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Review

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Peritoneal mesothelioma

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Abstract

This review provides an overview of articles about peritoneal mesothelioma (PM) to analyze the effect of treatment modalities on response rates, post-treatment side effects, morbidity and mortality, and survival. Median survival in months following systemic chemotherapy (SC) ranged from 8.7 to 26.8 months. However, no patient was reported to have survived for more than five years with SC alone. In contrast, comprehensive treatment that included cytoreductive surgery (CRS) + perioperative chemotherapy (POC) showed a significantly longer median survival time than SC alone. Additionally, CRS + POC demonstrated 10-year survival rates of 12%-35%. Accordingly, CRS + POC is an innovative treatment that provides long-term survival in selected patients with PM. Selection criteria are performance status (ECOG PS ≤ 1), the absence of extraperitoneal metastasis, PCI less than cutoff levels (from < 10 to < 28), MIB-1 index (< 10), and histologic type (epithelioid type). Postoperative morbidity and mortality rates after CRS + POC were significantly higher than with more conventional operations. Accordingly, CRS and POC should be done at the specialized peritoneal surface malignancy centers.

Keywords: Peritoneal mesothelioma, mesothelioma, intraperitoneal chemotherapy, HIPEC, peritonectomy

INTRODUCTION

Peritoneal mesothelioma (PM) is a rare peritoneal malignancy characterized by diffuse involvement of the peritoneal surface. It develops from mesothelial cells. Asbestos, talc, SV 40 virus, and chronic peritonitis are implicated as factors in the development of PM[1-3].

About 33%-50% of patients diagnosed with PM report known prior exposure to asbestos[4-7].

PM shows a lower male-to-female ratio and a lower mean age at death in comparison with pleural mesothelioma[5,6]. Age-standardized incidence rates generally range from 0.5 to 3 cases per million population[6], with a male-to-female ratio of 1.6:1[5]. The highest rates are reported in the UK, Australia, and New Zealand, with the lowest rate in Japan[7-9]. Now that asbestos usage has been banned by law, the number of PM deaths is expected to decrease[8].

Conventional classification comprises diffuse malignant peritoneal mesothelioma (DMPM), multicystic peritoneal mesothelioma (MCPM), and well-differentiate papillary peritoneal mesothelioma (WDPPM)[9]. MCPM has a low malignant potential with a favorable prognosis, and WDPPM shows less aggressive potential than DMPM, because it tends not to invade subperitoneal tissue and has weak proliferative activity[10].

In the past, DMPM has been regarded as a rapidly lethal disease because of its high capacity for invasion and lymph node metastasis. In addition, systemic chemotherapy (SC) has no effect on the long-term survival of patients with DMPM.

Recently, surgical treatment combined with hyperthermic intraperitoneal chemoperfusion (HIPEC) has emerged as a promising treatment that might improve survival and cure rates[11].

The purpose of this manuscript is to review both the efficacy of locoregional treatment for patients with DMPM and WDPPM using cytoreductive surgery (CRS) and HIPEC and the criteria for treatment selection by reviewing articles on more than 50 DMPM patients.

TREATMENT MODALITIES FOR PM

Several treatments have been reported, including SC, CRS, the combination of CRS plus perioperative chemotherapy (POC) including neoadjuvant systemic chemotherapy (NASC), neoadjuvant intraperitoneal/systemic chemotherapy (NIPS), laparoscopic neoadjuvant HIPEC, intraoperative HIPEC, early postoperative intraperitoneal chemotherapy (EPIC), and non-hyperthermic intraoperative chemotherapy (NIPEC)[10,12]. Among these treatments, CRS combined with POC is nominated as the most effective treatment to improve survival in DMPM patients with a low preoperative peritoneal cancer index (PCI) ≤ 19[10]. However, there have been no randomized phase III trials evaluating surgical treatment combined with POC in the past.

When the PCI is less than the threshold cutoff level determined by laparoscopy, positron emission tomography (PET), and/or computed tomography (CT), CRS should be performed after NASC or NIPS. However, chemotherapy is recommended in DMPM patients with PCI above cutoff levels or diffuse

involvement of the small bowel and its mesentery. The threshold level refers to the PCI cutoff count with a favorable prognosis. PCI cutoff levels were reported as less than 17 by Kusamura *et al.*[10].

In DMPM patients not amenable to surgery, SC is a standard treatment [Table 1][13-15]. Cartenni *et al.* reported the results of treatment using CDDP and pemetrexed versus pemetrexed alone[13,14]. Response rates and overall survival were significantly better in the CDDP plus pemetrexed group than those of the pemetrexed group alone. Simon *et al.* studied the effects of gemcitabine plus pemetrexed and found a superior response rate and survival to cisplatin with pemetrexed[15]. However, this protocol showed significantly more grade 3 and 4 adverse reactions, as well as one grade 5 reaction. Accordingly, the best regimen is proposed to be the combination of cisplatin and pemetrexed, with gemcitabine and pemetrexed as a second choice[13,15]. At present, a combination of cisplatin and pemetrexed is accepted as the standard first-line SC for DMPM. Median overall survival with these treatments ranges from 8.7 to 26.8 months[13-15], but with no survival for more than five years[13-16]. Recently, Sgarbura *et al.* started a phase II multicenter randomized trial to evaluate the effect of pressurized intraperitoneal aerosol chemotherapy and SC versus SC alone as first-line treatment for DMPM on survival[17]. However, the results have not been reported yet. In 2021, innovative treatment using nivolumab was reported by Fennel *et al.*[18]. They reported the results of a double-blind, randomized phase III trial of nivolumab for mesothelioma patients[18], including 316 (95.2%) patients with pleural mesotheliomas and 16 patients with non-pleural mesotheliomas, respectively. PD-L1 status was positive in 27% and 23% of patients in the nivolumab and placebo groups, respectively. The most frequently grade 3 or worse treatment-related adverse events were diarrhea in six (3%) of 221 in the nivolumab group versus two (2%) in the placebo group, and there were no treatment-related deaths in either group. The response rate in the nivolumab and placebo groups were 11% and 1%, respectively. Additionally, the median survival time (MST) of the treatment and placebo groups were 10.2 and 6.9 months, respectively, and overall survival in the nivolumab group was significantly better than in the placebo group (HR 0.69)[18]. However, only 16 of 332 malignant mesothelioma patients in the study by Fennel *et al.* had non-pleural mesothelioma, and the effects of nivolumab on non-pleural mesothelioma were not described[18]. Recently, several case reports about the effects of nivolumab on PM have been published[19]. However, the effects of nivolumab on PM are still unknown. Large studies of the effects of nivolumab on PM patients are awaited. The computed tomography (CT) scan in Figure 1 shows a large mass in the greater omentum of a patient with epithelioid-type PM before nivolumab treatment. After four cycles of nivolumab (240 mg/dose) infusion, a PR response was obtained. The residual subcutaneous tumor mass removed by surgical excision showed no evidence of tumor cells with necrosis. These results suggest that nivolumab may be effective in patients with DMPM. White *et al.* noted that PD-L1 expression is heterogeneous and that expression changes after chemotherapy[20]. Figure 2 shows PD-L1 expression in an epithelioid-type DMPM. PD-L1 is expressed on the cell membrane, but the expression is usually heterogeneous. This observation should be considered when initiating immune checkpoint inhibitor treatment of DMPM.

TREATMENT RATIONALE OF COMPREHENSIVE TREATMENT TO CURE PATIENTS WITH PERITONEAL METASTASIS

Neither surgery alone nor chemotherapy alone can cure patients with peritoneal surface malignancy (PSM). Patients with PSM treated with surgery alone will die due to the growth of residual micrometastasis on the peritoneal surface left even after complete resection of macroscopic metastasis[21]. After SC, multi-drug-resistant cancer cells always regrow. In addition, chemotherapy is negated by the development of severe side effects after several cycles. These two factors result in the treatment failure with chemotherapy.

Table 1. Treatment results of systemic chemotherapy for DMPM

Authors, years published	Study type	Eligibility	No of case	Regimen	Response rates	1-year survial	Median survival (months)	Side effects grade 3,4
Cartenni *et al.*, 2009[13]	Nonrandomized	DMPM	37	PEM + CDDP	0	1	NA	Neutropenia; 60%
	Open-label study	Not amenable to	34	PEM + CBDCA	0	NR	NA	Anemia 5%
		Curative surgery	38	PEM	0	0	13	Fatigue 10%, dehydration; 10%
Janne *et al.*, 2005[14]	Nonrandomized	DMPM	32	PEM + CDDP	0	1	13	Bone marrow; 0.1%-2.5%
	Open-label study	Not amenable to	66	PEM	0	0	9	Dehydration 7.25
		Curative surgery						Digestive tract: 3.8%-7.2%
Simon *et al.*, 2009[15]	Phase II	Not amenable to	20	GEM + PEM	0	1	27	Neutropenia; 60%
		Curative surgery						One patient; Grade 5
Le *et al.*, 2003[16]	Phase III	DMPM	62	Irrinitecan + CDDP	0	1	NR	No Grade 3,4 side effect
Sgarbura *et al.*, 2009[17]	Phase II	PCI > 27, small bowel PCI > 4	44	PIPAC + SC	UI	UI	UI	UI
			22	SC				
Fennell *et al.*, 2021[18]	Phase III randomized	Mesothelioma	221	Nivolumab	0	0	10	1%-3% (Grade 3)
		Pleural 318, non pleural 16	113	Placebo	0	0	7	0%-2% (Grade3)

DMPM: Diffuse malignant peritoneal mesothelioma; UI: under investigation; SC: systemic chemotherapy.

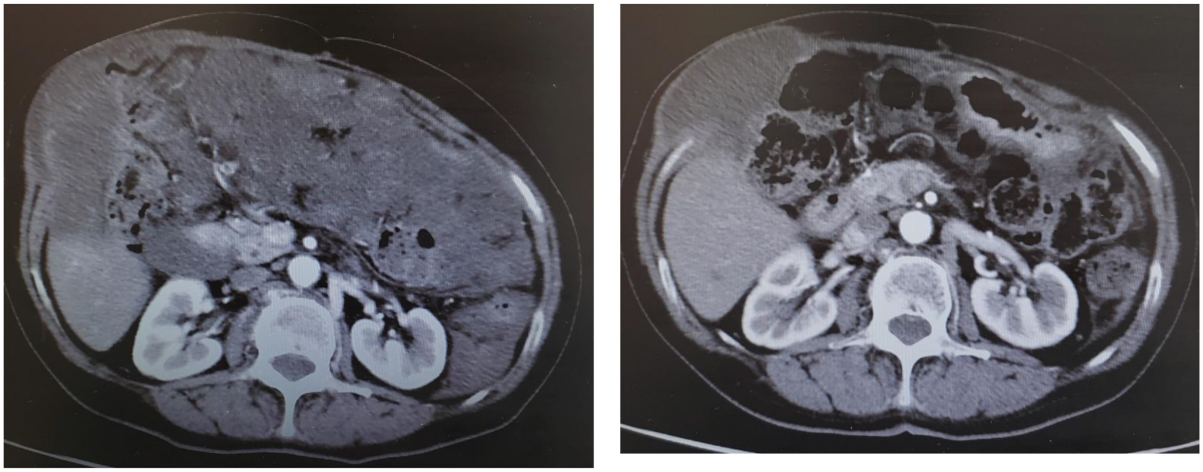

Figure 1. CT scan shows a big mass on the greater omentum before nivolumab treatment (left). After four cycles of nivolumab (240 mg/body) infusion, a PR response was obtained. The tumor mass removed by surgical excision showed no evidence of tumor cells.

In 2000, the Peritoneal Surface Oncology Group International (PSOGI) proposed comprehensive treatment with the potential to cure patients with PSM. Comprehensive treatment comprises complete resection of macroscopic tumors by CRS and elimination of micrometastasis left after CRS with POC. Treatment options used are different from disease to disease. In DMPM, six treatment options have been used: neoadjuvant chemotherapy (NASC, NIPS, and laparoscopic neoadjuvant HIPEC), CRS, intraoperative extensive intraperitoneal peritoneal lavage, intraoperative HIPEC, EPIC, and late postoperative

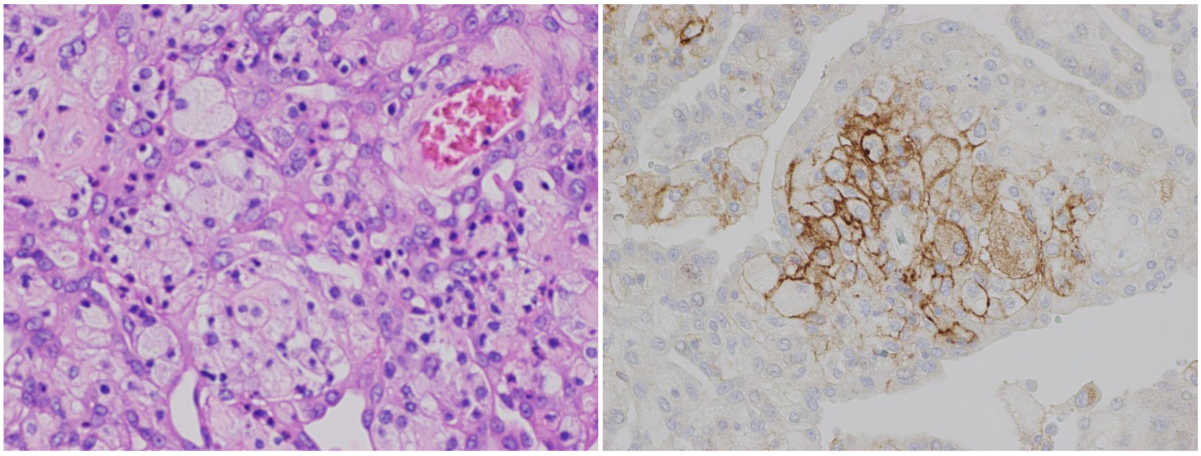

Figure 2. Hematoxylin-eosin staining of epithelial type of DMPM (left). PD-L1 immunostaining shows a strong reaction on the cell membrane, and the heterogeneity of positive cells was found (right).

chemotherapy [Figure 3][21]. Figure 4 shows the theoretical basis for cure using comprehensive treatment of PSM. In Courses A and B, NAC is not performed. NAC is done in Courses C and D. NAC can not only reduce macroscopic PM but also eliminate micrometastasis (MM) on the peritoneal surface remaining after CRS.

As shown in Course A of Figure 4, all patients will die after CRS + HIPEC due to the regrowth of MM, because the number of MM remaining after CRS exceeds the limit of complete eradication by intraoperative HIPEC, EPIC, and postoperative chemotherapy post-CRS chemotherapy (POCC).

With Course B [Figure 4], however, if the residual number of MM remaining after CRS is less than those that could be eliminated completely by POCC, patients will be cured.

With Course C, the residual MM burden remaining after CRS exceeds the threshold level that can be eliminated completely by POCC, and patients will die of recurrent disease. However, when NAC reduces the MM burden below the threshold level that can be completely eliminated by POCC, patients might be successfully treated by HIPEC. In contrast, if NAC fails to reduce this burden sufficiently, patients will die of recurrent disease [Figure 4, Course D].

As shown in Figure 3, the residual cancer cell burden is lowest immediately after CRS, and intraoperative HIPEC has a crucial role in curing patients with PSM. In trying to cure patients with PSM, our aim is to induce patients to follow Course B or C.

DIAGNOSIS OF DISEASE EXTENT AND THE DECISION MAKING FOR CRS

Treatment selection in patients with DMPM should be determined by the decisions of a multidisciplinary team[10]. The extent of disease should be diagnosed by positron emission tomography (PET) and CT[10]. PET is considered a promising tool with sensitivity, specificity, and accuracy of 86%, 89%, and 87%, respectively[22]. Laparoscopy has a crucial role in the precise diagnosis of PCI, histological diagnosis, and assessment of resectability. Laterza *et al.* reported that laparoscopic examination is an important tool in selecting patients for CRS[23], and the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 100%, 75%, 97%, 100%, and 97%, respectively.

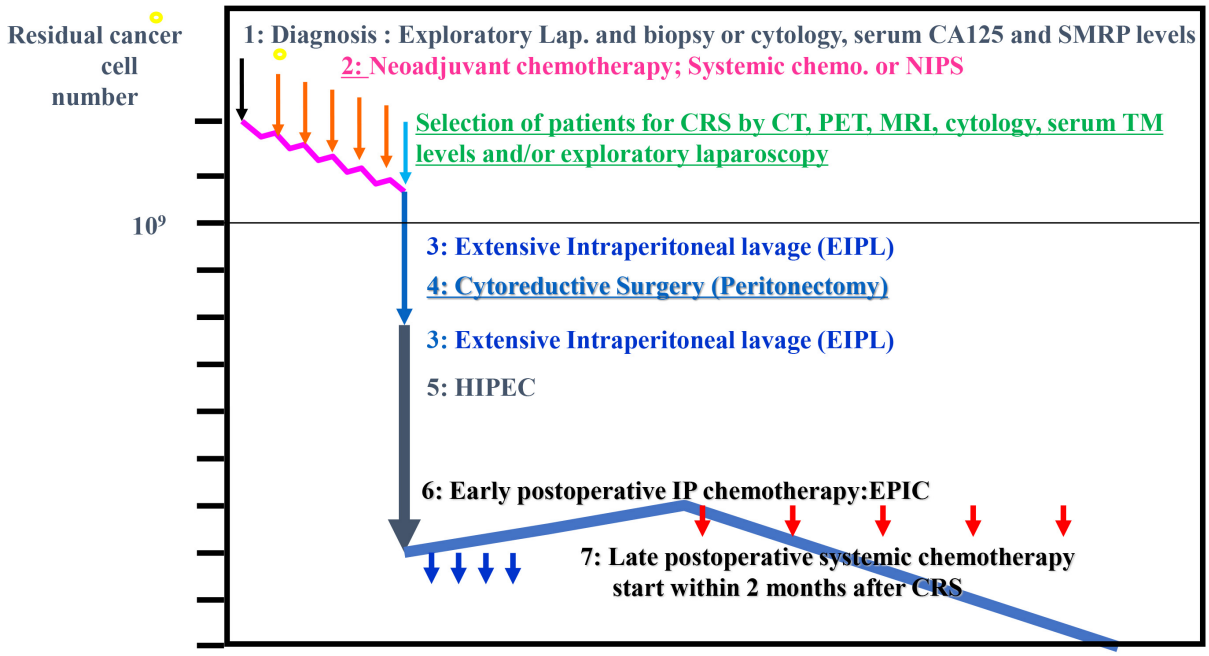

Figure 3. Treatment options for DMPM.

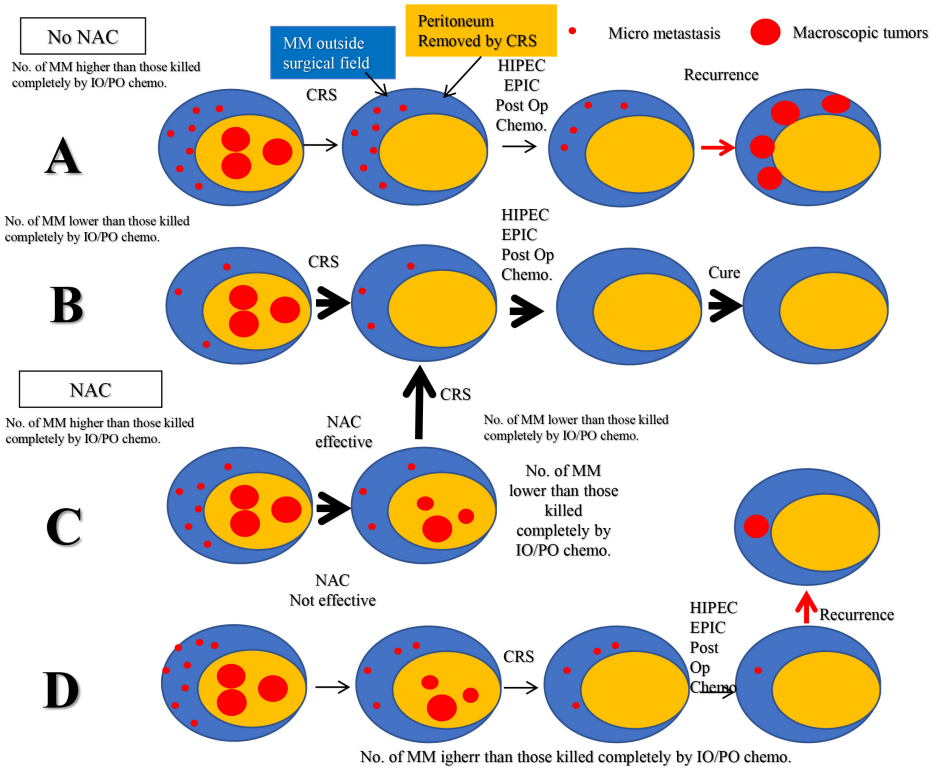

Figure 4. Rationale of cure by comprehensive treatment.

Baratti *et al.* evaluated the clinical utility of serum tumor marker levels[24]. The diagnostic sensitivity of CA125, CEA, CA19-9, and CA15-3 were 53%, 0%, 4%, and 49%, respectively. Postoperative serum CA125

levels within the normal ranges reflect complete cytoreduction[24]. Accordingly, serum CA125 levels could be an important selection criterion when used as a marker for the completeness of cytoreduction and recurrence [Figure 5].

Soluble mesothelin-related peptide (SMRP) is a circulating form of a 40 kDa glycoprotein, normally present on mesothelial cells[25]. Serum SMRP levels have sensitivity, specificity, and positive and negative predictive values of 70%, 100%, 100%, and 61%, respectively. Serum SMRP levels are useful not only for diagnosis of DMPM but also as a valuable assessment of response following drug therapy [Figure 5].

SURGICAL TREATMENT OF DMPM

The MST of DMPM patients who received no treatment was 16.2 months (2-52 months) with no five-year survival[26], and the prognosis of patients receiving palliative surgery or radiation alone was poor with MST of 1-2 months[27].

Additionally, the MST of DMPM patients treated with palliative SC ranged from 8.7 to 26.8 months[13-16,18], and no five-year survival was reported after SC.

In contrast, CRS + intraoperative HIPEC has been considered the preferred treatment in selected DMPM patients with low PCI, and their MST ranged from 23.4 to 66 months, with five-year survival rates of 28%-58% and 10-year survival rates of 12%-39%[10,28-34]. Multivariate analyses revealed PCI levels, CCR-0, an epithelioid histologic type, MIB-1 index < 10, absence of NASC, no grade 3 or 4 postoperative complications, age ≤ 60, and female sex as independent favorable prognostic factors[28-34][Table 2]. PCI cutoff levels for the selection criteria to achieve a better prognosis are reported to range from ≤ 12 to ≤ 28.

Histologic classification of DMPM consists of epithelioid, sarcomatoid, and biphasic variants. The epithelioid type shows a significantly more favorable prognosis than the biphasic and sarcomatoid variants. Sarcomatoid mesothelioma comprises 4% (15/248) of all DMPM[35], and the prognosis is very poor, with an MST of five months from diagnosis. Additionally, responses to chemotherapy are very poor, and organ invasion is common. Accordingly, this type of DMPM should be treated with systemic chemo-immunotherapy.

Complete cytoreduction (CCR-0) is a significantly better prognostic factor[10,28,30,31,34]. The rates of CCR-0 resection ranged from 37% to 60%, depending on the selection criteria for CRS. We experienced 84 DMPM and 8 WDPPM, and 68 (74%) patients underwent CRS. CCR-0 resection could be performed in only 25 (37%) patients. The main reasons for incomplete cytoreduction (CCR-1) resection were high PCI levels, diffuse involvement of the small bowel mesentery (high SB-PCI), and direct invasion of the diaphragm or abdominal muscle. SB-PCI levels of CCR-0 and CCR-1 were 2.9 ± 3.4 (range, 0-8) and 8.0 ± 4.2 (0-12) ($P < 0.0001$), respectively. Accordingly, reduction of PCI and SB-PCI by NAC is essential to increase CCR-0 resection rates, resulting in improved postoperative survival.

EFFECTS OF NASC, NEOADJUVANT LAPAROSCOPIC HIPEC, AND NIPS

Systemic chemotherapy, including pemetrexed + CDDP, gemcitabine + CDDP, or nivolumab therapy, showed a response rate of 11%-24%[13,18]. Currently, pemetrexed-based regimens are considered as the standard chemotherapy in DMPM patients[30]. However, Kepenekian *et al.* showed a significant survival disadvantage in patients treated with CRS + HIPEC after NASC, with five-year survival rates of 40%, 67%, 62%, and 56% for NASC, adjuvant chemotherapy, POC, and no chemotherapy before or after CRS + HIPEC, respectively[30]. They assumed that some NASC patients intrinsically have worse prognostic

Table 2. Results of no CRS and systemic chemotherapy[24], radiation and palliative surgery[25], and CRS + POC[26-32]

Authors + A22:I22	Study type	Eligibility, treatments	No of cases	Median survival (months)	Complications after CRS	1-year survival	5-, 10-year survival rate (-year)	Favorable prognostic factors
Kaya *et al.*[26]	Retrospective study	No CRS and SC	35	16.2 (2-52)		55	0%	Age ≤ 60 years old
	2005-2013			P				Asbestos exposure ≤ 20 years
								ECOG PS = 0-2
Salo *et al.*[27]	Retrospective study	Radiation/palliative surgery	46	1 to 2		100%	0%-14%	Not described
	2000-2012							
Sugarbaker *et al.*[28] + A26:J38	Retrospective study	Potentially curable	68	66	Grade 3,4:23.5%	83%	5- years: 50%	PCI ≤ 28, CCR-0-2,
	1989-2003	CRS + POC			Grade 5: 7%		10- years:35%	No metastasis
Baratti *et al.*[29]	Retrospective study	ECOG PS ≤ 2, age ≤ 75	108	63.2	Grade 3-5 38.9%	85%	5- years: 52.4%	Epithelial type, MIB1 index ≤ 10
	1996-2012	Potentially curable			Grade 5: 1.9%		10-years:44.6%	No LN meta.
		No extraperitoneal disease						
		CRS + POC (NAC, HIPEC)						
Kepenekian *et al.*[30]	Retrospective analysis	Age ≤ 80, ECOG PS ≤ 1	126	61	Grade 3,4: 39%	60%	5- years: 28%	PCI ≤ 30, CC-0,1,
	1991-2014	CRS + NAC + HIPEC			Grade 5: 3%		10- years: 14%	Absence of NAC
Alexander *et al.*[31]	Retrospective analysis	Potentially curable	211	38.4	Grade3,4: 30%		5- years: 41%	Age < 60, histologic grade: low
0	1992-2011	CRS + HIPEC			Grade 5: 2.3%		10- years: 26%	CCR0,1, HIPEC: CDDP *vs.* MMC
Helm *et al.*[32]	Review and meta-analysis	Mean PCI: 12-29	1047	29-92	Morbidity: 8%-90%	70%-87%	17%-49%	No relation with EPIC, PCI 19
		CRS + HIPEC			Mortality: 0%-8%			
Kusamura *et al.*[10]	PSOGI registration	Potential curable (PCI:14-29)	713	45		77.50%	5- years: 44.6%	Epitheloid, PCI-< 12, CC-0,1
	1981-2017	CRS + HIPEC						Postoperative complication: grade 0-2
Our experiences Yonemura *et al.*[33]	Retrospective analysis	Operable (PCI: 0-39)	68	23.4	Morbidity: 14.7%	57%	5- years: 29%	Female, PCI ≤ 26
		CRS plus or minus POC			Mortality: 2.9%		10- years: 12%	
Magge *et al.*[34]	Retrospective study	Potentially curable	65	46.20%		77%	5-years: 395	Age < 60, PCI < 15, CC-0,1, epitheloid
	2001-2010	CRS + HIPEC						

CRS: Cytoreductive surgery; POC: perioperative chemotherapy; HIPEC: hyperthermic intraperitoneal chemoperfusion; UI: under investigation; SC: systemic chemotherapy.

factors[30]. Naffouje *et al.* also reported that SC provided a short-term survival improvement at one year alone, without adding any survival benefit beyond this time point[36]. In contrast, Deraco *et al.* also studied the role of perioperative SC using pemetrexed and CDDP in 116 DMPM patients with an ECOG performance status of 0 and PCI < 20[37]. The patients were treated with CRS and HIPEC. They reported that there was no significant difference in terms of survival between groups with preoperative chemotherapy,

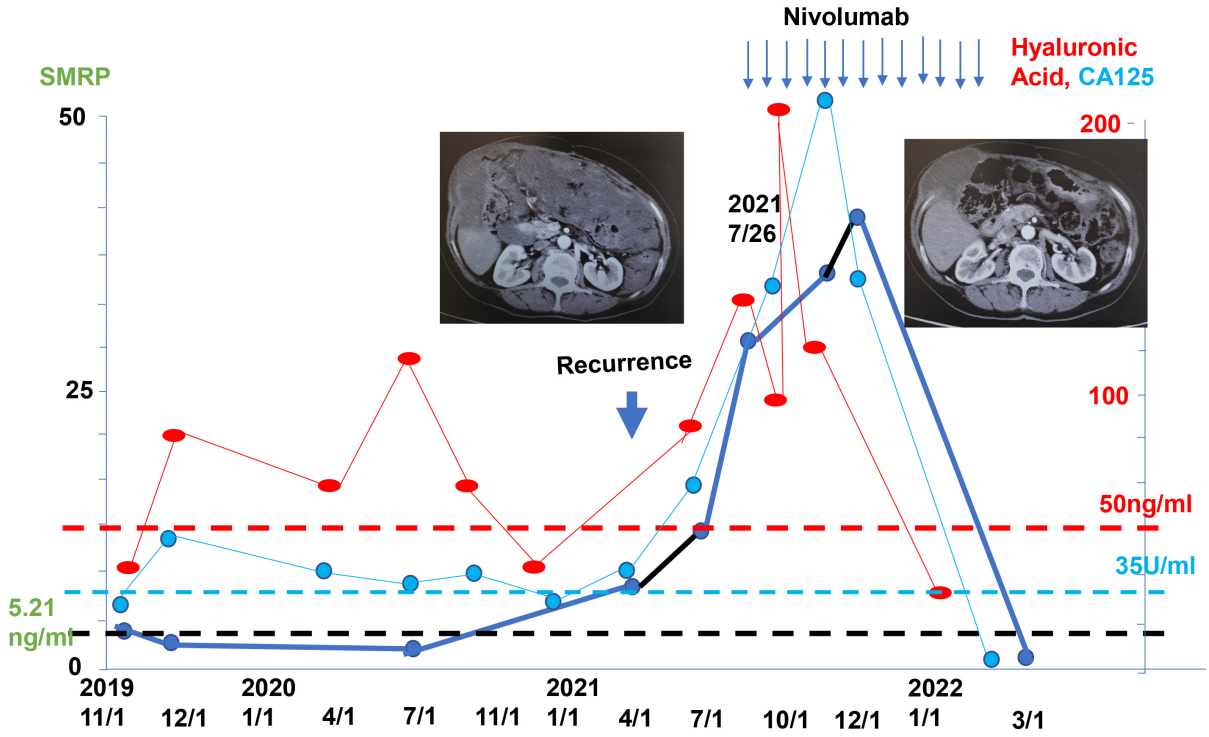

Figure 5. Serum CA125, hyaluronic acid, and SMRP levels during nivolumab treatment in a recurrent mesothelioma patient.

postoperative chemotherapy and no POC[37].

Kusamura *et al.* asserted that the benefit of NASC after CRS + HIPEC is uncertain[10]. To verify the role of NASC in DMPM patients, prospective randomized trials are mandatory.

CRS + HIPEC is now considered an effective treatment for DMPM patients[10] compared to SC alone. Hyperthermia over 43 °C induces irreversible changes in the three-dimensional structure of cellular protein, and 99% of cells can be killed after 60 min of hyperthermia at 43.5 °C[38].

In our experience of 12 DMPM patients treated with the same method, PCI changes were studied before and one month after laparoscopic HIPEC (LHIPEC). One cycle of LHIPEC reduced PCI from 21.1 ± 11.8 to 16.3 ± 13.1 (P = 0.033).

We treated three patients with WDPPM with LHIPEC alone. All three are alive 10, 3, and 4 years after LHIPEC. In WDPPM, mesothelioma cells grow diffusely on the peritoneal surface in a single layer with a low capacity to invade subperitoneal tissue. Accordingly, LHIPEC must be an effective method to treat WDPPM. However, precise histological examination of multiple sections from resected specimens of WDPPM may reveal subperitoneal invasion in localized peritoneal regions. In these cases, CRS is recommended[39].

NIPS is now considered as an effective treatment for PSM[21]. In NIPS, intraperitoneal administration of 40 mg of docetaxel and cisplatin with 500 mL of normal saline is performed on Days 1 and 14, and oral intake of 60 mg/m^2 of S1 is administered on Days 1-14[37]. After one week of rest (Days 15-21), NIPS is repeated for at least three cycles.

In our seven DMPM patients, NIPS reduced PCI from 28.1 ± 9.8 to 18.1 ± 7.4 (P = 0.008). EPIC has been used in DMPM patients to eliminate residual micrometastasis after CRS. Recently, Sugarbaker *et al*. studied the benefit of EPIC (NIPEC) on survival in 129 epithelioid DMPM patients after CRS, and the EPIC group showed significantly better survival than the other groups[12].

Locoregional adjuvant NIPEC could be proposed in DMPM patients submitted to CRS + HIPEC[10]. In our experiences, CCR-0 resection was performed in 31% (25/81)[33], and CCR-0 resection rates after no chemotherapy, NASC, and NIPS were 24% (5/21), 32% (9/28) and 34% (11/32), respectively.

The main reason for incomplete cytoreduction is diffuse involvement of the small bowel mesentery and serosal surface. Le Roy *et al*. reported that bidirectional chemotherapy using IP pemetrexed and IV cisplatin or carboplatin reduced PCI from 27 (range, 15-39) before bidirectional chemotherapy to 14 (range, 15-30)[40]. NASC usually does not achieve sufficient downstaging to convert patients to resectability, but bidirectional chemotherapy and NIPS + neoadjuvant LHIPEC could significantly reduce PCI on the small bowel mesentery, resulting in an increased rate of CCR-0 rate.

CRS + HIPEC has emerged as the preferred initial treatment in selected DMPM patients, but CRS + HIPEC carries a significant rate of grade 3/4 morbidity and mortality that range from 8% to 90% and from 1.9% to 8%, respectively [Table 2]. Accordingly, CRS + HIPEC should be performed with a strict selection of patients by performance status, PCI levels, histologic subtype, and age [Table 2] and be confined to specialized PSM centers.

FUTURE PERSPECTIVES

The data and results described above are from retrospective analyses. However, the efficacies of NASC, NIPS, and postoperative chemotherapy on safety and survival after CRS + HIPEC have not been clarified. The roles of these options should be verified by randomized clinical trials. Recent innovative treatment modalities such as immunotherapy may constitute a breakthrough in improving the survival of DMPM patients.

Additionally, we await the development of new molecular targeted drugs that focus on the target gene products specific for DMPM.

CONCLUSION

Based on articles on more than 50 DMPM patients, this review analyzed the efficiencies of treatment modalities on response rates, post-treatment side effects, morbidity and mortality, and survival. MST with SC using pemetrexed and cisplatin/gemcitabine ranged from 8.7% to 26.8%. However, no long-term survivors were reported after SC alone.

In contrast, comprehensive treatment combined with CRS + POC showed significantly longer MST than SC alone. In addition, CRS + POC demonstrated 10-year survivals of 12%-35%. Accordingly, CRS + POC is an innovative treatment that can cure selected DMPM patients. Selection criteria include performance status (ECOG PS ≤ 1), no extraperitoneal metastasis, PCI below cutoff levels, and histologic type (epithelioid type). However, after CRS, postoperative morbidity and mortality rates were significantly higher than with the more usual operations. Therefore, CRS and POC should be performed in specialized PSM centers.

DECLARATIONS

Authors' contributions

Writing: Yonemura Y
Conceptualization: Ishibashi H, Mizumoto A, Fujita T
Format anlaysis: Liu Y, Wakama S
Data analysis: Sako S, Takao N, Kitai T, Katayama K, Kamada Y Taniguchi K, Fujimoto D
All authors have read and agreed to the published version of the manuscript.

Availability of data and materials

No applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there is no conflict of interest.

Ethical approval and consent to participate

The study was approved by the ethical committee of Kishiwada Tokushukai hospital, the protocol; code of 19-35, that title is "A study of comprehensive treatment for peritoneal metastasis". It was approved on 15 Onctober 2007.

Consent for publication

Not applicable.

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