research article

Long-term outcomes following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for pseudomyxoma peritonei: a 15-year national referral centre experience

Rok Petric[1,2], Gasper Pilko[1,2]

[1] Department for Abdominal Surgical Oncology, Institute of Oncology Ljubljana, Ljubljana, Slovenia
[2] Medical Faculty, University of Ljubljana, Ljubljana, Slovenia

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Correspondence to: Assist. Prof. Rok Petrič, M.D., Ph.D., Department for Abdominal Surgical Oncology, Institute of Oncology Ljubljana, Zaloška 2, SI-1000 Ljubljana, Slovenia. E-mail: rpetric@onko-i.si

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Background. Pseudomyxoma peritonei (PMP) is a rare peritoneal malignancy most commonly originating from appendiceal mucinous neoplasms. Cytoreductive surgery (CRS) combined with has become the standard treatment for selected patients; however, evidence is largely based on retrospective single-centre series. We report the 15-year experience of the Slovenian National Referral Centre and evaluate long-term survival and prognostic factors following CRS and hyperthermic intraperitoneal chemotherapy (HIPEC).

Patients and methods. This retrospective study included all consecutive patients who underwent CRS and HIPEC for PMP between 2009 and 2024. Clinical, pathological, operative and follow-up data were prospectively collected and retrospectively analysed. Overall survival (OS) was the primary endpoint, while disease-free survival (DFS), postoperative morbidity and prognostic factors were secondary endpoints. Survival was analysed using the Kaplan-Meier method. Prognostic factors were evaluated using univariate and multivariate Cox regression analyses.

Results. Thirty-seven patients underwent CRS and HIPEC during the study period. The mean Peritoneal Cancer Index (PCI) was 17.2, and complete cytoreduction (CC-0/1) was achieved in 34 patients (91.9%). Major postoperative complications (Clavien-Dindo grade III–IV) occurred in seven patients (18.9%), while no 30-day postoperative mortality was observed. After a median follow-up of 68 months, the estimated 5-year and 10-year overall survival rates were 91.9% and 83.7%, respectively. Patients with a PCI ≤12 demonstrated significantly better overall survival than those with a PCI > 12 (log-rank $p = 0.028$). Multivariable analysis identified achievement of complete cytoreduction (CC-0/1) and elevated preoperative Carbohydrate Antigen 19-9 (CA19-9) as independent prognostic factors for overall survival.

Conclusions. CRS combined with HIPEC provides excellent long-term oncological outcomes with acceptable morbidity for patients with PMP when performed in a specialized national referral centre. Complete cytoreduction remains the principal determinant of survival, while preoperative CA19-9 provides additional prognostic information. These findings support continued centralization of PMP treatment for this rare disease.

Key words: pseudomyxoma peritonei; cytoreductive surgery; HIPEC; peritoneal cancer index

Introduction

Pseudomyxoma peritonei (PMP) is a rare clinical syndrome characterized by the progressive accumulation of mucinous ascites and disseminated mucin-producing epithelial implants throughout the peritoneal cavity.[1,2] In the vast majority of cases, PMP originates from a perforated appendiceal

mucinous neoplasm, whereas ovarian involvement most commonly represents secondary disease rather than a primary ovarian malignancy.[3,4] The estimated annual incidence ranges from 1 to 3.2 cases per million population, making PMP one of the rarest abdominal malignancies.[3,4-6]

The biological behaviour of PMP differs substantially from that of other gastrointestinal malignancies. Rather than developing distant metastases, the disease progresses predominantly within the peritoneal cavity, resulting in progressive mucin accumulation, intestinal compression, malnutrition and, ultimately, intestinal failure if left untreated.[1] Historically, treatment consisted of repeated debulking procedures aimed primarily at symptom relief. Although temporary improvement could often be achieved, repeated incomplete resections rarely altered the natural history of the disease, and long-term survival remained poor.[7]

The introduction of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has fundamentally changed the management of PMP.[8] CRS aims to achieve complete macroscopic tumour removal through peritonectomy procedures and visceral resections when required, while HIPEC targets microscopic residual disease by combining the cytotoxic effects of intraperitoneal chemotherapy with hyperthermia.[9] This multimodal approach has consistently demonstrated superior long-term survival compared with historical treatment strategies and is currently considered the standard of care for appropriately selected patients.[7]

Despite the widespread acceptance of CRS and HIPEC, the available evidence remains limited by the rarity of the disease. Most published data originate from retrospective single-centre series[10-13], while randomized controlled trials are lacking. Observational studies and multicentric registry have shown significant improvements in survival and disease control.[14-15] Consequently, current international recommendations are largely based on observational studies, registry data and expert consensus.[16] Furthermore, reports from smaller countries with centralized national referral programmes remain scarce.

Slovenia, with a population of approximately two million inhabitants, established a national referral programme for CRS and HIPEC in 2009. Since then, all patients considered candidates for surgical treatment of PMP have been evaluated and managed at a single specialized centre by a dedicated multidisciplinary team. This organization provides a unique opportunity to evaluate long-term outcomes of a nationwide programme for a rare disease within a standardized treatment pathway.

The aim of the present study was to evaluate the long-term outcomes of the Slovenian national CRS and HIPEC programme for pseudomyxoma peritonei, with particular emphasis on overall survival, disease-free survival, perioperative outcomes and prognostic factors associated with survival.

Patients and methods

Study design and patient selection

This retrospective cohort study included all consecutive patients who underwent CRS and HIPEC for pseudomyxoma peritonei (PMP) at the Slovenian National Referral Centre between January 2009 and December 2024. Clinical, pathological, operative and follow-up data were prospectively collected in an institutional database and retrospectively analysed.

Patients with low-grade appendiceal mucinous neoplasm (LAMN), high-grade appendiceal mucinous neoplasm (HAMN) and ovarian mucinous borderline tumours associated with PMP were eligible for inclusion. Patients with appendiceal adenocarcinoma, including tumours with signet ring cell differentiation or goblet cell adenocarcinoma, colorectal adenocarcinoma and primary ovarian carcinoma were excluded, as these entities differ substantially in biological behaviour and treatment strategy and were analysed separately. The cohort of patients with cytoreductive surgery and HIPEC for colorectal metastases was subject of different study.[17]

All patients underwent standardized preoperative evaluation including contrast-enhanced thoracoabdominal computed tomography (CT) and contrast-enhanced abdominal magnetic resonance imaging (MRI). Pathohistological confirmation was obtained either by image-guided core needle biopsy or diagnostic laparoscopy when previous pathology report was unavailable. All cases were reviewed at a dedicated multidisciplinary team meeting, where treatment eligibility was determined. The Prior Surgical Score (PSS) and radiological Peritoneal Cancer Index (PCI) were assessed preoperatively. The PSS was used to quantify the extent of previous abdominal surgery before cytoreductive surgery. Patients were classified as PSS-0 (no prior surgery or biopsy only), PSS-1 (surgery in one abdominal region), PSS-2 (surgery in two to five abdominal regions), or PSS-3 (sur-

gery involving more than five abdominal regions). Higher PSS values indicate more extensive previous surgical intervention and have been associated with less favourable oncological outcomes.[18]

The study was approved by the Institutional Review Board and Ethics Committee of the Institute of Oncology Ljubljana.

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)

All procedures were performed through a midline laparotomy extending from the xiphoid process to the pubic symphysis. Following abdominal exploration, the PCI was determined according to the classification described by Sugarbaker.[19] Cytoreductive surgery was performed according to Sugarbaker's technique[20] and consisted of peritonectomy procedures combined with visceral resections whenever tumour involvement was present, with the objective of achieving complete cytoreduction. Diaphragmatic peritonectomy was performed when required, followed by routine placement of an ipsilateral chest drain. Gastrointestinal reconstruction and stoma formation, when indicated, were completed before HIPEC.

The completeness of cytoreduction was assessed using the Completeness of Cytoreduction (CC) score. CC-0 indicated no visible residual disease, CC-1 residual tumour nodules measuring ≤ 2.5 mm, CC-2 residual nodules measuring > 2.5 mm and ≤ 2.5 cm, and CC-3 residual tumour deposits > 2.5 cm. Complete cytoreduction was defined as achievement of CC-0 or CC-1.[19]

Following CRS, all patients underwent HIPEC using the closed-abdomen technique. Six catheters were placed within the peritoneal cavity (three inflow and three outflow), after which the abdominal wall was closed. Prior to chemotherapy administration, the circuit was tested for leakage using 1.5% glucose solution. The target intraperitoneal temperature was maintained between 42°C and 43°C throughout the 90-minute perfusion.

The HIPEC regimen depended on tumour histology. Patients with LAMN received intraperitoneal mitomycin C (15 mg/m²) and doxorubicin (15 mg/m²), together with intravenous 5-fluorouracil (400 mg/m²). Patients with HAMN received high-dose mitomycin C according to the Dutch protocol (17.5 mg/m² followed by two additional doses of 8.8 mg/m²). Patients with ovarian mucinous borderline tumours received intraperitoneal cisplatin (50 mg/m²) and doxorubicin (15 mg/m²).

Follow-up and outcome measures

Patients were followed according to institutional surveillance protocols with regular clinical assessment, serum tumour markers and cross-sectional imaging. Overall survival (OS) was defined as the interval between CRS-HIPEC and death from any cause or last follow-up. Disease-free survival (DFS) was defined as the interval between CRS-HIPEC and radiological or histological evidence of disease recurrence.

Postoperative complications were graded according to the Clavien-Dindo classification. Major postoperative complications were defined as grade III or higher.[21] Thirty-day postoperative mortality was recorded for all patients.

Statistical analysis

Overall survival was used as the primary endpoint of this study. For categorical variables, the chi-square and Fisher's exact test were used as appropriate. Survival analysis was performed using the Kaplan-Meier method, and compared using the log-rank test. Multivariate analyses using Cox-regression models were performed in order to identify independent prognostic factors of survival. A p-value of less than 0.05 was considered statistically significant and the analysis was performed using IBM SPSS Statistics version 20 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Between January 2009 and December 2024, 37 consecutive patients underwent CRS and HIPEC for PMP at the Slovenian National Referral Centre. Baseline demographic and clinicopathological characteristics are summarized in Table 1.

The cohort comprised 28 women (75.7%) and 9 men (24.3%), with a mean age of 55 years (range, 30–78 years). Histopathological examination LAMN in 32 patients (86.5%), high-grade appendiceal mucinous neoplasm (HAMN) in 2 patients (5.4%), and ovarian mucinous borderline tumour in 3 patients (8.1%).

Before referral, 10 patients (27.0%) had undergone biopsy only (PSS 0), while 14 (37.8%), 8 (21.6%) and 5 patients (13.5%) had PSS scores of 1, 2 and 3, respectively. The mean intraoperative PCI was 17.2 (range, 1–39).

Operative outcomes

Complete cytoreduction (CC-0/1) was achieved in 34 patients (91.9%), whereas three patients (8.1%) underwent incomplete cytoreduction (CC-2). No patient had residual disease classified as CC-3.

Diaphragmatic peritonectomy was required in 26 patients (70.3%). All patients subsequently underwent HIPEC according to the institutional protocol. Repeat CRS and HIPEC for recurrent disease was performed in seven patients during follow-up. At the data cut-off three of these patients had died, two were alive with recurrent disease, and two were alive without evidence of disease.

Postoperative outcomes

The median length of hospital stay was 18 days (range, 8–112 days).

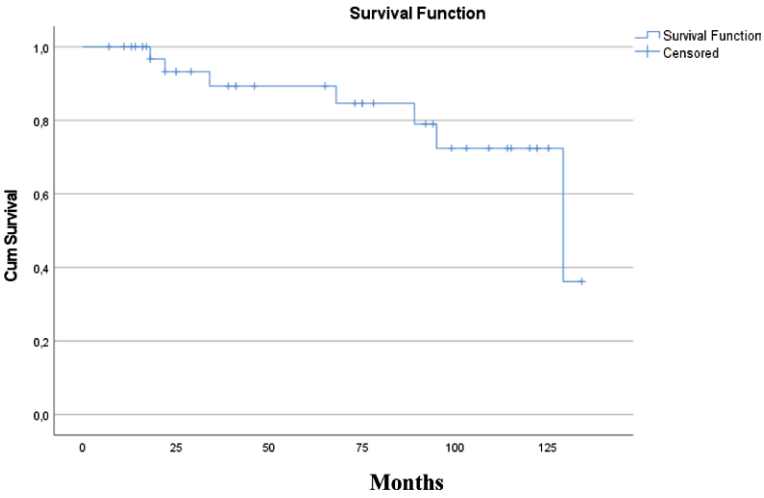


FIGURE 1. Kaplan- Meier curve: overall survival (OS) in presented patient cohort

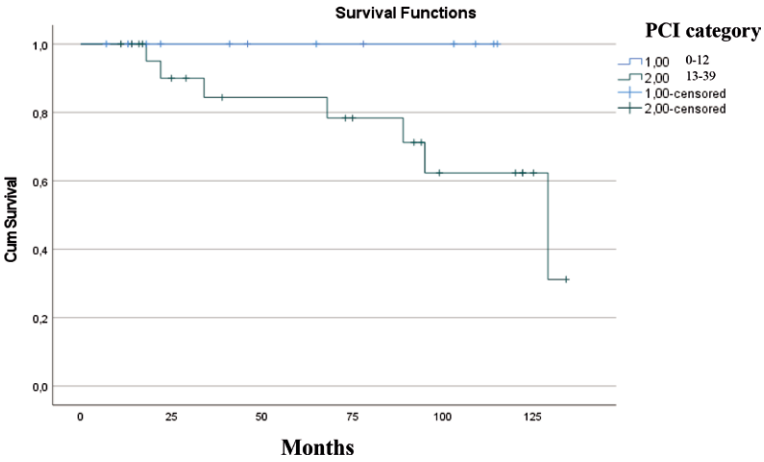


FIGURE 2. Kaplan-Meier curves: overall survival (OS) according to Peritoneal Cancer Index (PCI) score category

TABLE 1. Clinical data of patient and tumour characteristics

	N (%)
Sex	
Male	9 (24.3)
Female	28 (75.7)
Mean age, years (range)	55 (30–78)
Histopathological diagnosis	
LAMN	32 (86.5)
HAMN	2 (5.4)
Ovarian mucinous borderline tumour	3 (8.1)
Peritoneal Cancer Index (PCI)	17.19
Mean (range)	(1–39)
Completeness of Cytoreduction (CC) Score	
0/1	34 (91.9)
2	3 (8.1)
3	0
Prior Surgical Score (PSS)	
0	10 (27)
1	14 (37.8)
2	8 (21.6)
3	5 (13.5)
Median Lenght of Hospital Stay	18 (8-112)
days (range)	
Complications Clavien-Dindo III/IV	7 (18.9)

HAMN = high grade appendiceal mucinous neoplasm; LAMN = low grade appendiceal mucinous neoplasm

Major postoperative complications (Clavien-Dindo grade III–IV) occurred in seven patients (18.9%). Importantly, no patient died within 30 days following surgery, resulting in a 30-day postoperative mortality of 0%.

No clinicopathological variable was significantly associated with the occurrence of major postoperative complications.

Overall survival (OS)

After a median follow-up of 68 months (range, 7–134 months), three patients (8.1%) had died of disease.

Median OS was 129 months. Estimated 5-year and 10-year OS rates were 91.9% and 83.7%, respectively (Figure 1).

On univariate analysis, PCI ($p = 0.003$), CC score ($p = 0.025$), preoperative Carcinoembryonic Antigen (CEA) ($p = 0.004$) and Carbohydrate Antigen 19-9 (CA19-9) ($p = 0.008$) were significantly associated with OS, whereas age, sex, American Society of Anesthesiologists (ASA) Physical Status Classification, PSS, histopathological subtype and Cancer Antigen 125 (CA125) were not (Table 2).

Kaplan-Meier analysis demonstrated significantly improved overall survival among patients with a PCI ≤ 12 compared with those with a PCI > 12 (log-rank $p = 0.028$) (Figure 2). Similarly, patients who achieved complete cytoreduction (CC-0/1) had

TABLE 2. Univariate analysis, factors affecting overall survival (OS)

	P
Sex	NS
Age	NS
Prior Surgical Score (PSS)	NS
Peritoneal Cancer Index (PCI)	**0.003**
Completeness of Cytoreduction Score (CC)	**0.025**
ASA	NS
Histology	NS
CEA	**0.004**
CA 19-9	**0.008**
CA 125	NS

ASA = American Society of Anesthesiologists Physical Status Classification; CA 125 = Cancer Antigen 125; CA 19-9 = Carbohydrate Antigen 19-9; CEA = Carcinoembryonic Antigen; NS = not significant

TABLE 3. Multivariate analysis, independent prognostic factors of overall survival (OS)

	P
Sex	NS
Age	NS
Prior Surgical Score (PSS)	NS
Peritoneal Cancer Index (PCI)	NS
Completeness of Cytoreduction Score (CC)	0.013
ASA	NS
Histology	NS
CEA	NS
CA 19-9	**0.025**
CA 125	NS

ASA = American Society of Anesthesiologists Physical Status Classification; CA 125 = Cancer Antigen 125; CA 19-9 = Carbohydrate Antigen 19-9; CEA = Carcinoembryonic Antigen; NS = not significant

significantly better OS than those with incomplete cytoreduction.

Multivariable Cox regression analysis identified achievement of complete cytoreduction (CC-0/1) and preoperative CA19-9 level as independent prognostic factors for overall survival after adjustment for age, sex, ASA classification, PSS, PCI, histopathological subtype, CEA and CA125 (Table 3).

Disease-free survival (DFS)

Among patients who achieved complete cytoreduction (CC-0/1), disease recurrence developed in 14 patients (41.2%).

TABLE 4. Univariate analysis of factors affecting disease free survival (DFS)

	P
Sex	**0.005**
Age	**0.036**
Prior Surgical Score (PSS)	NS
Peritoneal Cancer Index (PCI)	**0.004**
Completeness of Cytoreduction Score (CC)	**0.007**
ASA	NS
Histology	NS
CEA	NS
CA 19-9	NS
CA 125	NS

ASA = American Society of Anesthesiologists Physical Status Classification; CA 125 = Cancer Antigen 125; CA 19-9 = Carbohydrate Antigen 19-9; CEA = Carcinoembryonic Antigen; NS = not significant

Median DFS was 86 months. Estimated 5-year and 10-year DFS rates were 70.3% and 64.8%, respectively.

On univariate analysis, sex (p = 0.005), age (p = 0.036), PCI (p = 0.004) and CC score (p = 0.007) were significantly associated with DFS (Table 4).

Multivariable analysis identified achievement of complete cytoreduction (CC-0/1) as the only independent prognostic factor for DFS (Table 5).

Discussion

The present study summarizes the 15-year experience of the Slovenian National Referral Centre

TABLE 5. Multivariate analysis, disease-free survival (DFS)

	P
Sex	NS
Age	NS
Prior Surgical Score (PSS)	NS
Peritoneal Cancer Index (PCI)	NS
Completeness of Cytoreduction Score (CC)	**0.014**
ASA	NS
Histology	NS
CEA	NS
CA 19-9	NS
CA 125	NS

ASA = American Society of Anesthesiologists Physical Status Classification; CA 125 = Cancer Antigen 125; CA 19-9 = Carbohydrate Antigen 19-9; CEA = Carcinoembryonic Antigen; NS = not significant

TABLE 6. Comparison of the present study with representative published series

Study	N	CC0/1	Major morbidity (Clavien-Dindo III-V)	Mortality (%)	5-year OS
Youssef[33]	456	66	7	1.6	69
Elias[10]	301	73	40	4.4	73
Deraco[11]	75	96		1	78
Narasimhan[13]	140	73	20.6	0	71
Santullo[12]	50	94	10	0	91
Present study	37	91.9	18.9	0	91.9

with CRS and HIPEC for PMP. Although the cohort is relatively small, reflecting the rarity of the disease, it represents almost the entire national experience during the study period. The principal findings are a high rate of complete cytoreduction (CC-0/1), low postoperative morbidity, absence of 30-day postoperative mortality and favourable long-term survival. Furthermore, achievement of complete cytoreduction (CC-0/1) remained the strongest independent prognostic factor for both OS and DFS, while elevated preoperative CA19-9 independently predicted poorer overall survival. Because of the limited number of outcome events, these prognostic findings should be considered exploratory.

CRS combined with HIPEC has fundamentally changed the management of PMP. Prior to its introduction, treatment relied on repeated debulking procedures that provided only temporary symptom control and rarely altered the natural history of the disease. Today, CRS and HIPEC are considered the standard treatment for appropriately selected patients because they combine complete macroscopic tumour removal with regional treatment of microscopic residual disease. Despite widespread acceptance of this approach, high-level evidence remains limited owing to the rarity of PMP[22], and current recommendations are based largely on retrospective studies and international expert consensus.[16] Consequently, institutional and national series remain important sources of evidence.

The long-term outcomes observed in our cohort compare favourably with those reported by experienced international referral centres. Elias *et al*.[10] reported a 5-year OS of 73% in a multicentre French study including more than 300 patients, whereas Deraco *et al*. reported a 5-year survival of approximately 78% after CRS and HIPEC.[11] More recent series have demonstrated progressive improvements in both perioperative outcomes and long-term survival. Santullo *et al*. reported a 5-year OS of 91%[12], while Narasimhan *et al*. demonstrated excellent perioperative safety with no postoperative mortality.[13] Our estimated 5-year OS of 91.9% lies within the upper range of these published series (Table 6). This favourable outcome most likely reflects careful patient selection, standardized multidisciplinary management, the predominance of low-grade appendiceal mucinous neoplasms and, above all, the high rate of complete cytoreduction achieved in our cohort.

The importance of complete cytoreduction is clearly illustrated by our findings. Achievement of complete cytoreduction (CC-0/1) was independently associated with both OS and DFS and remained the strongest prognostic factor after multivariable adjustment. This observation is entirely consistent with the published literature and reinforces the concept that complete removal of macroscopic disease remains the cornerstone of successful treatment.[10,11,22,23] Our findings are also consistent with the large multicentre study by Chua *et al*., who demonstrated that achievement of complete cytoreduction is the principal determinant of long-term survival irrespective of histological subtype.[15] Because PMP progresses predominantly within the peritoneal cavity rather than through distant metastases, residual macroscopic disease inevitably limits long-term disease control despite intraperitoneal chemotherapy. Consequently, careful patient selection should focus not only on disease extent but, more importantly, on the likelihood of achieving complete cytoreduction.

Tumour burden, as measured by the PCI, was associated with OS in the univariate analysis, with patients presenting a PCI ≤ 12 achieving significantly better survival than those with a PCI > 12 (log-rank $p = 0.028$). This finding is consistent with previous studies demonstrating improved long-term outcomes in patients with lower tumour burden.[10-13] However, PCI did not retain independ-

ent prognostic significance in the multivariable model. Although this result should be interpreted cautiously because of the limited sample size and number of events, it likely reflects the close relationship between PCI and the ability to achieve complete cytoreduction. In pseudomyxoma peritonei, unlike many other peritoneal surface malignancies, extensive intraperitoneal disease does not necessarily preclude long-term survival provided complete cytoreduction remains technically feasible. Consequently, the clinical relevance of PCI should therefore be regarded primarily a measure of tumour burden, disease distribution, and operative complexity, as well as an indicator of the technical feasibility of complete cytoreduction, rather than as an isolated predictor of prognosis. This distinction is particularly relevant for surgical decision making and patient selection: a high PCI should not necessarily be regarded as an absolute contraindication to CRS-HIPEC in PMP if preoperative assessment suggests that complete cytoreduction remains technically achievable.

Serum tumour markers may provide additional prognostic information beyond conventional clinicopathological variables.[25-31] In the present study, elevated preoperative CA19-9 remained independently associated with OS, supporting previous reports that identified CA19-9 as a marker of biologically more aggressive disease and increased risk of recurrence. Recent evidence further suggests that patterns of preoperative tumour markers may predict resectability and long-term outcome, supporting their integration into preoperative risk stratification.[30] Together with radiological assessment and PCI, serum tumour markers may therefore contribute to improved preoperative risk stratification and patient counselling.

Disease recurrence remains one of the principal challenges in the long-term management of PMP. Among patients who achieved complete cytoreduction, recurrence occurred in approximately 38% during follow-up, which is comparable with recurrence rates reported by other referral centres.[13,15,31,32] Importantly, recurrence should not automatically be regarded as treatment failure. Selected patients with limited recurrent disease may benefit from repeat CRS and HIPEC, resulting in prolonged disease control and survival. Seven patients in our cohort underwent repeat cytoreductive surgery, illustrating that repeated locoregional treatment may remain appropriate in carefully selected patients.

Despite the complexity of CRS and HIPEC, perioperative outcomes were favourable. Major postoperative complications (Clavien-Dindo grade III–IV) occurred in fewer than one-fifth of patients, while no patient died within 30 days of surgery. These findings compare favourably with those reported by high-volume referral centres. In one of the largest single-centre series, Youssef *et al*. analysed 456 patients with appendiceal pseudomyxoma peritonei and demonstrated low postoperative mortality together with acceptable morbidity despite the complexity of CRS and HIPEC.[33] Similar results have subsequently been reported by Elias *et al*., Santullo *et al*. and Narasimhan *et al*., supporting the safety of CRS and HIPEC when performed in experienced multidisciplinary centres.[10,12,13] An important strength of the present study is its national design. Unlike many published institutional series that represent selected referral populations, our cohort includes virtually all patients undergoing CRS and HIPEC for PMP in Slovenia over a 15-year period. Centralized referral pathways, multidisciplinary case selection, a standardized operative and HIPEC strategy, dedicated pathological assessment and structured long-term follow-up may all have contributed to the favourable outcomes observed in this cohort. Concentrating patients within a dedicated national referral centre also facilitates maintenance of surgical expertise and consistency of perioperative care. Consequently, referral bias is minimized and the presented outcomes closely reflect routine national practice. The study also illustrates the value of centralizing highly specialized oncological procedures. Concentration of patients within a dedicated referral centre facilitates maintenance of surgical expertise, standardized multidisciplinary decision-making, specialized pathological assessment and structured long-term follow-up. Our findings therefore support ongoing efforts to centralize the management of rare peritoneal malignancies.

Several limitations should be acknowledged. First, the retrospective design is associated with the inherent limitations of observational studies. Second, although the present cohort represents a nationwide experience, the relatively small number of patients limits statistical power, particularly for multivariable analyses. The low number of disease-specific deaths requires cautious interpretation of independent prognostic factors and should be regarded as exploratory. Third, improvements in imaging, pathology and perioperative management over the 15-year study period may have influenced treatment outcomes. Finally, the predominance of low-grade appendiceal neoplasms

precluded meaningful subgroup analyses according to histological subtype.

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy provides favourable long-term oncological outcomes with acceptable morbidity for patients with pseudomyxoma peritonei when performed in a specialized referral centre. Achievement of complete cytoreduction (CC-0/1) remains the principal determinant of long-term outcome, while lower tumour burden increases the likelihood of successful complete cytoreduction.

Despite the rarity of pseudomyxoma peritonei, our 15-year national experience demonstrates that centralization of care within a dedicated multidisciplinary referral programme enables long-term outcomes comparable with those reported by leading international centres. These findings support continued centralization of highly specialized treatment for rare peritoneal malignancies and reinforce the role of CRS and HIPEC as the standard treatment for appropriately selected patients.

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