An overview of cytoreductive surgery and heated intra-peritoneal chemotherapy in the management of peritoneal surface malignancies

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Abstract

Peritoneal metastasis has poor prognosis. In certain primary cancers with peritoneal metastasis, the prognosis is improved by cytoreductive surgery and heated intraperitoneal chemotherapy. The success of this treatment depends on careful patient selection, multidisciplinary decision-making process in high volume centres with high quality surgery and a system set up to deliver this procedure in a safe and effective way.

Introduction

Cancers affecting the peritoneal surface can arise primarily, as in the case of peritoneal mesothelioma. Most peritoneal surface tumours, however, arise from peritoneal metastases of major gastrointestinal and ovarian malignancies. These include metastases from colorectal, gastric and appendiceal cancers. Peritoneal surface malignancy has historically been associated with dismal prognosis. Colorectal peritoneal metastases (CRPM) for example when treated with standard therapy has a median survival of less than 17 months while in gastric cancer median survival less than 8 months[1].

However, advances in treatment modalities in the last two decades, has begun to offer hope for survival in patients once upon a time condemned to palliation. Chief among these treatment strategies has been the combination of surgical tumour cytoreduction with intra-operative delivery of heated chemotherapy to the peritoneal cavity. This approach pioneered by the likes of Paul Sugarbaker of the Washington Cancer Institute has showed significant improvement in the overall survival rates of peritoneal metastases from ovarian, colorectal, appendiceal and gastric carcinoma as well as from malignant peritoneal mesothelioma. It has also emerged as the standard of care in the management of peritoneal dissemination of low-grade mucinous neoplasms of the appendix, a condition known as pseudomyxoma peritonei (PMP).

What is the rationale behind this procedure?

With advances in surgical techniques, a complete macroscopic removal of the peritoneal metastases (Cytoreduction) is technically feasible in a number of patients. However there remains the possibility of microscopic tumour deposits giving rise to future recurrences. This is explained as the theory of tumour entrapment. Standard intravenous chemotherapy has had limited efficacy on peritoneal surface malignancy due to poor penetration. However direct intra-peritoneal instillation of chemotherapy can theoretically overcome this disadvantage. It was subsequently discovered that heat augmented the cytotoxic effects of chemotherapy[2]. This led to the development of the concept of Hyperthermic intra-peritoneal chemotherapy (HIPEC). In order for HIPEC to be effective however, the peritoneal disease burden must be reduced to a level where intra-peritoneal chemotherapeutic agents can successfully penetrate remaining tumour cells. This underlies the rationale for combining cytoreductive surgery (CRS) with HIPEC in the management of peritoneal surface malignancy. In addition, there is a significant proportion of patients where the metastasis is limited to the peritoneum with no evidence of systemic disease.

A number of factors appear associated with the treatment efficacy. These include the volume of peritoneal metastases, the completeness of cytoreduction and the type of malignancy[1].

Technique

Cytoreductive Surgery

The aim of cytoreduction is to ensure complete macroscopic removal of all peritoneal disease. In order to achieve this, the surgical procedures are performed include;

1. Segmental peritonectomy
2. Resection of disease affected viscera
3. Diathermy ablation of disease
4. Resection of structures with high risk of recurrence (Target organ resection)

Peritonectomy includes stripping of all areas of the peritoneum affected by tumour deposits. This may include stripping of the pelvic peritoneum, stripping of the under-surface of the diaphragm and stripping of the paracolic gutter. Areas of peritoneum with no macroscopic disease are preserved.

All affected organs or those with potential risks that can be safely sacrificed are also resected. This may include removal of the spleen, gall-bladder, appendix, uterus and ovaries as well as colonic and rectal resection.

High energy diathermy is used to ablate disease which may not be safely stripped or resected. This technique is used to achieve technical clearance of disease on the surface of the liver.

Certain structures are at high risk of developing peritoneal metastases. This includes the omentum which studies have shown may have a receptive vascular micro-environment for tumour attachment. Therefore, cytoreductive procedures include resection of the greater and lesser omentum, ligament of teres, ovaries and in certain situations the gallbladder even if unaffected by macroscopic disease.

Cytoreduction is conventionally performed via midline laparotomy. However, evidence is emerging that in low volume disease a laparoscopic approach may also be effective.

Hyperthermic intra-peritoneal chemotherapy

The cytoreductive procedure is then followed by the delivery of intraperitoneal chemotherapy. This is delivered via specifically designed or modified perfusion machines which circulate the chemotherapeutic agents within the peritoneal cavity for periods between 30-90 minutes. A number of drugs have been used for HIPEC and these vary depending on the primary tumour as well the history of prior chemo-sensitisation. The commonly used agents include mitomycin C, oxaliplatin, cisplatin and carboplatin[3]. Chemotherapeutic infusion is delivered at temperatures between 41-43 °C. The HIPEC can be delivered with abdomen open (Figure1) or closed.

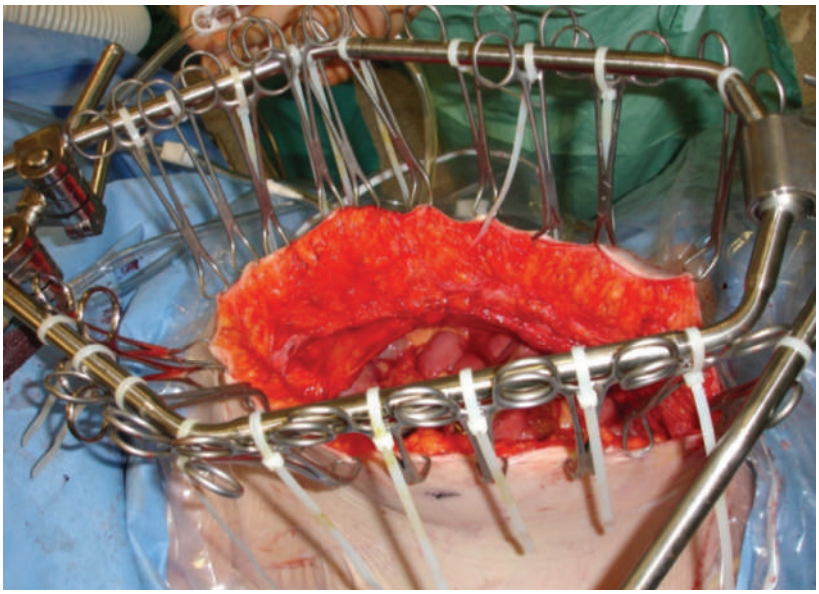

Figure 1: Open 'Coliseum' technique for HIPEC

Due to the complexity of procedure which usually exceeds 5-6 hours, there is high risk of complications. Nevertheless, results from high volume centres show that this can be performed with acceptable morbidity and mortality (<1%)[4].

What evidence do we have that it works?

Evidence for the efficacy of CRS and HIPEC in the management of this rather heterogenous group of conditions comes from a multitude of sources.

In general, the efficacy of this technique depends on several factors. The most important of these is the completeness of cytoreduction and extent of tumour burden. Tumour burden is objectively assessed by the Peritoneal Carcinomatosis Index (PCI Score) as proposed by Sugarbaker[5]. This gives a score of between 1 and 3 to thirteen regions of the peritoneal cavity based on the extent of tumour in each region (Figure 2) The higher the PCI score the less chance that CRS and HIPEC would be effective.

In addition to this the outcome benefit of each procedure varies based on the nature of the primary cancer.

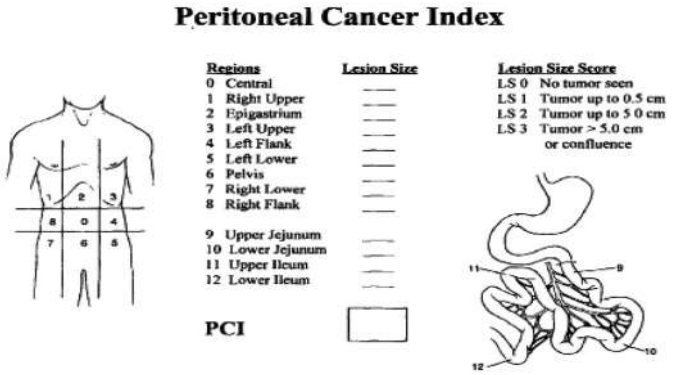

Figure 2: Peritoneal Carcinomatosis Index (After Sugarbaker(5))

Although there is a paucity of level 1 evidence to examine the effect of each of its components there is no doubt about its efficacy in Pseudomyxoma peritonei (PMP), appendix adenocarcinoma and malignant peritoneal mesothelioma. PMP is rare condition characterised by the presence of mucinous ascites and mucinous peritoneal deposits. The condition is mainly due to peritoneal dissemination of perforated mucin producing appendiceal neoplasms. The spectrum of this condition ranges from peritoneal dissemination of relatively indolent low-grade appendiceal mucinous neoplasms (LAMN) to mucinous adenocarcinoma. CRS and HIPEC has been showed to have excellent results in PMP due to LAMN lesions with 5-year survival rates in the region of 70-90%[4]. It now recommended as the standard of care for this condition. It is also offered in some centres as a risk-reducing procedure for perforated LAMN lesions with no obvious signs of peritoneal spread as an alternative to surveillance.

CRS and HIPEC also has showed good results in malignant peritoneal mesothelioma with 5-year survival of up to 80%6.

CRS and HIPEC has been attempted as treatment for colorectal peritoneal metastases (CRPM) since the 1980's and a growing body of mostly level II and III evidence shows promising

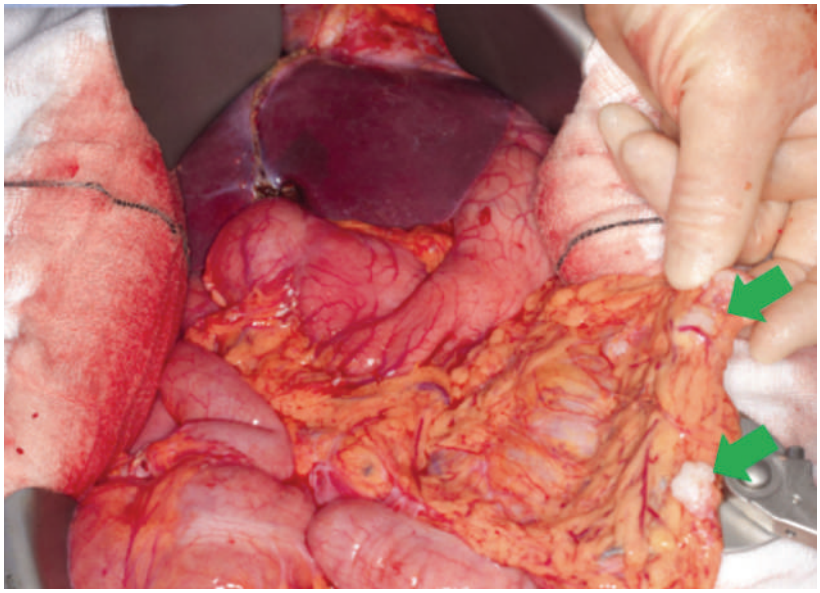

Figure 3: Low-volume colorectal peritoneal metastases (green arrows)

results in carefully selected patient groups with relatively low-volume disease (Figure 3). In 2003, Verwaal et al presented data from a Dutch RCT which showed significantly improved survival for CRS and HIPEC over standard chemotherapy (Median survival 22.3 months v 12.6 months)[7]. However, questions have been raised whether it is the complete cytoreduction which is responsible for the improved utcome as opposed to addition of HIPEC. This was the subject of investigation in the multicentric French RCT PRODIGE 7. This compared CRS and HIPEC for low to moderate volume CRPM versus CRS alone. The results of this study presented as an abstract at the American Society of Clinical Oncology (ASCO) meeting in 2018, concluded that while CRS significantly improves survival in CRPM, addition of HIPEC does not have any additional benefit[8]. These results have caused some controversy although several criticisms have been made of the methodology of PRODIGE 7 including the fact that it is under-powered and also included data from low-volume centres.

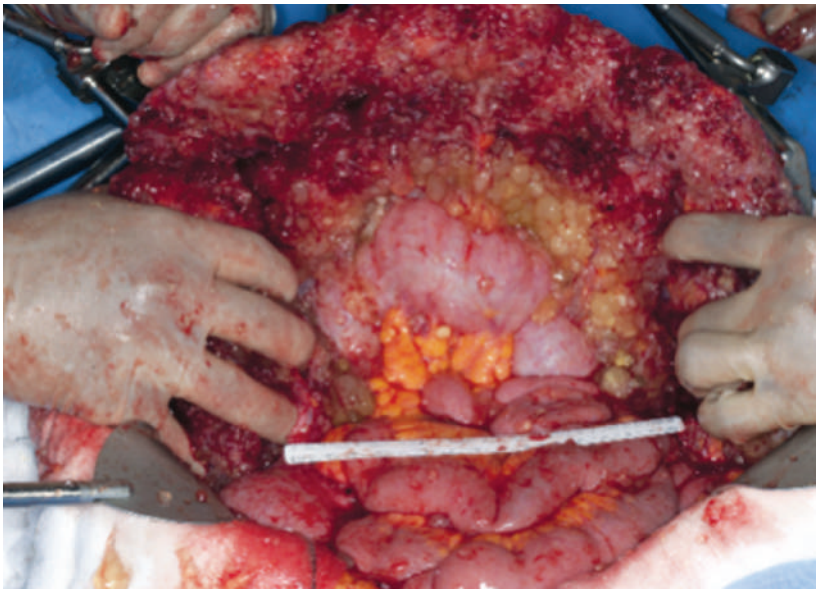

Figure 4: Extensive peritoneal disease with 'omental cake'

Cytoreduction for peritoneal metastases from ovarian cancer has been performed historically since the 1930s[2]. Following its use in gastro-intestinal cancer, CRS and HIPEC has been extended to ovarian cancer as well. Unlike in colorectal cancer, there is level 1 evidence that addition of HIPEC augments the effectiveness of cytoreduction[9]. A recent multicentre open label Dutch RCT comparing CRS and HIPEC versus CRS alone demonstrated improved overall and disease-free survival with the addition of HIPEC (OS 42 months versus 33 months)[10].

PRIMARY TUMOUR	5-YEAR SURVIVAL AFTER CRS AND HIPEC FOR PERITONEAL MATASTASES
PMP / Appendix	70 – 90 %
Ovarian carcinoma	42 – 68 %
Colorectal carcinoma	13 – 51 %
Gastric carcinoma	13 %
Malignant peritoneal mesothelioma	40 – 50 %

Table 1: 5-year survival following CRS and HIPEC

While results in gastric cancer are relatively modest, it does appear that CRS and HIPEC offers some hope in this notoriously aggressive disease.

It must be noted that CRS and HIPEC is not a panacea for all situations. High volume disease (Figure 4), inability to achieve complete cytoreduction, presence of non-responsive systemic disease are instances where this procedure will not alter outcome.

In the United Kingdom, there are two centres established to manage these patients. One is at the Christie and the 2nd at Basingstoke. These two units provide high volume service through a multi-disciplinary process to ensure those patients requiring this surgery are treated in a safe and effective way.

Conclusion

Peritoneal metastasis is a notoriously difficult condition to treat with a long history of poor prognosis. The emergence of cytoreduction and HIPEC has begun to offer hope to selected groups of patients with this condition.

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Did you know?

The UK is ranked 15th by the 2016 Euro health consumer index. The issue is the lowest score on accessibility to health care. "waiting times" and "an autocratic management culture" are responsible for this performance. The Netherlands and Switzerland lead the way in providing good, consumer friendly healthcare.

The UK has 300 beds per 100,000 population; in the Irish Republic it's 500; in Belgium 650; in France it's over 700.