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Well differentiated papillary peritoneal mesothelioma treated by cytoreduction and hyperthermic intraperitoneal chemotherapy-the experience of the PSOGI registry

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ABSTRACT

Background: Well differentiated papillary peritoneal mesothelioma (WDPPM) is a rare variant of mesothelioma which affects mainly women in the reproductive age. The disease may present multifocally and recur after primary resection. Our aim was to describe the outcomes of cytoreduction (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in this disease.

Methods: Patients with histological diagnosis of WDPPM were retrieved from the PSOGI registry. Demographical and clinical data were extracted as well as outcomes data (overall survival (OS) and recurrence free survival (RFS)).

Results: We analyzed 45 patients for whom complete data was available. The majority of patients were women (n = 33, 73%) with a median age of 44 years. Preoperative chemotherapy (CT) was administered in 8 patients (18%). Median peritoneal carcinomatosis index was 9 (1–30), and complete cytoreduction was achieved in 69% of patients. There was one case (2%) of postoperative mortality, and 24% rate of severe morbidity.

Overall, there were 4 deaths and 5 years OS was 80%. 8 patients (18%) had disease recurrence, all within 5 years from operation. On univariate analysis preoperative CT, high PCI and severe morbidity were associated with reduced RFS. On multivariate analysis, only preoperative CT (HR = 32.6, 95% CI: 2.39–446.2, p = 0.009) and high PCI (HR = 21.7, 95% CI: 1.11–425.7, p = 0.04) remained significant risk factors.

Conclusions: WDPPM can be a lethal disease with substantial recurrence even after aggressive treatment. Patients presenting with extensive disease or disease recurrence after surgical excision are at increased risk for relapse. CRS + HIPEC can be safely applied to WDPPM in specialized centers.

Introduction

Well differentiated papillary peritoneal mesothelioma (WDPPM) is a rare, distinct tumor of mesothelial origin, with papillary architecture, bland cytological features, and a tendency towards superficial spread without invasion [1]. Clinical presentation of WDPPM is variable and can be incidental in unifocal asymptomatic disease or present symptomatically (abdominal fullness and pain) with advanced multifocal disease [2]. Whereas the presentation of incidental finding is more common in young women, the symptomatic presentation tends to occur in older women [3]. WDPPM is apparently unrelated to asbestos, and it may

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arise in the pleura or tunica vaginalis [4,5]. Although histological findings are consistent with a benign lesion, i.e. papillary projections of mesothelial-cuboidal cells without atypia or mitoses and absence of invasion to other organs [3], the disease tend to recur and several cases of malignant transformation to DMPM were also described [6,7].

Treatment is not standardized, and includes observation alone, systemic chemotherapy and excisional biopsy [2,3,7]. As the disease may recur after simple excision and may have multifocal presentation, the modality of cytoreduction (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) was also suggested as a treatment option [3,6]. Based on the success of CRS + HIPEC in DMPM [8], it was assumed that this modality may decrease disease recurrence. However, due to its rarity, current literature on outcomes of CRS + HIPEC in WDPPM is scarce and limited to small numbers. Our aim in this study was to describe the outcomes of WDPPM patients treated by CRS + HIPEC according to the Peritoneal Surface Oncology Group International (PSOGI) registry. As this experience comes from centers established in CRS + HIPEC, tuned for long term follow up of patients, we believe it can shed some light on disease course and management options.

Patients and methods

Patients

Patients in this cohort are part of the PSOGI registry. Participating institutions in this cohort were from North America (n = 1), Australia (n = 1) and Europe (n = 12). Patients were treated between May 1997 and January 2014. Inclusion criteria were histologically confirmed WDPPM, patients deemed medically fit for CRS + HIPEC, and surgical resectability as assessed by pre-operative evaluation. Overall, 56 patients with histological diagnosis of WDPPM were identified in the registry; however details on surgical treatment and follow-up were present only for 45 of them.

Operative treatment

The generic surgical approach involves peritonectomy procedures and visceral resections called CRS as described by Sugarbaker [9]. Hyperthermic intraperitoneal chemotherapy (HIPEC) was administered at the completion of cytoreduction using an open coliseum (n = 22) or closed (n = 15) technique depending on the individual unit's preference. The chemoperfusate heated to achieve a temperature ranging between 40 °C and 42 °C and administered between 60 and 90 min. Most of the patients (n = 27) were treated with cisplatin based doublets [8], of which 10 received cisplatin and doxorubicin [6]. Oxaliplatin based treatment alone was given to 4 patients or combined with irinotecan (n = 6) [10]. Early postoperative intraperitoneal chemotherapy (EPIC) was given in only one patient. The peritoneal cancer index (PCI) was determined intraoperatively and comprised a score of 0–3 in 13 abdominopelvic regions to a computed index ranging from 1 to 39. Residual disease following CRS was scored according to the completeness of cytoreduction (CCR) score. CCR0 indicates that no macroscopic residual cancer remained; CCR1 indicates that no nodule larger than 2.5 mm in diameter remained; CCR2 indicates that nodules between 2.5 mm and 2.5 cm in diameter remained; and CCR3 indicates that nodules larger than 2.5 cm in diameter remained [11]. Major complications were scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCICTCAE), version 3.0, and 30 days postoperative mortality was also recorded.

Table 1
Patient and treatment characteristics.

	median (IQR)
Age (years)	44 (33–54)
Female/male	33/12 (73%/27%)
Operation time (min)	457 (333.2–558)
PCI	9 (5–16)
CCR (0/1)	31/13 (69%/29%)
Length of stay (days)	16 (13–24)

Statistical analysis

Descriptive statistics for normally distributed parameters was done using mean and standard deviation (S.D.), whereas median and range were used for non-normally distributed parameters. Overall survival (OS) was defined as the time from CRS + HIPEC to death. Recurrence free survival (RFS) was

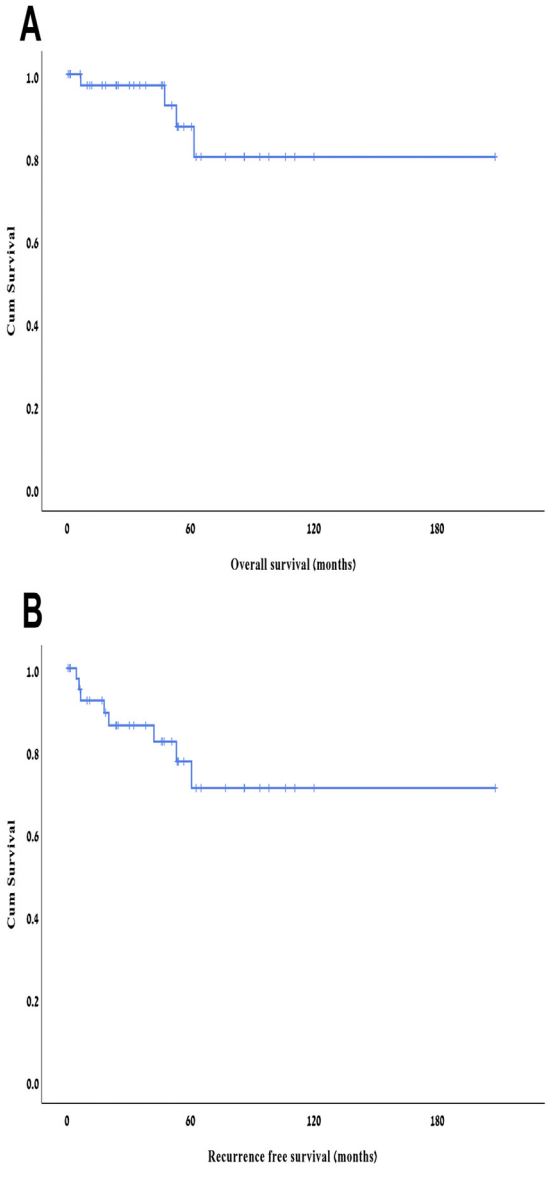

Fig. 1. Whole cohort outcome for patients with WDPPM. A. Overall survival. B. Recurrence free survival.

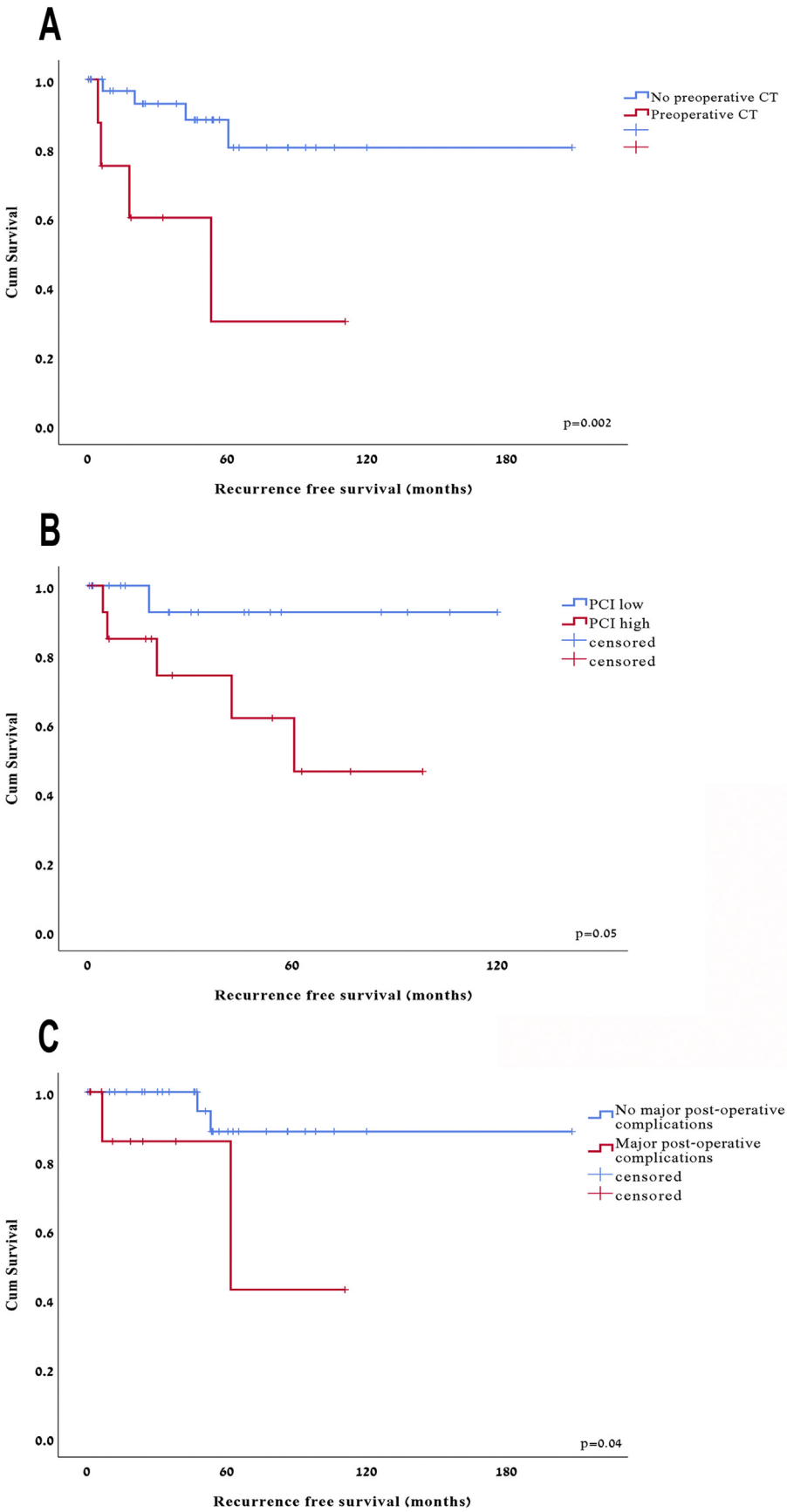

Fig. 2. Risk factors associated with worse prognosis. A. Preoperative chemotherapy (CT) (p=0.002). B. High PCI (defined as PCI>9) (p=0.05) C. Severe postoperative complications (as defined by NCICTCAE v3) (p=0.04)

Table 2
Multivariate analysis of factors associated with reduced RFS.

	univariate analysis	multivariate analysis		
	p	HR	95% CI	p
Preoperative CT	0.02	32.6	2.39–446.2	0.009
CCR	0.4	1.05	0.13–8.41	0.96
High PCI	0.05	21.7	1.11–425.7	0.04
Severe postoperative morbidity	0.04	0.48	0.34–6.36	0.56

defined as the period from the day of CRS + HIPEC to recurrence. OS and RFS were calculated according to the Kaplan-Meier method, patients without death or recurrence were censored at the time of the last follow up visit. Inter-group difference for RFS was calculated using the log-rank test. Multivariate analysis was done according to the Cox proportional hazards regression model. All statistical analyses were performed using SPSS for Windows version 25 (SPSS, Munich, Germany). $p < 0.05$ was considered significant.

Results

Patients and treatment characteristics

Table 1 describes various characteristics of the 45 patients which constitute this cohort. As can be seen, the majority of patients were women (n = 33, 73%) and median age is 44 years as also described in the previous series outlined above. Serum levels of CEA and CA19-9 were normal, whereas CA-125 was elevated in 3 patients (7%). Preoperative chemotherapy (CT) was given to 8 patients (18%), whereas postoperative CT was given to two patients (4.5%). Median PCI (9, IQR: 5–16) and operative times are consistent with multifocal disease. Post operatively, major complications rate was 24% (n = 11), and post-operative mortality was recorded in one case (2%).

Long term outcomes

Outcomes were analyzed for 44 patients, excluding the patient who died post-operatively. Median follow up was 46 months (4–220). Overall, there were 4 deaths and OS is presented in Fig. 1 A. 5 years OS was 80%. RFS of the whole cohort is presented in Fig. 1 B. 8 patients (18%) had disease recurrence, all within 5 years from CRS + HIPEC. For the 4 patients with recurrences and no death, follow up was 29.5, 7.5, 10 and 1 months after recurrence.

Risk factors associated with disease recurrence

We analyzed several risk factors for disease recurrence. Both preoperative CT (mean RFS = 53.2 ± 17.8 for preoperative CT vs. 175 ± 15.6 months for no treatment, $p = 0.002$) and high PCI (determined according to median PCI = 9) (median RFS = 62.9 ± 11.6 for high PCI vs. 112.2 ± 7.5 months for low, $p = 0.05$) were associated with worse prognosis, as shown in Fig. 2 A and B. Preoperative CT was also associated with significantly reduced OS (mean RFS = 70.5 ± 16.5 vs. 188.3 ± 13.7, $p = 0.03$). In addition, major post-operative complications were also associated with reduced RFS (mean RFS = 75 ± 18.2 vs. 190.1 ± 12 months for no major post-operative complications, $p = 0.04$) (Fig. 2 C). Complete cytoreduction (CCR = 0) showed strong, albeit not significant, tendency to improved prognosis (188.8 ± 13.3 vs. 96.8 ± 13.2, $p = 0.4$). Same is true for complete parietal peritonectomy for which no recurrence was recorded (n = 9, $p = 0.14$). On multivariate analysis, described in Table 2, only preoperative CT and high PCI retained their significant association with RFS.

Discussion

Our series is the largest series to report outcomes of CRS + HIPEC in WDDPM, and in fact, also to report long term outcomes in general in this rare entity. Our data show that although considered clinically indolent, WDPPM caused mortality in 4 patients, even when treated aggressively with CRS + HIPEC. This contrasts with previous reports applying less aggressive modalities and even observation alone [2,3] and point to the heterogeneity of this disease. The clinical dilemma is how to stratify patients to treatment according to disease risk. Clearly, a multifocal presentation can represent aggressive biology in comparison to a unifocal one. We evaluated PCI as a measure of disease extent, and indeed patient with high PCI had shorter RFS. Patients with PCI<4 (n = 4), which correspond to unifocal presentation, had no recurrence after CRS + HIPEC, but the results were not significant ($p = 0.56$) due to the small patient number. Indeed the majority of patients in our cohort had multifocal disease (91%), and this stand in contrast to other series which had about 50% [3,7,12]. Preoperative CT was the single most important risk factor for reduced RFS in our series, as demonstrated by the multivariate analysis. Although the criteria for preoperative CT are not clearly defined in the registry, we suppose that these patients are those with recurrence after previous surgery, or patients progressing after initiation of chemotherapy as part of a non-surgical management. Clearly, these both groups represent more aggressive disease biology.

Another factor univariably associated with RFS was major post-operative complications, although this factor lost its significant in the multivariate analysis.

We previously reported the use of complete peritonectomy in DMPM [13] and we further adopted this approach for other primary neoplasia of the mesothelium, such as multicystic peritoneal mesothelioma [14]. In WDPPM, complete peritonectomy showed a strong tendency for improved outcomes, as no patient recurred.

An important issue in the management of WDPPM is diagnostic accuracy. The differentiation between DMPM and WDPPM may be challenging when based solely on morphological criteria. Thus cases with aggressive biology may actually represent cases of DMPM. On the other hand, cases with DMPM may be initially diagnosed as WDPPM and undertreated, when excisional biopsy or observation are applied. New molecular targets were suggested for the discrimination between the two entities, such as BAP1 [7,15,16] and mutations in TRAF7 and CDC42 [17]. However data is either contradictory, or validated only in a small patient cohort. Thus at present correct WDPPM diagnosis resides on pathological expertise. Fortunately, institutions that contributed patients to the registry treat DMPM patients on a regular basis, and pathologists are supposedly acquainted with the distinction between the entities.

This study has several limitations. First, as an international registry, data completeness differs between different institutions, and was a limiting factor in the selection of patients for the analysis. Diversity also existed in different protocols of preoperative CT and HIPEC. In addition, no comparison between CRS + HIPEC to other

treatment modalities was made, and may be even impractical in this rare entity. However, the relative low severe morbidity rate achieved in specialized centers may encourage the use of CRS + HIPEC in cases in which high recurrence rate is expected, such as in cases with multifocal presentation and recurrence after primary excisional surgery.

To conclude, our data show that WDPPM can be an aggressive and fatal disease. Extensive disease and recurrence after previous surgery may indicate unfavorable disease biology and outcomes. CRS + HIPEC can be safely applied in experienced centers. Future studies should be conducted to better select patients for this procedure.

Declarations of interest

None.

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