Challenges in setting up the first cyto-reductive surgery (CRS) and hyperthermic intra-peritoneal chemotherapy (HIPEC) service in Malaysia

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ABSTRACT

Introduction: Cyto-Reductive Surgery (CRS) with Hyperthermic Intra-Peritoneal Chemotherapy (HIPeC) improves survival in selected patients with peritoneal surface malignancies (PSM) of various tumour entities. This treatment was not available in the Malaysian public health sector prior to 2018, due to lack of expertise, funding and accessibility. We report our challenges in establishing the first such service.

Materials and Methods: Patients referred for CRS-HIPeC between February 2018 and November 2023 were discussed in a multidisciplinary team meeting. Prospectively collected data, including patient demographics, extent of disease (radiological stage, peritoneal carcinomatosis index - PCI), pre-operative workup, completeness of cytoreduction (CCR) score and surgical outcomes, were analysed.

Results: Of 162 patients referred, 47 (30.0%) underwent CRS-HIPeC. The median age was 59 years (range 20-76 years). Median PCI was 11 (range 1-39). CCR distribution was as follows: CCR 0 - 40 (85.1%), CCR 1 - 2 (4.3%), CCR 2 - 2 (4.3%) and CCR 3 – 3 (6.3%). Median operative time was 645 minutes (range 360 –1575 minutes) with a median length of in-hospital stay of 11 days (range 6–146 days). All patients were initially managed in the intensive care unit. Sixteen (34.0%) patients developed complications of Clavien-Dindo Class 3 and above, with three operative mortalities (6.3%).

Conclusion: CRS-HIPeC requires adequate clinical expertise, facilities and volume. Its labour and resource-intensive nature mean that centralization of services is necessary for sustainability. Further evaluation of its cost-benefit in our setting will be required.

KEYWORDS:
Cyto-reductive Surgery, Hospital service, Hyperthermic Intra-Peritoneal Chemotherapy, Malaysia, Peritoneal Surface Malignancy

INTRODUCTION

Peritoneal surface malignancies (PSM) are rare, and difficult to diagnose. Primary subtypes are primary peritoneal carcinoma and malignant mesothelioma. Secondary subtypes are metastases from other primaries, such as gynaecologic, urologic and gastrointestinal cancers. Overall, PSM is associated with poor prognosis, as evident from the EVOCAPE 1 study.[1]

However, there is mounting evidence that Cytoreductive Surgery with Hyperthermic Intra-Peritoneal Chemotherapy (CRS-HIPeC) significantly improves overall survival, particularly for those with secondary PSM. In this technique, the primary disease and affected organs are resected together with the peritoneum followed by heated intraperitoneal chemotherapy.

Malaysia is a middle-income country with a population of 32.7 million.[2] Public healthcare in Malaysia is subsidized by local taxes and government general revenue, whereas private healthcare is funded by medical insurers and/or out-of-pocket expenditure. Diseases that carry a large socio-economic impact, such as cancers and cardiovascular diseases, are understandably prioritized to receive public funding. Unfortunately, lack of awareness often results in cancers presenting at an advanced stage.

As a public teaching hospital and tertiary referral centre, University Malaya Medical Centre (UMMC) receives significant numbers of patients with PSM. Until recently, they would primarily be referred to oncologists for palliative chemotherapy. Nevertheless, it was apparent that a subset of these patients could benefit from CRS-HIPeC. CRS-HIPeC is complex, and requires multi-disciplinary involvement, comprising specialized surgeons, oncologists, anaesthetists, intensivists, and radiologists.[3–5] Consensus on patient selection is of paramount importance, and establishing a service is associated with a significant learning curve, particularly with limited resources.[6,7] We report our initial experience with CRS-HIPeC, including the challenges and obstacles.

MATERIALS AND METHODS

PHASE 1: ESTABLISHMENT OF SERVICE

We engaged with established centres and reviewed existing guidelines for the development of our CRS-HIPeC services. Hospital administration was involved at an early stage of planning for logistics and funding. Multidisciplinary team members were identified and underwent training. Subsequently, we created our protocol, including patient

This article was accepted: 14 April 2025
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selection criteria. Following establishment of protocols, we were proctored by an established regional centre, in both patient selection and conduct of the procedure.

PHASE 2: EVALUATION OF OUTCOMES

Data on all patients was prospectively collected. Variables analysed included demographics, operative time, disease burden, completeness of cytoreduction (CCR), primary pathology, morbidity, mortality and length of stay. Frequency was evaluated using median (range). Number of surgeons and types of subspeciality were also included. Performance status was classified according to the Eastern Cooperative Oncology Group (ECOG). The disease burden was defined by the Peritoneal Cancer Index (PCI).8 The CCR score was determined at the completion of cytoreduction and prior to HIPeC.[9,10] Cytoreduction was performed as described by P. Bao and O. Glehen et al.[9,11] Following CRS, HIPeC was performed via a closed technique using the Hyperthemia Pump™ (Belmont Medical Technologies, Billerica, Massachusetts, USA) to infuse cytotoxic chemotherapeutic drugs at 42 degree Celsius for 60 minutes. Anastomosis, stoma and drain placement were performed after copious washout upon the completion of HIPEC. Patients were monitored in the intensive care unit post-operatively and transferred to the surgical ward when appropriate. Post-operative morbidity events were graded using the Clavien-Dindo Classification.[12] Follow-up was performed at 3 weeks, 6 weeks, 3 months and 6 months, at which time physical examination, tumour markers (CEA, CA 125 and CA 19-9) and computed tomography (CT) scan were performed.

RESULTS

PHASE 1

The pioneer members included surgeons, anaesthetists, oncologists, and operating theatre nursing staff. The proposal for establishing the service was approved by the hospital administration. Pioneer members underwent training in an established regional centre (National Cancer Centre, Singapore). Funding was through a novel public-private partnership. The CRS-HIPEC team was established by a colorectal surgeon with special interest in the management of PSM. Following careful case selection through a multi-disciplinary team discussion, the first case was performed on 8 February 2018. Additional colorectal surgeons joined the team from 2019 onwards, with one assigned to lead the management of peritoneal malignancies from December 2022 onwards (Fig. 1). The CRS-HIPeC team expanded to 13 people within a year, including supporting sub-specialities such as gynaecologists, hepatobiliary surgeons, urologists and anaesthetists. This allowed a doubling of case volume from the first to the second year (Fig. 2).

A clinical database was constructed and maintained prospectively. Agreed selection criteria included every patient with incidental or symptomatic peritoneal disease seen on imaging or intra-operatively. Referred patients were initially discussed in our institutional tumour board. Shortlisted patients were then further discussed in an international inter-institutional multidisciplinary tumour board, which allowed for proctoring on patient selection. Fifteen cases were discussed in the international MDT board, over a period of six months, which allowed the UMMC team to reach a comfort level on independent decision-making. On-site proctoring by an experienced visiting surgeon was provided for the conduct of the operations in our initial cases.

A Temporary Practicing Certificate (TPC) was obtained for the proctor. This required submission of numerous documents to the Malaysian Medical Council, and took several months to complete. In addition, a trained perfusionist was needed to operate the HIPeC infusor. The infusor required prior compatibility and safety assessment by our institutional Biomedical Engineering Department. Occupational, Safety, Health and Environmental (OSHE) standards were followed to safeguard patients, staff and the environment, in handling chemotherapy peri-operatively.

Patients with good Eastern Cooperative Oncology Group (ECOG) performance status (ECOG 0 or 1) and potentially resectable disease, based on pre-operative imaging and diagnostic laparoscopy, were considered for CRS-HIPeC. In some patients, the performance status was assessed objectively with cardiopulmonary exercise testing (CPET) to provide a thorough integrative assessment of multi-organ physiological function to exercise.[13]

PHASE 2

A total of 162 patients with PSM were assessed from February 2018 to November 2023 for consideration of CRS-HIPEC. Of these, 17.5% were from other centres around Peninsular and East Malaysia, while two patients (1.2%) were referred from Indonesia. Eighty percent were referrals from oncologists, gynaecologists or other surgical units within our centre. Thirty-one percent of patients were receiving systemic chemotherapy at the time of referral, and were referred due to disease progression. Fifty (30.9%) were PSM with colorectal primaries. Following assessment, fifty-one patients (31.5%) underwent surgery but three were found unresectable. An additional patient developed intraoperative pneumothorax preventing completion of the surgery.

Demographics of patients who had CRS-HIPeC are summarized in Table I.

The median age was 59 years, and the majority were female (68%). The Chinese were the predominant ethnic group (68.1%), in keeping with the national ethnic distribution of overall cancer incidence as reported in the Malaysian National Cancer Report 2016. Eighty percent were ECOG status 0. Of 47 patients who successfully completed CRS-HIPeC (Table II), 28 (59.6%) patients had multi-visceral resection. The median PCI score was 11 (range 1 - 39). The median operative time was 645 minutes with a range of 360 – 1575 minutes. Mean total blood loss was 2 litres with a range of 0.2 – 4.0 L . The majority of patients had two organs resected (42.6%).

All patients with colorectal primaries and low grade mucinous neoplasia (LAMN) received mitomycin for HIPeC component. During the initial set-up, the majority of the ovarian-PM (12.6%) received cisplatin and doxorubin for the HIPeC. The sarcomatosis peritonei patient received doxorubicin.

Table I: Patient demographic and clinical characteristics (n=47)

Variable	Results
Age [years; median (range)]	59 (20-76)
Body Mass Index [kg/m^2; median (range)]	23.9 (15.7-33.7)
Race	
Malay	12 (25.5%)
Chinese	32 (68.1%)
Indian	2 (4.3%)
Other	1 (2.1%)
Gender	
Male	15 (31.9%)
Female	32 (68.1%)
ECOG Status	
0	38 (80.9%)
1	8 (17.0%)
2	1 (2.1%)
Primary Pathology	
Appendix carcinoma	5 (10.6%)
Ovary	11 (23.4%)
Colon	13 (27.7%)
Primary peritoneal cancer	3 (6.4%)
Sarcoma	1 (2.4%)
LAMN	14 (29.8%)
Pre-operative tumour markers [U/ml; median (range)]	
CEA	6.3 (0.3-202)
CA 19-9	26.0 (1-2600)
CA-125	55.5 (4-9939)

Values are presented as n (%) unless otherwise stated.

Table II: Operative characteristics

Variables	Results
Operative time [minutes; median (range)]	645 (360-1575)
PCI score [median (range)]	11 (1-39)
Cytoreductive score (CC)	
CC – 0	n=40(85.1%)
CC – 1	n=2 (4.3%)
CC – 2	n=2 (4.3%)
CC – 3	n=3 (6.3%)
Chemo drugs	
Mitomycin	34 (72.4%)
Cisplatin and doxorubicin	6 (12.8%)
Cisplatin and paclitaxel	1 (2.1%)
Cisplatin	5 (10.6%)
Doxorubicin	1 (2.1%)
Estimated blood loss [L; median (range)]	2.0 (0.2 – 4.0)
No organ of resection	
1	19 (40.4%)
2	20 (42.6%)
3	8 (17.0%)

Values are presented as n (%) unless otherwise stated.

Morbidity requiring intervention (Grade III – IV) was 31.9%, while overall operative mortality was 6.3%. There was one early operative mortality, with death occurring on the fifth post-operative day, due to neutropenic sepsis where cisplatin was used in the HIPeC regimen. Another two patients died at four and five months post-operatively, within the index admission, due to complications of pneumonia and pulmonary embolism respectively (Table III).

Median follow up was 33 months. At last follow up, 17 patients (36.2%) had no evidence of disease recurrence or progression. Of the 42 patients who had CC0 or CC1 clearance, 13 (31%) had local recurrence. Six of these recurred within six months, while the others recurred after more than a year. There were seven (16.7%) distant recurrences in these 42 patients, five occurring within a year (Table III). The five patients with CC2 or CC3 clearance all progressed within a year.

DISCUSSION

CRS-HIPeC has been in practice for many decades in some countries.[14] Peritoneal surface malignancy generally has a poor prognosis, but selected patients do benefit from this

Table III: Post-operative outcomes

Variables	Results
Hospital stay [days; median (range)]	11 (6-146)
ICU stay [days; median (range)]	2 (1-29)
30-day morbidity	
Clavien-Dindo	
I	13 (27.7%)
II	18 (38.3%)
IIIa	10 (21.3%)
IIIb	3 (6.4%)
IVa	1 (2.1%)
IVb	1 (2.1%)
V	1 (2.1%)
Operative Mortality	3(6.3%)
Oncologic outcomes	
1-year disease free survival	27 (57.4%)
1-year local recurrence	6 (14.3%)
1-year distant recurrence	5 (11.9%)
1-year overall survival	43 (91.5%)

Values are presented as n (%) unless otherwise stated.

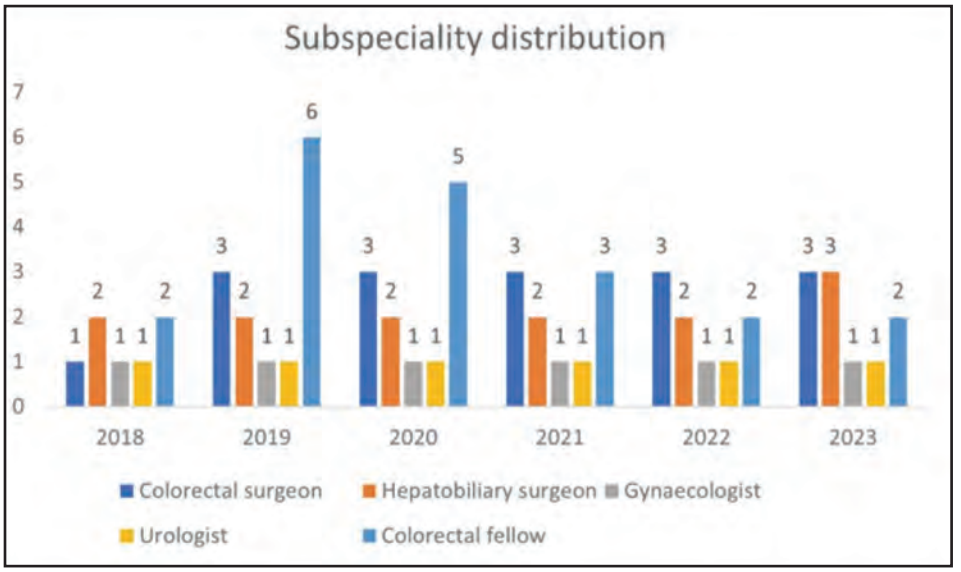

Fig. 1: Multidisciplinary team composition

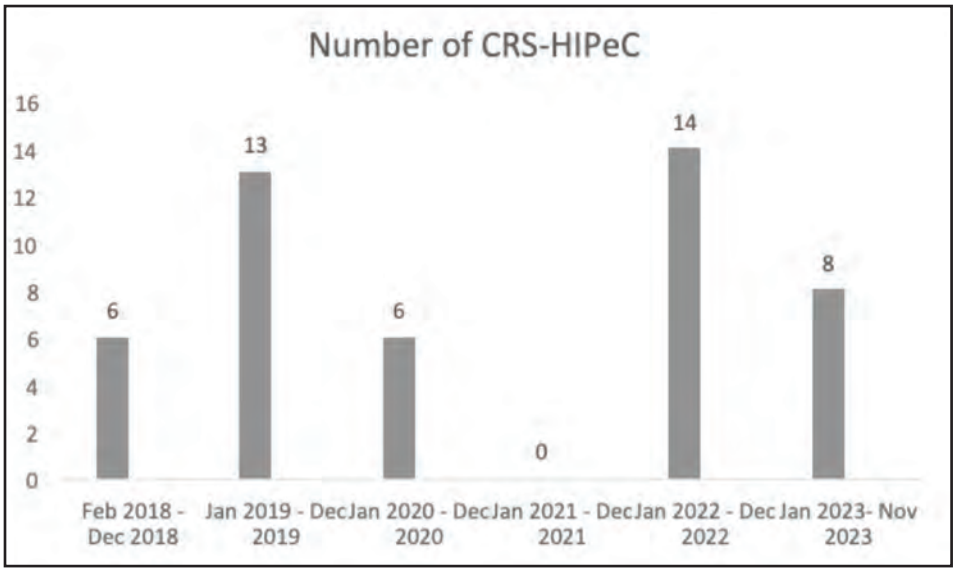

Fig. 2: Annual cases of CRS-HIPeC

treatment modality even though it is time consuming, associated with significant morbidity and mortality, and is an expensive operation to conduct.[15,16]

Tumour biology impacts outcomes, and influences selection. Simkins GA et al reported that the median survival for colorectal cancer peritoneal metastasis (CRC-PM) is 36 months, with one year mortality rate and recurrence rate post-CRS-HIPeC procedure of 13% and 35% respectively.[17] Nevertheless, while there are recommended PCI ceilings for CRC and gastric carcinomas (15 and 9 respectively), there are no stipulated PCI ceilings for primary PSMs or sarcomas, as there is a survival benefit for the latter two even with very high PCIs.

Oncologic clearance is the primary goal, and affects survival. Adherence to adjuvant therapies is also critical for optimal survival. Following discharge, three of our patients (6.4%) died due to disease progression post CRS-HIPeC. Our 13th patient had a dedifferentiated liposarcoma arising from the retroperitoneum, with gastrointestinal symptoms from extrinsic compression; his PCI was 21 and we achieved CC-1 clearance. His symptoms improved significantly, but he recurred seven months after surgery. He commenced palliative chemotherapy with overall survival of 15 months. Another patient had appendicular mucinous adenocarcinoma with PCI of 39, CC-2 clearance, was symptom free for nine months. He developed obstructive symptoms and died 18 months after surgery. A third patient had sigmoid carcinoma recurrence which was KRAS mutated. Her PCI was 10 and we achieved CC-0, all good prognostic features, but she refused adjuvant chemotherapy. She was disease free for six months and died from liver and lung metastasis at 15 months post-operatively.

While CRS-HIPeC can improve survival, morbidity is significant. The National Cancer Centre Singapore analysis of morbidity post-CRS-HIPeC over a 10-year period showed that for every additional resection performed, there was a 53% increase in the odds of experiencing post-operative complications.[18] The number of resections performed and intraoperative blood loss is directly proportion to the morbidity.[18]

Our outcomes also reflect the increase in morbidity with more extensive resections. Sixteen of our patients (34.0%) had severe complications (Clavien-Dindo III and above). One patient developed abdominal compartment syndrome that required an emergency laparostomy. Two developed pancreatic fistula post-distal pancreatectomy for appendicular carcinoma with peritoneal metastasis and sarcomatosis peritonei. These two patients had three organs resected with blood loss of 500 ml and 1500 ml respectively. It is clear that as centres become more experienced and attempt more complex cases, managing the associated morbidities will add to the overall cost of CRS-HIPeC.

Malaysian healthcare has a complex funding framework. While much of public healthcare is subsidized by the government, specialized equipment and pharmaceuticals often require out-of-pocket funding. In addition, only 14.2% of the population has personal medical insurance coverage.[19]

There are also differences in public hospitals within the Ministry of Health compared with teaching hospitals under the Ministry of Higher Education. In the latter, civil servants undergoing CRS-HIPeC would need to pay out-of-pocket for consumables, amounting to, on average, RM9888.00 (USD2088.35). Non-government staff would, in addition, have to pay the costs of medication and hospital stay. Three of our patients were unable to proceed with the operation due to financial constraint. One of them struggled financially to travel to the Peninsular of Malaysia for pre-operative assessment. While patients may avail of social welfare services, funding is limited. Given that the average household income in Malaysia is RM5,228 (USD1173.25) per month, public hospitals, which have a higher proportion of low income patients, are often unable to fully subsidize expensive treatments.[20]

There are also logistic challenges. Workup for, and subsequent review of CRS-HIPeC patients in the outpatient setting often requires long consultation times. Clinical decision-making is frequently shared with the family. CRS-HIPeC patients in our hospital are reviewed in the general colorectal clinic, comprising 100 to 120 patients with variable colorectal conditions. This limits the duration of each consultation, and some patients may require additional consultations with the presence of other family members to discuss high morbidity and financing. In addition, follow-up telephone calls are needed to ensure there is no miscommunication regarding the subsequent investigations and surgery.

A further obstacle is the limited availability of operating time. This means that the interval to surgery generally may be as long as three months. Although CRC-PM patients are prioritized, this is sometimes at the expense of deferring surgery for other patients.

CRS-HIPeC draws intensive resources: lengthy operation which requires extra anaesthetic and theatre support, complexity of surgical procedures which require multi-disciplinary surgical teams, and several days of ICU stays and ward stays requires specialist nurse and allied healthcare professional supports. Therefore, it becomes an expensive treatment modality, which also carries a high morbidity and mortality rate with the overall 5-year survival being considerably low. At the moment, the cost-effectiveness of CRS-HIPeC is yet to be determined in our setting, in order to draw full financial support from the government fund.

The recently published results from the PRODIGE 7 phase III multicenter randomized control trial showed no significant difference in the overall survival (OS) and relapse free survival (RFS) comparing patients undergoing CRS with or without HIPeC for peritoneal metastases from colorectal cancer.[21] The study also demonstrated that despite no significant difference in 30-day mortality, the 60 day morbidity was higher in the HIPeC group. These results have further raised the conundrum, if HIPeC should really be offered to patients with CRC-PM, especially in our setting with resource limitations.

The result of PRODIGE 7 has had an impact in the treatment of CRC-PM around the world. A web-based survey was conducted among the countries that registered under Peritoneal Surface Oncology Group International (PSOGI) to achieve expert opinion and consensus on the study. Among the several critiques of PRODIGE 7 were the use of oxaliplatin for a duration of 30 minutes during the HIPeC, and PCI score of less than 25 as a criterion for patient selection. Since cytotoxic activity of the chemotherapy is dependent on the duration of exposure and temperature, the 30 minutes exposure used in the PRODIGE 7 was sub-optimal to achieve the optimal oncological activity.

Authors also stated that there was a reduction of using adjuvant HIPeC in 2 out of 18 countries that participated, perhaps due to the PRODIGE 7 results showing no advantage on overall survival.[22] In addition, there was a shift towards mitomycin-based regimens, and increased duration of exposure from 30 minutes to either 60 or 90 minutes. Perhaps, patient selection is the key here, given that subgroup analysis from PRODIGE 7 suggests that a subset of patients could benefit from HIPeC. Furthermore, CRS-HIPeC is used to treat peritoneal metastases from a wide variety of primary malignancies, thus there would still be a need for this service, even if indications in CRC diminish.

Two of our patients with PMP and a patient with peritoneal mesothelioma had CCR-3 because of extensive disease especially on the diaphragm, with PCI scores of 39. In a study by Verwaal et al, prognostic factors depend on the gross residual disease. Residual disease of more than 2.5 cm had a median survival of just 5 months as compared to 17 months in patients with residual disease between 2.5mm – 2.5cm and 39 months in patient with CCR-0.[23] In addition, Konstantinos et al reported that a repeat CRS-HIPeC should not be due to previous CCR-2. Tumour biology plays a crucial role in selecting patients for repeat CRS-HIPeC. A repeat CRS-HIPeC can be undertaken if it can improve survival and control symptomatic disease with good quality of life.[24] Our median DFS is 13 months and median survival is 31 months. Due to the small distribution from the primary cancer in our initial experience, we are unable to analyse individual primary cancer with peritoneal malignancies.

Moving forward, the provision of CRS-HIPeC services in Malaysia must evolve. Given the complexity of resources needed, and considering the logistic and financial challenges to both healthcare providers and patients, we believe that it is essential to centralize such services for each region: Peninsular Malaysia – north, central, south and east coast; East Malaysia – Sabah & Sarawak.

There is limited literature on learning curves for CRS-HIPEC, which can vary widely, depending on the baseline expertise of the team.[25] For example, Kusamura estimated that approximately 140 cases are necessary to ensure surgical proficiency in CRS and HIPEC.[26] Our team members were already experienced general surgeons in independent practice, and were regularly managing other complex colorectal surgeries prior to their fellowships in CRS-HIPEC, so independence was achieved rapidly. These were high volume centres, thus each team member was able to complete 60-100 independently conducted cases each before returning to Malaysia. This exceeds the European School of Peritoneal Surface Oncology (ESPSO) recommendation of a minimum of 20 cases performed independently to overcome learning curves.

Since establishing our service, we have also facilitated the development of public hospital services in Peninsular Malaysia (North – Penang; Central – Seremban). We face obstacles to developing services in other regions, especially in East Malaysia, primarily due to lack of human resource. Thus, we anticipate that patients will still need to travel in the short-term to avail of CRS-HIPeC services. Consideration needs to be given for government funding to support such logistics.

CONCLUSION

We have initiated and provided CRS-HIPEC treatment safely, and the practice should be continued, but quality control, collaboration work and support are required in order to meet international standards. We were able to rapidly set up the CRS-HIPeC multidisciplinary team due to ready availability of experienced specialists in colorectal, hepatobiliary, gynae-oncology, radiology, oncology, anaesthesia and critical care. Coupled with experienced proctoring, our learning curve in establishing our CRS-HIPEC service was relatively short. At the time of establishment, we were the only public hospital offering this service, but since then, we have facilitated the establishment of two more centres, illustrating the demand for PSM management in this country. This demand would only be expected to increase. Therefore, more funding and resources is needed in order to sustain and improve the management of PSM in Malaysia.

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