUT1}$ vs $KRAS^{WT}$ OS** (HR 0.4, p 1/4 0.163), **$KRAS^{MUT2}$ vs $KRAS^{WT}$ OS** (HR 2.1, $p < 0.001$) **$KRAS^{MUT1}$ vs $KRAS^{MUT2}$** *median DFS:* 12.3 Vs 10.5 months $p = 0.0001$; *median LDFS*[c]: 30.3 Vs 17.2 months, $p < 0.001$) Multivariate analysis **$KRAS^{MUT1}$ vs RAS^{WT}** *DFS* HR 1.2, $p = 0.469$; Vs HR 1.93, $p < 0.001$; *LDFS* HR 0.9, $p = 0.858$; Vs HR 2.49, $p < 0.001$	$KRAS^{MUT1}$ showed a similar survival rate to $KRAS^{WT}$ patients, whereas $KRAS^{MUT2}$ was independently associated with poorer prognosis.

[a]Defined as CSS (cancer specific survival) in the study.
[b]PRS = Post recurrence survival, defined as the time from date of relapse to date of last follow up or death.
[c]LDFS = Local (peritoneal) disease free survival.
[d]SR = Systemic recurrence.

the most common, and 5 BRAF subtypes, with V600E being the most frequent variant (80%). BRAF V600E and KRAS G12V mutations were significant prognostic determinants of DFS, with a median DFS of 9 months for the G12V variant compared to 11 months for other variants ($p = 0.016$). In multivariate analysis, the G12V variant was associated with a worse DFS (HR 2.63, $p = 0.016$).

Other studies [26–30] found no significant difference in median survival between mKRAS, mBRAF, and wild-type patients. Massalou et al. [31] noted, however, a correlation between mKRAS/BRAF and the mucinous component of the tumor.

Impact of BRAF mutation

The impact of mBRAF mutations was also somewhat controversial across the reviewed studies. Five studies [17,23,27,29,31] did not find a statistically significant correlation between BRAF status and patient survival.

On the other hand, BRAF mutation was identified as a negative prognostic factor in eight studies, including those by Tonello et al. [21], (HR, 3.3; 95% CI, 1.7–6.1), Di Giorgio et al. [32] (HR: 4.55; 95% CI: 1.21– 17.2) in multivariate analysis, and Wu et al. [26], who reported a worse median OS of 8.4 months compared to 34.4 months in wild-type patients and a poorer median DFS of 4.2 months versus 10.2 months in wild-type patients. Wu et al. specifically associated this with an increased risk for patients with synchronous PM. Some studies, while confirming the negative impact of mBRAF on overall survival, also highlighted its effect on reducing DFS. Schneider et al. [16], reported a reduction of median DFS by 7 months in the mBRAF group, aligning with Solomon et al. [30] who found a median DFS of 7 months for mBRAF patients compared to 16 months for wild-type patients ($p = 0.008$). Flood et al. [25] similarly observed a reduction in median DFS associated with the BRAF V600 subtype, at 8 months for mBRAF compared to 14 months for wild-type patients ($p = 0.006$).

Regarding the BRAF V600 subtype specifically, Bhullar et al. [28] noted a trend toward poorer median OS of 17.2 months (95% CI 1.0–33.4) versus 32.1 months (95% CI 19.7–44.5) in wild-type patients; $p = 0.109$.

Hamed et al. [19] also associated mBRAF with poorer OS in univariate analysis (HR 1.7), particularly when BRAF was combined with PIK3CA mutations (HR 4.9; $p = 0.02$).

Impact of MSI

The impact of MSI on survival varied across the studies. Larsen et al. [27] reported that the small subgroup with mBRAF/MSI had the best outcomes, with a median survival not reached and a 5-year OS exceeding 58.3%. In this study mBRAF and MSI were identified as independent prognostic factors in mCRC. A significant difference in 5-year OS was observed between the mBRAF/MSS and mBRAF/MSI groups (25.2% vs. 58.3%, $p = 0.022$), with the latter showing better DFS ($p = 0.022$). MSI was also associated with synchronous peritoneal metastases from colorectal cancer (50% vs. 17.9%, $p = 0.047$) and poorly differentiated tumors (83.8% vs. 15.4%, $p < 0.001$).

Hamed et al. [19] highlighted MSI status as a marker of superior survival, with an independent time-varying effect

Table 2. Included systematic review with meta-analysis and literature review.

Criteria	Systematic Review + Meta-Analysis (Gao et al., 2024)	Literature Review (Zhong et al., 2023)
Objective	To systematically assess the impact of RAS/BRAF mutations on peritoneal metastasis (PM) risk and the efficacy of CRS/HIPEC in colorectal cancer (CRC).	To gain a comprehensive understanding of how molecular status impacts CRS in CRC-PM patients and identify biomarkers predictive or prognostic of treatment outcomes.
Key Findings	- BRAF mutations significantly increase the risk of PM. - Both RAS and BRAF mutations are associated with worse overall survival (OS) and disease-free survival (DFS) after CRS/HIPEC.	- RAS mutations are linked to shorter DFS and increased peritoneal recurrence, but findings on OS are mixed. - BRAF mutations are associated with aggressive tumor biology and poorer survival outcomes. - Suggests that molecular biomarkers like RAS and BRAF guide treatment selection and prognosis.
Limitations	- Most studies are retrospective, with no high-quality randomized controlled trials (RCTs). - Lack of subgroup analysis for KRAS and NRAS mutations. - The mutation sites and detection methods differ among studies, leading to a potential heterogeneity of the results. - Many included articles did not distinguish left or right side of the colon.	- Relatively few studies on the impact of molecular markers on CRS outcomes. - A need for large cohort studies with better regional and population representation. - Most patients included in studies underwent both CRS and HIPEC, potentially affecting results.
Additional Observations	BRAF mutation, rather than RAS mutation, is a high risk factor for PM. BRAF mutated patients may require strict follow-up and preventive HIPEC. Both RAS and BRAF mutations negatively affect the prognosis after CRS/HIPEC.	Emphasizes the need for better diagnostic tools, early detection, and the use of molecular markers like KRAS/BRAF to personalize therapy in CRC-PM patients.

that reduces mortality risk after one year post-CRS-HIPEC. In univariate analysis, MSI status was associated with better OS in mRAS/BRAF patients (HR 0.3; $p = 0.01$), and a reduced mortality risk following CRS-HIPEC at one year (HR 0.4) and two years (HR 0.3).

Massalou et al. [31] found that MSI status correlated with improved median survival compared to MSS (85 months vs. 35.7 months, $p = 0.01$) and better DFS (24.9 months vs. 12.4 months), while Flood et al. [25] reported only a marginal difference in median OS (27 months vs. 29 months, $p = 0.025$).

Tonello et al. [21] showed that MSI status mitigates the negative effect of mKRAS/BRAF mutations and is linked to improved OS in both mKRAS/BRAF and wild-type patients. MSS/mutated patients exhibited the worst outcomes, with a 5-year OS of 23.4% and a 5-year DFS of 3.6%, versus 70.6% and 62.5% for MSI/all-WT patients ($p = 0.00001$). In multivariable analysis, MSI/WT patients showed a trend toward improved OS (HR 0.4; $p = 0.08$), while MSI/mutated patients had a significantly better OS (HR 0.5; $p = 0.0001$).

Allievi et al. [22] demonstrated a positive prognostic role of MSI status, showing better OS (HR 0.73, $p = 0.009$), DFS (HR 0.25, $p = 0.002$), and reduced risks of PR (OR 0.33, $p = 0.048$) and systemic recurrence (OR 0.12, $p = 0.005$) in univariate analysis.

Literary and systematic reviews with meta-analysis

The findings from the literature review by Zhong et al. [33] align with data from previous studies, showing a trend associating RAS and BRAF mutations with a generally poorer prognosis in terms of both DFS and OS, as well as an increased risk of PR. The paper highlights several important limitations in the reviewed studies that should be considered. The paper highlights key limitations in the reviewed studies, including a lack of large-cohort studies, heterogeneity in molecular research due to variable lab instrumentation, and a shortage of studies on certain molecular markers, which limits understanding of their roles in CRS for CRC-PM patients. Additionally, variations in patient treatment, with most receiving both CRS and HIPEC, may have affected findings on molecular markers in CRS.

The systematic review by Gao et al. [34] included studies focusing on patients receiving CRS/HIPEC for CRC-PM with available gene mutation information, resulting in 18 articles and a sample size of 5,567 subjects. An analysis of five studies, encompassing a total of 2,340 subjects, showed that patients with BRAF mutations are more likely to develop PM (OR = 2.28, 95% CI = 1.73–3.01, $p < 0.001$). Additionally, the analysis of nine studies involving 1,903 patients treated with CRS/HIPEC demonstrated that RAS mutations were associated with poor OS (HR = 1.68, 95% CI = 1.39–2.02, $p < 0.001$) and DFS (HR = 1.61, 95% CI = 1.34–1.94, $p < 0.001$). The analysis of six studies, with a sample size of 1,598 patients, further confirmed that the prognostic effect of BRAF mutations was consistent with that of RAS, with poorer OS (HR = 2.57, 95% CI = 1.93–3.44, $p < 0.001$) and DFS (HR = 1.90, 95% CI = 1.40–2.56, $p < 0.001$).

The study reports several limitations, primarily the retrospective nature of most included studies and the lack of high-quality randomized controlled trials. Additionally, there was no subgroup analysis for KRAS and NRAS mutations, with variations in mutation sites and detection methods contributing to potential heterogeneity. Many studies also failed to differentiate between left- and right-sided colon cancers (Table 2).

Discussion

RAS

RAS is one of the first genes to undergo mutation in many types of cancer, leading to dysregulated cell proliferation through constitutive activation of the Epidermal Growth Factor Receptor (EGFR) downstream pathway. Anti-EGFR monoclonal antibodies like cetuximab and panitumumab target the extracellular domain of EGFR, blocking downstream signaling involved in tumor proliferation, survival, and metastasis [35].

Randomized clinical trials have shown that anti-EGFR agents, particularly when combined with chemotherapy, are effective in treating mCRC in patients without mutations in KRAS (exons 2–4) and NRAS (exons 2–4) [36]. Mutations in downstream genes in the EGFR pathway, such as KRAS and BRAF V600E, are linked to resistance to anti-EGFR therapies and serve as biomarkers of poor prognosis.

The most common mutated subtype in CRC is KRAS (86%), and is generally mutually exclusive with NRAS or BRAF mutations [37]. NRAS mutations accounts for 14% of the patients, and HRAS mutations have not been reported [38].

Most stage IV CRC patients with PM, except for select cases with low PCI, are treated with systemic chemotherapy rather than upfront surgery. RAS mutation is currently one of the key factors in determining whether metastatic patients should receive therapy with anti-EGFR monoclonal antibodies or undergo CRS combined with HIPEC.

The overall trend in the literature indicates that RAS mutations generally negatively impact survival following CRS + HIPEC, although some studies show no significant association (Tables 3 and 4).

For instance, Shneider et al. [16] observed significantly worse outcomes for mRAS patients, with a reduction in both OS and DFS compared to RAS wild-type patients.

Similarly, Arjona-Sanchez et al. [17] demonstrated that mRAS, along with higher stages of the Peritoneal Surface Disease Severity Score (PSDSS), was a crucial determinant of poorer outcomes. Interestingly, even in early PSDSS stages I and II, the presence of mRAS impaired OS, with no significant difference compared to PSDSS stage III, underscoring the importance of considering both genetic and clinical staging in predicting patient prognosis post-CRS + HIPEC.

While the majority of studies, such as those by Hamed et al. [19] and Morgan et al. [20], emphasize the association of RAS/BRAF mutations with worse survival, they vary in the magnitude of the effect, particularly in terms of DFS, indicating that RAS mutations contribute to quicker recurrence but not necessarily to reduced life expectancy.

A deeper exploration of KRAS mutational subtypes adds further complexity to the prognostic landscape. Tonello et al. [24] distinguished between $KRAS^{MUT1}$ and $KRAS^{MUT2}$ variants, noting that $KRAS^{MUT2}$ mutations were associated with a significantly poorer prognosis, whereas $KRAS^{MUT1}$ mutations showed survival rates akin to KRAS wild-type patients. Similarly, Flood et al. identified the KRAS G12V mutation as a significant predictor of poorer DFS compared to other KRAS variants, underscoring that not all KRAS mutations are equal in their impact on survival outcomes.

Several studies [26–30], found no statistically significant difference in median survival between patients with mKRAS, mBRAF, or wild-type tumors. This suggests that, in some cases, the presence of KRAS mutations may not have as profound an impact as seen in other studies, possibly due to variations in sample size, patient selection, or tumor characteristics.

Despite these inconsistencies, the trend leans toward a detrimental effect of RAS mutations on survival, reporting reductions in both DFS and OS, as well as an increased risk of systemic and peritoneal recurrences [22,25]. However, the fact that several studies did not find a significant correlation between RAS mutations and overall outcomes indicates that the prognostic role of KRAS mutations, while largely negative, may be context-dependent and influenced by other tumor- or patient-related factors.

Furthermore, the differential impacts of KRAS subtype (such as $KRAS^{MUT1}$, $KRAS^{MUT2}$, and specific mutations like KRAS G12V) reveal that not all KRAS mutations confer the same

Table 3. Impact of molecular alterations on CRC-PM treated with CRS + HIPEC.

Molecular alteration	Impact on CRS outcomes
RAS mutation	Trend toward a negative impact on survival, with worse DSF and OS and increased risk of systemic and peritoneal recurrence. Some variants (KRAS G12V and KRASMUT2 profile) seem to be linked to a worse prognosis.
BRAF mutation	Negative prognostic factor for DFS and OS, increased risk of synchronous peritoneal metastasis and association with right sided cancers and mucinous component. The most frequent variant (BRAF V600) appears to be linked with a reduction of median DFS/OS.
microsatellite instability	MSI appears to mitigate the negative effect of mKRAS/BRAF mutations and is linked to improved survival in both mKRAS/BRAF and wild-type patients. MSS/mutated patients exhibit the worst outcomes.

Table 4. Impact of molecular alterations on overall survival (OS) and disease-free survival (DFS).

			Effect of mutational status on OS					Effect of mutational status on DFS				
Author	Year	Sample size	RAS wt	RAS m	BRAF wt	BRAF m	MSI	RAS wt	RAS m	BRAF wt	BRAF m	MSI
Massalou	2017	84	=	=	=	=	↑	↓	↑	=	=	↑
Schneider	2018	524	↑	↓	↑	↓	**NA**	↑	↓	↑	↓	**NA**
Arjona-Sanchez	2019	77	↑	↓	**NA**	**NA**	**NA**	=	=	**NA**	**NA**	**NA**
Morgan	2019	47	=	=	=	=	=	↑	↓	=	=	=
Shubin	2020	45	=	=	=	=	=	=	=	=	=	=
Breuer	2021	505	↑	↓	=	=	=	↑	↓	=	=	=
Bhullar	2021	195	=	=	=	↓	=	=	=	=	=	=
Solomon	2021	100	=	=	↑	↓	=	=	=	↑	↓	=
Di Giorgio	2021	66	=	=	↑	↓ BRAF V600E	=	=	=	=	=	=
Tonello	2022	437	↑	↓	↑	↓	↑	↑	↓	↑	↓	↑
Larsen	2022	180	=	=	=	=	↑ expecially mBRAF/ MSI	=	=	=	=	↑ expecially mBRAF/ MSI
Wu	2023	142	=	=	↑	↓	**NA**	=	=	↑	↓	**NA**
Flood	2022	174	=	=	=	↓ BRAF V600E	=	=	↓ G12V variant	=	↓ BRAF V600E	=
Hamed	2023	250	↑	↓	↑	↓	↑	=	=	=	=	↑
Allievi	2024	555	↑	↓	=	=	↑	↑	↓	=	=	↑
Tonello	2024	362	=	=KRASMUT1 ↓KRASMUT2	**NA**	**NA**	**NA**	=	=KRASMUT1 ↓KRASMUT2	**NA**	**NA**	**NA**

Better OS or DFS; ↓ Worse OS or DFS; = no influence on OS or DFS; NA, not assessed; in red, in the DSF columns, the mutational effects that differ with respect to OS.

prognosis, advocating for subtype-specific stratification in treatment planning.

These findings underscore the importance of assessing mutation variants within RAS and other molecular markers. An improved DFS may correlate with prolonged peritoneal recurrence-free survival, which is particularly impactful given that PM contributes significantly to poor prognosis. Effective local control over peritoneal spread could offer a survival advantage by 'chronicizing' the disease, allowing for better management of metastases in other sites (e.g., liver, lungs) and potentially extending survival. This variability supports the incorporation of expanded mutational analysis, including RAS subvariants, into routine clinical assessments for mCRC.

BRAF

BRAF mutations are present in approximately 10% of patients with colorectal cancer (CRC). The literature generally associates class I BRAF mutations, particularly BRAF V600E, with more aggressive tumor biology, increased risk of peritoneal spread and resistance to standard therapies [39].

In light of the reduced response of this patient subgroup to standard chemotherapy, the BEACON study [40] found that encorafenib plus cetuximab (with or without binimetinib) outperformed standard chemotherapy regimens (irinotecan plus cetuximab or FOLFIRI plus cetuximab) in patients with disease progression after one or two prior treatment regimens. In the study, objective response rates were notably higher in the encorafenib plus cetuximab groups, with an ORR of 27% for the triplet combination (encorafenib, binimetinib, and cetuximab) and 20% for the doublet combination (encorafenib and cetuximab), compared to only 2% in the control group receiving standard chemotherapy. This groundbreaking finding established the combination of encorafenib/cetuximab as a new standard of care for previously treated BRAF V600E mCRC.

BREAKWATER [41] is an ongoing, open-label, multicenter, randomized phase 3 study specifically targeting BRAF V600E-mutant mCRC by evaluating the efficacy and safety of encorafenib/cetuximab plus chemotherapy as a first- or second-line treatment compared to standard-of-care chemotherapy, aiming to improve outcomes for this patient population. Promising preliminary results have shown an Overall Response Rate (ORR) confirmed by Blinded Independent Central Review (BICR) of 68.4% for encorafenib/cetuximab + mFOLFOX6 and 75% for encorafenib/cetuximab + FOLFIRI in first-line treatment, and 37.5% and 44.4%, respectively, in second-line treatment. Similarly, median progression-free survival (mPFS) has shown encouraging results; however, the upper limit of the confidence interval is not yet estimable, and data for this treatment is still under evaluation.

In this scoping review, the studies examined generally highlight a trend toward poorer survival in BRAF mutated patients. However, the findings are somewhat conflicting. While several studies [17,23,27,29,31] did not find a statistically significant correlation between BRAF status and survival (Tables 3 and 4).

However, these findings do not necessarily contradict the potential biological impact of BRAF mutations. Massalou et al. [31] observed a correlation between mBRAF and the mucinous component of tumors, suggesting a link to tumor characteristics that might not directly influence survival but could have other clinical implications. Moreover, studies [26,34] documented a correlation between BRAF mutations and the risk of PM, which has significant repercussions on overall prognosis. An important portion of the studies identified BRAF mutations as a negative prognostic factor. For instance, Tonello et al. [21] and Di Giorgio et al. [32] reported significantly higher hazard ratio for poor OS in multivariate analyses, indicating that BRAF mutations confer a survival disadvantage. Wu et al. [26] provided particularly striking results, with mBRAF patients showing a median OS of only 8.4 months compared to 34.4 months for wild-type patients, along with a reduced median DFS.

Studies focusing on DFS consistently reported worse outcomes for mBRAF patients.

Schneider [16] and Solomon et al. [30] both noted a significant impact in median DFS among mBRAF patients, with reductions of 7 and 9 months, respectively, compared to wild-type patients. These results strongly imply that BRAF mutations not only impact OS but also substantially reduce the time to recurrence or disease progression.

The specific impact of the BRAF V600 mutation subtype was examined by several studies, such as Bhullar et al. [28], reporting a trend toward poorer OS, and Flood et al. [25] showing an 8-month median DFS in mBRAF patients versus 14 months in the wild-type cohort. The consistent reporting of worse survival outcomes among patients with BRAF V600 mutation across multiple studies points to its potential relevance as a negative prognostic marker. Furthermore, Hamed et al. [19] suggested that the negative impact of mBRAF could be compounded by co-occurring mutations, such as PIK3CA, further worsening survival outcomes. This highlights the complex interplay between BRAF and other molecular alterations in shaping the prognosis of CRC patients.

The consistently worse outcomes observed in BRAF-mutant patients underscore the importance of utilizing molecular profiling to more effectively identify candidates for major interventions like cytoreduction, where achieving long-term disease control is the primary aim. Notably, significant advances have been made in treating BRAF V600E mutant mCRC using BRAF inhibitors combined with anti-EGFR agents, with or without MEK inhibition.

MSI

The role of MSI as a biomarker for predicting positive responses to immune checkpoint inhibitors is well established. In early-stage disease, particularly in stage II colon cancer, MSI is linked to a more favorable prognosis [42,43]. However, in metastatic settings, especially with peritoneal involvement, the evidence becomes more variable. In 2020, the KEYNOTE-177 trial [44] explored the effectiveness of PD-1 blockade therapy, specifically pembrolizumab, in treating patients with advanced or metastatic colorectal cancer characterized by MSI. Pembrolizumab demonstrated a median PFS of 16.5 months versus 8.2 months with standard chemotherapy and achieved a higher ORR (29.4% versus 12.3%) making it the first-line standard treatment for patients with metastatic CRC exhibiting MSI.

A review of the available literature reveals both positive trends and inconsistencies regarding the impact of MMR

status on survival in patients with CRC-PM treated with CRS and HIPEC.

Overall, MSI status tends to be associated with better outcomes (Tables 3 and 4).

Larsen et al. [27] reported that MSI status, particularly in patients with mBRAF mutations, correlated with significantly improved survival, with median OS not reached and a higher 5-year survival rate compared to MSS patients. Hamed et al. [19], demonstrated that MSI status reduced mortality risk, especially after the first year post-surgery, and was linked to better survival outcomes in patients with RAS/BRAF mutations., further supported by Massalou et al. [31], who reported a significant improvement in median OS and DFS. Tonello et al. [24] also showed that MSI could mitigate the negative impact of KRAS/BRAF mutations, leading to superior long-term survival outcomes compared to MSS patients. Collectively, these studies underline the importance of MSI status in predicting better survival outcomes, especially associated with other mutations. However, not all studies support these conclusions. Flood et al. [25] reported only a marginal survival difference between MSI and MSS patients, while Solomon et al. [30] found no substantial effect of MSI status on survival, suggesting that the benefit of MSI could depend on other clinical or molecular factors and its prognostic value may not be significant across all patient groups.

MSI also appears to be associated with a higher prevalence of poorly differentiated tumors and synchronous peritoneal metastases [27], suggesting more aggressive tumor biology, which is consistent with existing literature.

Given that MSI can attenuate the negative effects of KRAS/BRAF mutations, it should be considered an important factor for risk stratification in patients undergoing CRS-HIPEC. Additionally, the durable clinical response of MSI tumors to immune checkpoint inhibitors in first-line therapy, regardless of BRAF V600E mutation status, highlights the importance of considering MMR status in multidisciplinary discussions about the risks and benefits of CRS.

Conclusions

Despite the advancements, there are inherent limitations to the current body of research, including single-center experiences, observational cohort designs, and a predominant focus on surgically treatable disease. Details on systemic therapies, such as specific treatment regimens, are often lacking. As research progresses, addressing these gaps will be essential for refining therapeutic strategies and improving patient outcomes.

The consistently negative impact of RAS and BRAF mutations on prognosis in patients with PM from CRC highlights the critical need for a personalized approach that factors in mutation analysis and subvariant impact on survival. Given that different KRAS and BRAF subtypes influence DFS and OS outcomes uniquely, future research should prioritize understanding how these mutation profiles can guide the selection of HIPEC regimens. Additionally, while most evidence suggests that MSI is a favorable prognostic marker, particularly when coexisting with BRAF and KRAS mutations, variability in current findings underscores the need to further clarify the conditions under which it may confer the greatest survival benefit.

Although the PRODIGE7 trial did not find an OS benefit for HIPEC, the incorporation of mutation-specific data into HIPEC studies could reveal benefits not previously observed. Specifically, tailoring HIPEC regimens based on molecular subtypes holds promise for optimizing local disease control and extending peritoneal recurrence-free survival, which is a key factor in improving long-term outcomes for this challenging patient population.

In conclusion, expanding mutational analysis to include KRAS and BRAF subvariants in future studies may enable a more nuanced approach to selecting the most effective chemotherapeutic agents, ultimately enhancing local control, reducing peritoneal recurrence, and extending survival in patients with mCRC.

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