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ARTICLE TITLE	CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN MALIGNANT PERITONEAL MESOTHELIOMA: A CURRENT NARRATIVE REVIEW OF SURVIVAL OUTCOMES AND PROGNOSTIC FACTORS
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CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY IN MALIGNANT PERITONEAL MESOTHELIOMA: A CURRENT NARRATIVE REVIEW OF SURVIVAL OUTCOMES AND PROGNOSTIC FACTORS

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ABSTRACT

Research Objectives. To summarize current evidence on survival outcomes and prognostic factors following CRS-HIPEC for MPM.

Methods. Narrative review of studies published from 2021–2026, including multicenter studies, single-center series, and international consensus guidelines (Acs et al., 2022; Deban et al., 2023; Kusamura et al., 2025; Kusamura et al., 2021; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023) . Data on treatment protocols, perioperative outcomes, survival, and prognostic factors were analyzed.

Key findings. Across >1,400 patients, complete cytoreduction (CC-0/1) was achieved in 78.6–85.7% of cases (Acs et al., 2022; Deban et al., 2023). Median OS ranged from 38–42 months (Acs et al., 2022; Liang et al., 2025; Valenzuela et al., 2023) and was not reached in upfront-resectable patients (Noiret et al., 2026). Five-year OS reached 84.6% in upfront-resectable disease versus 12.9% in inoperable cases (Noiret et al., 2026), markedly exceeding outcomes with systemic chemotherapy alone (Kusamura et al., 2021). Complete resection strongly affected survival, with median OS of 127 months after R0-1 versus 3 months after R2c resection (Valenzuela et al., 2023). Favorable prognostic factors included PCI ≤20, fewer transfusions, and absence of major complications (Liang et al., 2025), whereas older age, male sex, and borderline-resectable disease predicted worse outcomes (Noiret et al., 2026). Major morbidity ranged from 16.9–50.9% (Acs et al., 2022; Deban et al., 2023; Noiret et al., 2026), while perioperative mortality remained below 4% (Kusamura et al., 2025; Kusamura et al., 2021; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023). High-volume centers demonstrated lower morbidity (Noiret et al., 2026). International PSOGI guidelines strongly recommend CRS-HIPEC in carefully selected patients despite low-certainty evidence (Kusamura et al., 2025; Kusamura et al., 2021).

Conclusion. CRS-HIPEC is the current standard treatment for resectable MPM in expert centers, providing median OS exceeding 40 months and durable long-term survival in selected patients. Careful patient selection and treatment centralization optimize outcomes.

KEYWORDS

Malignant Peritoneal Mesothelioma, Cytoreductive Surgery, Hyperthermic Intraperitoneal Chemotherapy (HIPEC), Prognostic Factors, Survival Outcomes

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1. Introduction

Malignant peritoneal mesothelioma (MPM) is a rare and aggressive malignancy originating from the mesothelial cells lining the peritoneum, accounting for 7–30% of all mesotheliomas (Kusamura et al., 2021). Unlike its more common pleural counterpart, MPM presents unique challenges due to its insidious intra-abdominal spread, often mimicking other peritoneal surface malignancies or chronic inflammatory conditions. Histologically, MPM is classified into three main subtypes: epithelioid (the most prevalent, comprising approximately 75% of cases and associated with the best prognosis), biphasic (mixed epithelioid and sarcomatoid features), and sarcomatoid (least common but most aggressive) (Deban et al., 2023; Kusamura et al., 2021). Risk factors include prior asbestos exposure, though a substantial proportion of cases lack this association, highlighting potential genetic and environmental contributors (Kusamura et al., 2021).

Without effective intervention, MPM carries a dismal prognosis. Patients managed with best supportive care or systemic chemotherapy alone experience median overall survival (OS) of just 8–13 months (Kusamura et al., 2021). For decades, platinum-based doublet chemotherapy—particularly pemetrexed plus cisplatin—has remained the historical standard of care for inoperable patients, informed by phase III trials originally conducted in pleural mesothelioma (Kusamura et al., 2021). While this regimen yields response rates up to approximately 20-30% and median survival of 13.1 months in peritoneal subsets (Kusamura et al., 2021), its benefits remain limited.

Over the past two decades, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a curative-intent paradigm shift for carefully selected MPM patients (Kusamura et al., 2021). CRS seeks complete macroscopic cytoreduction (CCR-0/1), often requiring extensive peritonectomy and multi-organ resections, followed by HIPEC (typically with cisplatin or mitomycin C) to target residual microscopic disease via hyperthermia-enhanced cytotoxicity and pharmacokinetic advantages confined to the peritoneal cavity (Kusamura et al., 2025; Kusamura et al., 2021). Landmark single-center, multicenter, and meta-analytic series now report median OS ranging from 34 to 92 months in optimally treated cohorts of patients with DMPM (Kusamura et al., 2021). These gains underscore CRS-HIPEC's superiority over systemic therapy alone, particularly when complete cytoreduction is achieved (Kusamura et al., 2025; Kusamura et al., 2021).

Success hinges on meticulous patient selection using tools like the Peritoneal Cancer Index (PCI), radiographic staging, and histological subtype, alongside treatment centralization in high-volume expert centers (Kusamura et al., 2025; Kusamura et al., 2021; Noiret et al., 2026) to ensure optimal care and reduce mortality. Multidisciplinary evaluation ensures only resectable candidates—typically those with lower PCI and favorable histology—undergo this complex procedure.

This narrative review aims to summarize current evidence on survival outcomes and prognostic factors in MPM patients treated with CRS-HIPEC, drawing on recent large-scale national, multicenter, and single-center studies.

1.1 Research Objective

This narrative review aims to synthesize contemporary evidence on survival outcomes and prognostic factors among malignant peritoneal mesothelioma (MPM) patients undergoing cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC), drawing from a large-scale national study (Noiret et al., 2026), a multicenter series (Deban et al., 2023), and two-center and single-center institutional experiences (Acs et al., 2022; Liang et al., 2025; Valenzuela et al., 2023), alongside two international consensus documents (Kusamura et al., 2025; Kusamura et al., 2021). By integrating data from over 1,400 patients across diverse cohorts, it evaluates median overall survival (OS) ranging from 34–92 months in optimally cytoreduced (CC-0/1) cases, alongside key predictors such as the Peritoneal Cancer Index (PCI), histological subtype, and postoperative complications (Acs et al., 2022; Deban et al., 2023; Kusamura et al., 2025; Kusamura et al., 2021; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023). A particular focus is placed on conditional survival (CS), a dynamic prognostic tool that refines risk assessment by accounting for time already survived post-treatment: Liang et al. (2025) report 5-year CS rising from 27% at baseline to 84% at 4 years postoperatively, while Valenzuela et al. (2023) demonstrate CS improving from a median of 39.0 months at baseline to 58.4 months conditional on surviving the first postoperative year. This synthesis aims to inform patient selection criteria and multimodal treatment strategies within expert peritoneal surface malignancy centers (Kusamura et al., 2025; Kusamura et al., 2021).

1.2 Research Problems

Despite advances, the rarity of MPM (incidence 1–2 per million (Valenzuela et al., 2023)) constitutes a fundamental research problem by precluding randomized controlled trials (RCTs), compelling reliance on retrospective single-center and multicenter registry data, complicating achievement of large enough sample sizes to draw universal conclusions, and fostering heterogeneity in treatment protocols and outcome reporting across institutions and countries (Acs et al., 2022; Deban et al., 2023; Kusamura et al., 2025; Kusamura et al., 2021; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023). Several critical gaps persist in CRS+HIPEC for MPM, justifying this review. First, substantial heterogeneity in HIPEC protocols—varying drugs (cisplatin vs. mitomycin C), doses, durations, and temperatures—complicates outcome comparisons across studies, with no standardization endorsed beyond guidelines (Deban et al., 2023; Kusamura et al., 2021; Liang et al., 2025; Valenzuela et al., 2023). Second, the absence of randomized controlled trials (RCTs) leaves causality unproven, relying on observational data prone to selection bias (Acs et al., 2022; Deban et al., 2023; Kusamura et al., 2025; Kusamura et al., 2021; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023). Third, identifying universal prognostic factors proves challenging due to population differences; while low PCI (<20) and epithelioid histology consistently predict better survival in multicenter analyses (Kusamura et al., 2025; Noiret et al., 2026), factors like lymph node involvement vary in significance across cohorts (Deban et al., 2023; Valenzuela et al., 2023). Fourth, conditional survival analysis remains underutilized in MPM, limiting dynamic prognostication (Kusamura et al., 2025; Noiret et al., 2026). Finally, centralization challenges hinder widespread adoption, as low-volume centers report higher morbidity without survival gains (Kusamura et al., 2021; Liang et al., 2025).

2. Methodology

A narrative literature review was performed using the PubMed database. Publications from 1 January 2021 onward were considered. A broad PubMed (selected as the primary database due to its comprehensive indexing of peer-reviewed biomedical literature) search was conducted using combinations of terms such as "peritoneal mesothelioma," "malignant peritoneal mesothelioma," "HIPEC," "hyperthermic intraperitoneal chemotherapy," "cytoreductive surgery," and "CRS" in titles and abstracts, identifying 131 records. After restricting the results to human studies written in English, 81 records remained. These 81 records were then manually screened.

Following full-text review of 15 records, seven studies were ultimately selected for synthesis, representing a mix of high-quality observational data and expert consensus: Noiret et al. (2026) — 10-year French national database study (n=924); Valenzuela et al. (2023) — 28-year single-center US series (n=111); Acs et al. (2022) — 10-year single-center German series (n=84); Deban et al. (2023) — multicenter Canadian series (n=72); Liang et al. (2025) — two-center Chinese series (n=212); Kusamura et al. (2021)— multisocietal GRADE-based consensus statement (PSOGI, ISSPP, SSO, EURACAN, IMIG, ESSO); and Kusamura et al. (2025) — PSOGI/EURACAN international clinical practice guidelines.

Data extraction from five retrospective observational clinical studies (Acs et al., 2022; Deban et al., 2023; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023) and two consensus/guideline documents—Kusamura et al. (2021) and Kusamura et al. (2025)—that provide recommendation-level evidence rather than original clinical outcome data—focused on study design, patient demographics, CRS-HIPEC protocols, survival metrics (e.g., median OS, 5-year rates, conditional survival), prognostic factors, and perioperative outcomes. As this is a narrative rather than systematic review, no PRISMA flow diagram was prepared. Narrative synthesis was employed due to methodological heterogeneity, with no statistical pooling or meta-analysis; findings are presented thematically, corresponding to subsections on survival outcomes (3.1), prognostic factors (3.2), perioperative outcomes and safety (3.3), and the role of centralization and expert-center care (3.4). Quality of (Acs et al., 2022; Deban et al., 2023; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023) was assessed by sample size (n=72 (Deban et al., 2023) to n=924 (Noiret et al., 2026); (Liang et al., 2025) n=212 full cohort for conditional survival, n=90 [53 LTS + 37 STS] for prognostic factor comparisons with multivariate logistic regression), follow-up length (median 24 months (Deban et al., 2023) to 5.0 years (Acs et al., 2022); 28-year series [1993–2021] (Kusamura et al., 2021)), and multivariate analysis use (present in (Acs et al., 2022; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023); absent in Deban et al. (2023), which used Kaplan-Meier/descriptive methods). Given MPM rarity (incidence 1–2 per million (Liang et al., 2025); 300–400 annual US cases (Kusamura et al., 2021)), prospective randomized trials are unfeasible, making high-quality retrospective data the highest evidence level, as acknowledged in Kusamura et al. (2021) and Kusamura et al. (2025). The retrospective design of all five clinical studies (Acs et al., 2022; Deban et al., 2023; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023) introduces inherent limitations, including selection bias and absence of randomized comparators, as acknowledged in Kusamura et al. (2021) and Kusamura et al. (2025).

3. Results

3.1 Survival Outcomes

Median overall survival (OS) clustered around 38–42 months in single-center series (Acs et al., 2022; Valenzuela et al., 2023), while Deban et al. (2023) did not reach median OS at a median follow-up of 24 months. The 5-year OS range across all surgical cohorts spans from 27% in the full Chinese cohort (Liang et al., 2025) to 84.6% in upfront-resectable patients in the French national series (Noiret et al., 2026), substantially exceeding historical systemic chemotherapy benchmarks of 8–13 months with pemetrexed-based regimens (Kusamura et al., 2021)—where the lower bound of ~8–10 months reflects pemetrexed monotherapy and 12–13 months reflects the pemetrexed/cisplatin doublet.

Noiret et al., 2026 reported outcomes from a 10-year French nationwide database (n=924 DMPM patients), stratified by resectability status: 5-year OS was 84.6% for upfront-resectable cases, 55% for borderline-resectable patients, and 12.9% for inoperable patients; corresponding 1-year OS rates were 95.4%, 83.5%, and 31.9%, respectively. Median OS was not reached in the upfront-resectable group, underscoring the profound survival benefit of CRS-HIPEC in patients deemed suitable for upfront surgical resection.

Valenzuela et al. (2023) described a 28-year single-institution experience (1993–2021) with 111 patients undergoing CRS-HIPEC, reporting a median OS of 39.0 months for the full cohort. Survival curves appeared to plateau around 6 years postoperatively, suggesting long-term cure in a subset of patients. Conditional survival escalated from 58.4 months at 1 year to 67.7 months at 2 years and 73.3 months at 3 years following CRS-HIPEC. Notably, 17 of 111 patients (15.3%) underwent repeat CRS-HIPEC, achieving superior median OS of 67.7 months versus 35.9 months for those without repeat procedures (p=0.037); however, this subgroup was younger (mean age 47.1 vs 55.1 years), had better performance status (ECOG 0–1 in 100% vs 69.7%), and lower mean peritoneal cancer index (PCI; 15.0 vs 18.7), limiting generalizability to unselected patients.

Acs et al. (2022) reported outcomes from a 10-year single-center German series (n=84; median follow-up 5.0 years), documenting median OS of 38.4 months and 5-year OS of 42%, consistent with other expert-center institutional data.

Deban et al. (2023) analyzed 72 patients treated with CRS-HIPEC, achieving 5-year OS of 61% overall; median time to recurrence was 38.0 months with 5-year recurrence-free survival (RFS) of 35%, whereas the epithelioid/biphasic subgroup experienced a shorter median time to recurrence of 29.0 months alongside 5-year OS of 53% and 5-year RFS of 25%. Median OS was not reached at a median follow-up of 24 months, reflecting the relatively short observation period.

Liang et al. (2025) reported median OS of 41.6 months in their full cohort of 212 patients; PCI ≤20 conferred markedly superior outcomes (71.3 months) versus PCI >20 (29.9 months), with survival curves flattening at postoperative year 5 and the authors concluding that "some patients may achieve clinical cure 5 years after surgery" (Liang et al., 2025). Five-year conditional survival improved from 27% at baseline—the lowest 5-year OS across included series and representative of the whole cohort—to 84% conditional on having already survived 4 years post-surgery (Liang et al., 2025).

Collectively, these data confirm CRS-HIPEC's potential for long-term survival in expert settings, with 5-year OS ranging from 27% (Liang et al., 2025) to 84.6% (Noiret et al., 2026) depending on patient selection and resectability status, and survival curves flattening beyond 5–6 years in multiple cohorts (Liang et al., 2025; Valenzuela et al., 2023), suggesting functional cure is achievable in carefully selected patients—a stark contrast to the 8–13 months median OS reported with pemetrexed-based systemic chemotherapy (Kusamura et al., 2021).

3.2 Prognostic Factors

Multivariate analyses in four of the five clinical studies (Acs et al., 2022; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023) identified key prognostic factors influencing OS and long-term outcomes in MPM patients undergoing CRS-HIPEC, emphasizing histological subtype, disease burden, cytoreduction completeness, and patient characteristics as dominant predictors, while Deban et al. (2023) contributed descriptive and literature-referenced prognostic insights without formal multivariate modeling.

Noiret et al. (2026) highlighted male gender (HR 2.72, p<0.0001), age >70 years (HR 8.55, p=0.005), major morbidity (HR 2.11, p=0.003), borderline-resectable status (HR 2.74, p<0.0001), and adjuvant chemotherapy (HR 1.76, p=0.012) as independent adverse factors for 5-year survival; notably, the association between adjuvant chemotherapy and worse survival likely reflects indication bias, as higher-risk patients were selectively offered adjuvant treatment, an effect particularly pronounced in the borderline-resectable subgroup (HR 2.01, p=0.002) (Noiret et al., 2026).

Valenzuela et al. (2023) similarly reported increased age (p=0.008), R2a or worse resection versus R0-1 (p<0.005), and ECOG 3 (p<0.001) as predictors of higher postoperative mortality hazard; platinum-based perfusate outperformed mitomycin C (median OS 42.4 versus 11.6 months, p=0.007) (Valenzuela et al., 2023); however, this comparison is subject to era bias, as mitomycin C was used predominantly before 2010 and cisplatin thereafter, meaning the observed survival difference may partly reflect concurrent improvements in patient selection and perioperative management over time rather than perfusate choice alone (Valenzuela et al., 2023), with R0-1 resections achieving 127 months median OS compared to 35.9 months (R2a), 11.4 months (R2b), and 3.0 months (R2c).

Acs et al. (2022) identified older age, female gender, thrombocytosis, elevated BMI, and CC-1 resection (versus CC-0 as reference) as independent adverse or favorable OS correlates on multivariate analysis, while CC-2 resection and preoperative chemotherapy did not reach independent significance.

Deban et al. (2023), whose analysis was descriptive rather than multivariate, noted consistency with established prognostic literature regarding completeness of cytoreduction, epithelioid histology, age, and

disease extent (Deban et al., 2023), with no sarcomatoid cases proceeding to surgery and 5-year OS at 61% overall versus 53% for epithelioid/biphasic.

Liang et al. (2025) linked PCI ≤20 (OR 0.025, p=0.002), reduced intraoperative red blood cell transfusion (OR 0.581, p=0.003), and absence of severe adverse events (OR 0.077, p=0.001) to long-term survival multivariately; univariate factors included epithelioid type, Ki-67 ≤9%, and lack of lymphatic/vascular invasion.

Kusamura et al. (2021) guidelines affirmed histological subtype (epithelioid > biphasic > sarcomatoid), CC-0/1 versus CC-2/3, lymph node involvement, Ki-67 >9%, and PCI >17 as established negative prognosticators. Echoing this, Kusamura et al. (2021) consensus recommended CRS-HIPEC selection for Ki-67 <10%, PCI ≤17, epithelioid subtype, and resectability to CC-0/1. These convergent factors advocate rigorous preoperative stratification to maximize benefit.

3.3 Perioperative Outcomes and Safety

Perioperative morbidity following CRS-HIPEC for MPM was substantial yet manageable in expert centers, with major complication rates of 16.9–50.9% offset by relatively low mortality (below 5%), reinforcing the procedure's safety profile when centralized.

Noiret et al. (2026) reported 90-day postoperative mortality (POM) of 2.1%, major morbidity (Clavien-Dindo grade 3–4) at 50.9%, failure-to-rescue rate of 4.1%, and mean length of stay (LOS) of 21.2 days; borderline-resectable patients experienced more extensive resections (≥3 organs: 45.3% versus 33.3%), abdominal complications (71.8% versus 59.3%), and hemorrhagic events (38.5% versus 19.6%), without differences in POM or failure-to-rescue versus upfront-resectable cases.

Valenzuela et al. (2023) reported 30-day mortality of 2.7% (n=3) in their 28-year institutional series, consistent with the low mortality profile observed across all included expert centers.

Acs et al. (2022) observed major morbidity (grade ≥III) in 26.2%, acute kidney injury (stage I–III) in 35.7%, 30-day mortality of 3.6% (n=3), and median LOS of 17 days; HIPEC duration (90 versus 60 minutes) did not influence survival or morbidity, though this comparison was limited by the small size of the 90-minute group (n=14, 16.7%), precluding definitive conclusions (Acs et al., 2022).

Deban et al. (2023) reported Clavien-Dindo grade III complications in 9.9% and grade IV in 7.0% of patients, with zero 30-day mortality and a mean LOS of 19 days; these outcomes were achieved in the context of a mean PCI of 22 and a CC-0/1 rate of 85.7%, underscoring the surgical complexity of the procedures performed (Deban et al., 2023).

Liang et al. (2025) linked severe adverse events (SAEs) to poorer prognosis (67.6% in short-term survivors versus 28.3% in long-term survivors), with respiratory SAEs higher in short-term cases (40.5% versus 15.1%, p=0.006) and 30-day mortality of 5.4% (2 of 37 short-term survival patients), with no perioperative deaths in the long-term survival group (Liang et al., 2025).

Kusamura et al. (2025) summarized severe complications at 30–41% and POM at 2.0–2.6% across series. This pattern—high morbidity but low mortality—highlights procedural intensity alongside expert-center proficiency.

3.4 Role of Centralization and Expert-Center Care

Centralization in high-volume expert centers emerged as a critical determinant of outcomes, with data advocating referral to specialized peritoneal surface malignancy units to mitigate risks and optimize results.

Noiret et al. (2026) revealed 97.7% of surgical patients treated at RENAPE expert centers, where volumes ≥7 CRS-HIPEC/year reduced major morbidity (41.2% versus 53.4%, p=0.02) and ≥9/year further to 35.6%; lower exploratory laparoscopy rates in inoperable cases (44.3%) versus upfront-resectable (90.7%) and borderline-resectable (61.5%) groups. Only 59.7% of laparoscopies in the inoperable group were performed in RENAPE centers (versus 84.9% and 79.2% in upfront-resectable and borderline-resectable groups respectively), highlighting the risk of misclassification when patients are not referred to expert centers (Noiret et al., 2026).

Kusamura et al. (2021) consensus emphasized CRS-HIPEC's resource demands, steep learning curve, and real-world variability, urging concentration in dedicated centers.

Kusamura et al. (2025) recommended expert-surgeon laparoscopy and mandatory multidisciplinary team (MDT) management (Recommendation 12; consensus 26/27), with centralization averting inoperable misclassification.

Valenzuela et al. (2023) and Acs et al. (2022), from high-volume single centers, reported low mortality (2.7% and 3.6%), exemplifying the benefits of institutional expertise.

Deban et al. (2023), whose multicenter Canadian series spanning four peritoneal disease centers achieved zero 30-day mortality, attributed favorable outcomes to appropriate patient selection and institutional expertise, advocating standardization via collaborative networks such as the Canadian HIPEC Collaborative (CHIC) (Deban et al., 2023).

Overall, centralization in expert peritoneal surface malignancy centers enhances safety, patient selection accuracy, and survival outcomes, a principle unanimously endorsed by both PSOGI consensus documents (Kusamura et al., 2025; Kusamura et al., 2021).

4. Discussion

4.1 Treatment Paradigm and Efficacy

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) has fundamentally transformed malignant peritoneal mesothelioma (MPM) from a uniformly fatal disease to one with curative potential in selected patients (Kusamura et al., 2025; Kusamura et al., 2021). This paradigm shift is evident when contrasting median overall survival (OS) of 8–13 months with pemetrexed-based systemic chemotherapy (Kusamura et al., 2021) against 38–42 months in institutional series (Acs et al., 2022; Liang et al., 2025; Valenzuela et al., 2023) and 84.6% 5-year OS in upfront-resectable patients (Noiret et al., 2026). Completeness of cytoreduction emerges as the dominant efficacy driver, with R0-1 resection achieving 127 months median OS versus 35.9 months (R2a), 11.4 months (R2b), and 3.0 months (R2c) (Valenzuela et al., 2023); complete cytoreduction (CC-0/1) rates ranged from 78.6–85.7% (Acs et al., 2022; Deban et al., 2023). HIPEC agent selection influences outcomes, as platinum-based perfusate outperformed mitomycin C (42.4 vs 11.6 months median OS, p=0.007) (Valenzuela et al., 2023), though this comparison is subject to era bias since mitomycin C was used predominantly before 2010 (Valenzuela et al., 2023); cisplatin-based regimens are preferred (Kusamura et al., 2021), yet no single standardized protocol exists across centers (Acs et al., 2022; Deban et al., 2023; Kusamura et al., 2021; Valenzuela et al., 2023). The PSOGI multisocietal GRADE consensus issued a strong recommendation for CRS-HIPEC despite very low certainty of evidence, reflecting MPM's life-threatening nature and the near impossibility of conducting randomized controlled trials (RCTs) given the disease's rarity (Kusamura et al., 2025; Kusamura et al., 2021).

The considerable heterogeneity in HIPEC protocols across included series warrants explicit discussion. Chemotherapy agents, temperatures, durations, and delivery techniques varied substantially: Valenzuela et al. (2023) most commonly used cisplatin at 200–250 mg/m² for 90 minutes via a closed-abdomen technique with a target outflow temperature of 40°C; Acs et al. (2022) administered cisplatin 75 mg/m² combined with doxorubicin 15 mg/m² at 42°C for 60 or 90 minutes via a closed technique with five patients (6%) receiving gemcitabine (2000 mg/m2 of body surface area) HIPEC due to intolerance of cisplatin during preoperative systemic chemotherapy. Liang et al. (2025) used cisplatin 120 mg combined with docetaxel 120 mg, or cisplatin 120 mg with mitomycin C 30 mg, or single-agent cisplatin 120 mg at 43°C for 60 minutes via an open technique at a flow rate of 400 mL/min; and Deban et al. (2023) reported the widest protocol variability across four Canadian centers, with cisplatin plus doxorubicin used in 51.6%, oxaliplatin in 29.7%, mitomycin alone in 17.2%, and cisplatin alone in 1.6%, with temperatures ranging from 40–43°C and durations from 30 to 90 minutes. The PSOGI/EURACAN guidelines (Kusamura et al., 2021) report five frequently used HIPEC regimens with a preference for cisplatin-based combinations but without mandating a single standardized protocol. Although Valenzuela et al. (2023) reported superior OS with platinum-based versus mitomycin C perfusate, this comparison was subject to era bias and does not constitute a controlled protocol evaluation; no randomized or prospective head-to-head protocol comparison has been performed within any included study. This heterogeneity precludes direct cross-study comparison of oncological outcomes and represents a fundamental obstacle to protocol optimization, reinforcing the need for prospective standardization efforts.

4.2 Prognostic Factors and Patient Selection

Multivariate analyses in four of five clinical studies (Acs et al., 2022; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023) identified convergent prognostic factors supporting a rigorous preoperative selection framework. Disease burden, quantified by peritoneal cancer index (PCI), was independently associated with long-term survival (OR 0.025, p=0.002), conferring 71.3 versus 29.9 months median OS for PCI ≤20 versus >20 (Liang et al., 2025); PCI ≤17 alongside Ki-67 <10% is recommended as a selection threshold (Kusamura et al., 2025; Kusamura et al., 2021). Completeness of cytoreduction was independently prognostic, with CC-1 resection associated with significantly worse OS compared with CC-0 (HR 4.322, p=0.001), while CC-2 did not reach independent significance (p=0.403), likely reflecting limited statistical power in this subgroup (n=18); consistent with Acs et al.'s own conclusion that CC-1 and CC-2 outcomes were similarly poor (Acs et al., 2022), these findings underscore the necessity of achieving complete rather than near-complete cytoreduction. Histological subtype consistently influences prognosis, with epithelioid morphology associated with better outcomes (Acs et al., 2022; Deban et al., 2023; Kusamura et al., 2021); no sarcomatoid cases underwent surgery (Deban et al., 2023), and biphasic subtype was linked to shorter median time to recurrence (29.0 months) and lower 5-year OS (53%) (Deban et al., 2023). Intraoperative red blood cell (RBC) transfusion emerged as a modifiable prognostic factor (OR 0.581, p=0.003) (Liang et al., 2025), attributed to transfusion-related immunomodulation, emphasizing the importance of improving surgical technique to minimize blood loss for long-term survival (Liang et al., 2025). Preoperative laparoscopy (Recommendation 11.1, consensus 24/27) aids in accurately characterizing PCI and minimizing futile laparotomies (Kusamura et al., 2021); only 44.3% of inoperable versus 90.7% of upfront-resectable patients underwent laparoscopy, with just 59.7% in the inoperable group performed in RENAPE centers, highlighting misclassification risk (Noiret et al., 2026). Adjuvant chemotherapy was independently associated with worse 5-year survival (HR 1.76, p=0.012) (Noiret et al., 2026), an association most likely reflecting indication bias rather than inherent harm — higher-risk patients were selectively offered adjuvant treatment per PSOGI criteria (Kusamura et al., 2021), an effect particularly pronounced in the borderline-resectable subgroup (HR 2.01, p=0.002) (Noiret et al., 2026).

An important finding from Valenzuela et al. (2023) is the potential survival benefit of repeat CRS-HIPEC in carefully selected patients with disease recurrence. Among 111 patients, 17 (15.3%) underwent a second CRS-HIPEC procedure, achieving a superior median OS of 67.7 versus 35.9 months compared with those receiving a single procedure (p=0.037) (Valenzuela et al., 2023). However, this subgroup was significantly younger (mean age 47.1 vs 55.1 years, p<0.01), had better performance status (ECOG 0–1 in 100 % vs 69.7%), and lower mean PCI (15.0 vs 18.7), indicating that patients selected for repeat CRS-HIPEC represent a highly favorable subset unlikely to be representative of the broader MPM population. Nevertheless, these data suggest that in expert centers, recurrence should not automatically preclude consideration of further surgical intervention, and that structured surveillance protocols enabling early detection of resectable recurrence may offer meaningful additional survival benefit in appropriately selected patients (Valenzuela et al., 2023).

Conditional survival (CS) analysis represents an underutilized but clinically valuable prognostic tool in MPM that deserves broader adoption in post-treatment follow-up consultations. Unlike traditional Kaplan–Meier estimates calculated from the time of diagnosis or surgery, CS accounts for the time a patient has already survived, providing a continuously updated probability of future survival that more accurately reflects the patient's current prognosis (Liang et al., 2025). Liang et al. (2025) demonstrated this dynamic progression explicitly: the probability of achieving 5-year survival rises from 27% at baseline to 38% conditional on surviving 1 year, 51% on surviving 2 years, 67% on surviving 3 years, and 84% on surviving 4 years post-surgery, with the curve reaching 100% at 5 years — consistent with the authors' conclusion that clinical cure is achievable at this milestone (Liang et al., 2025). Valenzuela et al. (2023) corroborate the clinical significance of the 1-year postoperative anniversary as a statistically significant turning point (log-rank p=0.007), after which CS from 39.0 months at baseline improves to 58.4 months, with further improvements at 2 years (67.7 months, p=0.105) and 3 years (73.3 months, p=0.034). The progressive flattening of survival curves beyond 5–6 years in both cohorts (Liang et al., 2025; Valenzuela et al., 2023) supports the emerging clinical consensus that CRS-HIPEC can convert MPM into an indolent condition in a meaningful subset of patients. Practically, CS data allow clinicians to provide patients with updated, time-sensitive prognostic information at each follow-up visit — shifting the conversation from initial diagnosis-based statistics to current, personalized survival probabilities that more accurately reflect the patient's trajectory (Liang et al., 2025).

4.3 Perioperative Safety and Centralization

CRS-HIPEC carries substantial but manageable perioperative morbidity (16.9–50.9% Clavien-Dindo III-IV) with consistently low mortality (below 5%) across series (Acs et al., 2022; Deban et al., 2023; Liang et al., 2025; Noiret et al., 2026). Zero 30-day mortality was achieved across four centers (Deban et al., 2023), and 90-day postoperative mortality was only 2.1% among 387 surgical patients (Noiret et al., 2026), exemplifying expert-center proficiency. Cisplatin-related acute kidney injury represents a specific safety signal, occurring in 35.7% of patients (predominantly stage I at 21.4%) with cisplatin+doxorubicin HIPEC (Acs et al., 2022). Respiratory complications were the most clinically significant serious adverse event (SAE) category, significantly higher in short-term survivors (40.5% vs 15.1%, p=0.006) and the only SAE with a statistically significant between-group difference (Liang et al., 2025); prophylactic thoracic drainage may mitigate this (Liang et al., 2025). A volume-outcome relationship exists, with centers performing ≥7 CRS-HIPEC/year showing lower major morbidity (41.2% vs 53.4%, p=0.02), further reduced at ≥9/year (35.6%) (Noiret et al., 2026). CRS-HIPEC's steep learning curve, resource intensity, and real-world variability necessitate concentration in dedicated peritoneal surface malignancy centers with requisite expertise and infrastructure (Kusamura et al., 2025).

The safety profile of CRS-HIPEC in borderline-resectable patients deserves specific consideration, as this subgroup represents a clinically challenging population requiring careful risk-benefit assessment. Noiret et al. (2026) demonstrated that borderline-resectable patients underwent significantly more extensive surgery than upfront-resectable cases, with at least three organ resections in 45.3% versus 33.3% (p=0.025), higher rates of splenectomy (40.2% vs 21.9%, p<0.001), and stoma formation (13.7% vs 7.4%, p=0.05). Abdominal complications were significantly more frequent (71.8% vs 59.3%, p=0.02), with particularly elevated rates of hemorrhagic complications (38.5% vs 19.6%, p<0.001), abscess formation (20.5% vs 12.2%, p=0.03), and peritonitis (15.4% vs 8.5%, p=0.04). Despite this substantially greater surgical burden, 90-day postoperative mortality (2.6% vs 1.9%, p=0.65) and failure-to-rescue rates (4.5% vs 3.8%, p=0.83) did not differ significantly between groups (Noiret et al., 2026). This finding is clinically important: it demonstrates that with appropriate centralization and multidisciplinary expertise, borderline-resectable patients can undergo more extensive cytoreductive procedures without incurring meaningfully higher mortality risk, supporting the extension of CRS-HIPEC to this population when performed at experienced centers (Noiret et al., 2026). Nevertheless, the significantly worse 5-year OS in borderline-resectable versus upfront-resectable patients (55% vs 84.6%) (Noiret et al., 2026) underscores that resectability status remains a powerful determinant of long-term outcomes, reinforcing the importance of early referral to expert centers before disease progression renders curative resection unachievable.

4.4 Limitations and Future Directions

All five clinical studies represent retrospective observational designs (Acs et al., 2022; Deban et al., 2023; Liang et al., 2025; Noiret et al., 2026; Valenzuela et al., 2023)—the highest currently available evidence level given MPM's rarity (1–2 per million) (Liang et al., 2025) and the near impossibility of RCTs (Kusamura et al., 2025; Kusamura et al., 2021). HIPEC protocol heterogeneity poses a major limitation: agents varied from cisplatin+doxorubicin (Acs et al., 2022; Deban et al., 2023) to cisplatin+docetaxel, cisplatin+mitomycin C, or single-agent cisplatin (Liang et al., 2025), and platinum-based agents or mitomycin C (Valenzuela et al., 2023); temperatures ranged from 40–43°C (Acs et al., 2022; Deban et al., 2023; Liang et al., 2025; Valenzuela et al., 2023) and durations from 30–90 minutes (Acs et al., 2022; Deban et al., 2023; Liang et al., 2025; Valenzuela et al., 2023); no single standardized protocol has been established, with guidelines offering preferred regimens but not mandating a uniform approach (Kusamura et al., 2021). Limited sample size (n=72) precluded multivariate analysis (Deban et al., 2023), reducing comparability of prognostic factors. Short median follow-up (24 months) limits 5-year survival estimates (Deban et al., 2023), while the administrative database design precluded detailed pathological variables including PCI, CC score, Ki-67, and histological subtype (Noiret et al., 2026). Future directions include prospective multicenter registries such as RENAPE (Noiret et al., 2026) and CHIC (Deban et al., 2023) to standardize data collection and enhance evidence quality; HIPEC regimen standardization per PSOGI guidelines (Kusamura et al., 2021); incorporation of evolving systemic therapies, as immunotherapy's rapid evolution in pleural mesothelioma will likely necessitate revision of diffuse malignant peritoneal mesothelioma recommendations (Kusamura et al., 2025); and pressurized intraperitoneal aerosol chemotherapy (PIPAC) for borderline or unresectable MPM, including the ongoing MESOTIP trial combining PIPAC with systemic chemotherapy (Noiret et al., 2026).

The role of perioperative systemic chemotherapy in MPM patients undergoing CRS-HIPEC remains unresolved and represents an ongoing controversy in the field. Kusamura et al. (2025) summarize three large retrospective series with conflicting findings: one multicenter French series reported that neoadjuvant chemotherapy was independently associated with worse outcomes on multivariate analysis, with 5-year OS of 40% in the neoadjuvant group versus 67% in those receiving no systemic chemotherapy (Kusamura et al., 2021); conversely, another series reported that platinum-pemetrexed and platinum-gemcitabine combinations produced disease control rates of 86% and 82% respectively as neoadjuvant treatment, with median progression-free survival of 14.4 months for both regimens (Kusamura et al., 2021). In the French nationwide series (Noiret et al., 2026), adjuvant chemotherapy was independently associated with worse 5-year survival in the borderline-resectable subgroup (HR 2.01, p=0.002), an association most likely explained by indication bias — patients with higher-risk pathological features such as incomplete cytoreduction, sarcomatoid or biphasic histology, lymph node involvement, Ki-67 >9%, or PCI >17 were more likely to receive adjuvant treatment per PSOGI recommendations (Kusamura et al., 2021), confounding any direct survival comparison. Until prospective data are available, perioperative systemic chemotherapy should be considered individually within a multidisciplinary framework (Kusamura et al., 2025; Kusamura et al., 2021), with adjuvant therapy reserved for patients with established adverse pathological or surgical features (Kusamura et al., 2021).

5. Conclusions

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) stands as the sole treatment modality offering curative potential for selected patients with malignant peritoneal mesothelioma (MPM), as consistently demonstrated across large international retrospective series and unequivocally endorsed by authoritative guidelines such as the PSOGI multisocietal GRADE consensus and PSOGI/EURACAN recommendations (Kusamura et al., 2025; Kusamura et al., 2021). In the French nationwide study (Noiret et al., 2026) encompassing 924 patients, 5-year overall survival (OS) reached an impressive 84.6% for upfront-resectable cases and 55% for borderline-resectable disease, starkly contrasting with 12.9% in inoperable patients and historical systemic chemotherapy benchmarks of 8–13 months with pemetrexed-based regimens (Kusamura et al., 2021). Similarly, institutional series from Canada, the United States, China, and Germany report median OS ranging from 38 to 42 months (Acs et al., 2022; Liang et al., 2025; Valenzuela et al., 2023), with 5-year OS rates ranging from 27% (Liang et al., 2025) to 61% (Deban et al., 2023) in single and multicenter surgical cohorts, and survival extending to 127 months in optimally resected cases achieving R0-1 cytoreduction (Valenzuela et al., 2023). These findings underscore that meticulous patient selection—anchored by low Peritoneal Cancer Index (PCI ≤17-20), low Ki-67 proliferation index (<10%), epithelioid histology, favorable performance status, and achievable complete macroscopic cytoreduction—forms the cornerstone of transformative outcomes, mitigating risks while maximizing long-term disease control (Kusamura et al., 2025; Kusamura et al., 2021, Liang et al., 2025).

Operationalizing patient selection requires systematic preoperative assessment combining imaging-based PCI estimation, histological subtyping, Ki-67 proliferation index, and performance status evaluation within a dedicated multidisciplinary team — a process mandated by both PSOGI consensus documents (Kusamura et al., 2025; Kusamura et al., 2021). Kusamura et al. (2025) recommend preoperative laparoscopy performed by a surgeon with expertise in peritoneal surface malignancies (Recommendation 11.1; consensus 24/27) to accurately characterize PCI and disease resectability, thereby minimizing futile laparotomies in patients unlikely to achieve complete cytoreduction. The PSOGI multisocietal GRADE consensus (Kusamura et al., 2025) further refines eligibility by restricting CRS-HIPEC to patients with Ki-67 below 10% and PCI ≤17 alongside epithelioid histology and resectability to CC-0/1, reflecting the poor outcomes observed beyond these thresholds (Liang et al., 2025). Complementing preoperative stratification, conditional survival analysis provides a dynamic prognostic tool for post-treatment consultations: Liang et al. (2025) demonstrate that the probability of achieving 5-year survival rises from 27% at baseline to 51% conditional on surviving 2 years, 67% on surviving 3 years, and 84% on surviving 4 years post-surgery, while Valenzuela et al. (2023) identify the 1-year postoperative anniversary as a statistically significant prognostic milestone (p=0.007), after which conditional survival improves markedly from 39.0 to 58.4 months. The progressive flattening of survival curves beyond 5–6 years in multiple cohorts (Liang et al., 2025; Valenzuela et al., 2023) further supports the emerging concept that CRS-HIPEC may convert MPM from a uniformly fatal disease into an indolent condition in carefully selected patients, with Liang et al. (2025) explicitly concluding that clinical cure is achievable at the 5-year mark.

Centralization in high-volume expert centers, exemplified by RENAPE-designated institutions, emerges as indispensable for optimizing results, with 90-day postoperative mortality rates as low as 2.1% (Noiret et al., 2026) and substantial reductions in major morbidity (Noiret et al., 2026) through refined multidisciplinary protocols. Perioperative morbidity, while significant — including respiratory complications, hemorrhagic events, and abdominal infections (Acs et al., 2022; Liang et al., 2025; Noiret et al., 2026)— remains manageable in specialized settings, with Clavien-Dindo grade III-IV complication rates of 16.9–50.9% tempered by institutional experience and centralized multidisciplinary care (Acs et al., 2022; Deban et al., 2023; Noiret et al., 2026).

Notwithstanding these advances, persistent heterogeneity in HIPEC protocols (Acs et al., 2022; Deban et al., 2023; Kusamura et al., 2021; Valenzuela et al., 2023)—encompassing agents (platinum-based versus mitomycin C), temperatures, durations, and techniques—coupled with the absence of randomized controlled trials (Kusamura et al., 2025; Kusamura et al., 2021), constitutes a critical limitation, perpetuating variability across centers. Looking forward, prospective multicenter registries (Deban et al., 2023; Noiret et al., 2026), standardization of HIPEC regimens (Kusamura et al., 2021), and exploration of novel multimodal strategies, including neoadjuvant/adjuvant immunotherapy (Kusamura et al., 2025) and pressurized intraperitoneal aerosol chemotherapy (Kusamura et al., 2021; Noiret et al., 2026) for borderline or unresectable cases, promise to refine this paradigm, potentially extending benefits to broader MPM populations while upholding the curative benchmark set by CRS-HIPEC in expert hands.

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