Review Article

Peritoneal-based Malignancies and Their Treatment

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Abstract

Introduction: Patients with peritoneal carcinomatosis (PC) usually have dismal prognoses, even with traditional systemic therapy. Peritonectomy or cytoreductive surgery (CRS) has been used to treat selected patients. It is also commonly used in the management of pseudomyxoma peritonei (PMP), often in combination with hyperthermic intraperitoneal chemotherapy (HIPEC). Methods and Results: In the present review article, the indications for CRS and HIPEC are examined, along with its technical aspects, resulting morbidity and mortality. Patients with documented peritoneal carcinomatosis from colorectal and ovarian cancer or PMP, absence of extra-abdominal metastases and liver parenchymal metastases and with an ECOG performance status of <2 should be considered for CRS and HIPEC. Conclusion: It is important to recognise the role of and indications for CRS and HIPEC. Biologic factors of the disease and completeness of resection are important prognostic factors. Cytoreductive surgery, combined with intraperitoneal chemotherapy, can improve survival in selected patients with peritoneal-based malignancies.

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Key words: Cytoreductive surgery, Intraperitoneal chemotherapy, Peritonectomy, Peritoneal carcinomatosis, Pseudomyxoma peritonei

Introduction

Peritonectomy or cytoreductive surgery has been described as the treatment of choice for selected patients with evidence of peritoneal carcinomatosis (PC) from the gastrointestinal tract, peritoneum, ovaries and the disease of pseudomyxoma peritonei.[1-3] Median survivals in a carefully selected patient population have been shown to exceed that of systemic chemotherapy or conservative management in patients with PC, who traditionally run a palliative course with a median survival of about 6 months.[4] However, the advent of systemic therapy with newer chemotherapeutic agents and targeted therapy has allowed some patients to survive beyond 20 months.[5,6] A recent comparison of survival rates in patients with resectable PC from colorectal cancer treated with modern systemic chemotherapy containing oxaliplatin or irinotecan or by cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), showed a significant difference in favour of the latter.[7] Two- and 5-year survivals of 81% and 51%, and 65% and 13%, were attained in the CRS/HIPEC and systemic chemotherapy alone groups, respectively. The median survivals in the respective groups were 63 and 24 months. It becomes important to assess the benefit of an aggressive surgical procedure such as CRS, with or without the addition of HIPEC, in view of such results and to identify the patients in whom this may be suitable.

Pseudomyxoma Peritonei (PMP)

PMP is a rare condition that is characterised by the presence of widespread mucinous deposits within the peritoneal cavity and has been shown to primarily result from a rupture of appendiceal mucinous tumours, or less commonly, from a mucinous ovarian tumour or primary peritoneal origin. It has been conventionally treated with serial debulking and systemic chemotherapy but this is associated with a high recurrence rate and greater difficulty in obtaining optimal debulking with each ensuing operation.[8] Eventually, these patients succumb to their disease with failure to thrive from an inability to eat and are often very symptomatic from their massive ascites. Aggressive CRS with HIPEC has been popularised by Sugarbaker, with 20-year survival of 70% in some patients.[1] The role of biologic factors is significant, with prognoses improving across the categories of peritoneal mucinous carcinomatosis (PMCA), intermediate (I) and disseminated peritoneal adenomucinosis (DPAM).[8,9] Another significant prognostic factor is the completeness of resection, with patients experiencing far superior overall survivals when

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complete cytoreduction is achieved compared to those with near-complete or incomplete cytoreduction. Jacquet and Sugarbaker's scoring of CCR-0, -1 and -2[10] is commonly used to describe residual disease of <2.5 mm, 2.5 to 25 mm and >25 mm which shows good correlation with survivals.[10] The importance of leaving minimal or no disease is highlighted when the potential benefit of instilling intraperitoneal chemotherapy is explored. The depth of penetration of this locoregional chemotherapy has been shown to be a few millimetres, hence its efficacy decreases markedly if bulky tumours remain.[11-13]

Peritoneal Carcinomatosis from Colorectal Cancer and Other Gastrointestinal Tumours

Colorectal cancer presents with metastases to the peritoneum in up to 15% of patients at the time of diagnosis.[14] In patients who have been treated curatively, involvement of the peritoneum at recurrence occurs in up to 50% of these patients and in up to 25% of these patients, the peritoneum appears to be the sole site of recurrence. The prognosis of these patients has been uniformly dismal, with few surviving beyond 6 months.[15-17] Whilst this has improved with newer and better systemic chemotherapy, many phase II and 1 phase III studies suggest that the treatment of choice should be aggressive CRS with HIPEC.[18] These centres report 5-year survivals of 20% to 40% for selected patients, which approach the results obtained by metastectomy for liver and lung secondaries.[14] Completeness of resection and tumour biological characteristics have been shown to be significant prognostic factors.[19,20] Biology of the disease is reflected in the disease-free interval, involvement of lymph nodes and response to systemic chemotherapy.

PC from gastric cancer is discovered at the time of initial surgery in 10% to 20% of patients and in up to 60% of patients who have undergone a curative resection for T3/T4 tumours.[17] In 40% to 60% of patients with recurrence of their disease, the peritoneum is the only site of recurrence. CRS and HIPEC have been used by a few institutions, with 5-year survival of almost 20% shown in selected patients.[21-23] However, intra-abdominal abscesses and neutropenia were found to be of increased incidence.[23]

PC from Ovarian Tumours

Ovarian cancer commonly spreads to involve the peritoneum with almost 70% of women having stage 3 or 4 disease at the time of initial presentation. The peritoneum is often the first and only site of recurrence.[24] The median time to recurrence varies from 11 to 29 months in early-staged and 18 to 24 months in advanced-staged disease.[17] Traditionally, these patients have been treated with systemic chemotherapy for advanced disease or primary surgery followed by systemic platinum-based chemotherapy but many patients have persistent disease or relapse after a short disease-free interval.[25] Two randomised, phase III trials comparing intraperitoneal and intravenous chemotherapy in advanced, low-volume ovarian cancer showed a survival advantage with the former route of therapy.[26,27] This has led to the performance of another phase III trial comparing intraperitoneal and intravenous cisplatin, with both groups of patients receiving intravenous platinum-based therapy. In this study, the progression-free survival (PFS) and overall survival (OS) were significantly higher in the group of patients who were treated with intraperitoneal cisplatin, with PFS and OS of 23.8 months and 65.6 months, respectively.[28] Whilst the quality of life (QOL) was significantly worse in the intraperitoneal therapy group initially, there was no difference in the QOL 1 year after treatment.

Patient Selection: Indications

It is important to carefully select patients who will benefit from this aggressive procedure. Radiological investigations such as computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) scans have been used, as has diagnostic laparoscopy, to better select the patients who may benefit from this aggressive procedure. CT scans and laparoscopic assessment of peritoneal disease was felt to be insufficient,[29] and PET-CT was shown to be highly sensitive with a high positive predictive value by Bristow et al[30] and altered treatment plans in 60%,[31] but its limited sensitivity is recognised in small volume disease. A consensus was reached at the Fifth International Workshop on Peritoneal Surface Malignancy, stating that contrast-enhanced multi-sliced CT remains the fundamental imaging modality, whilst MRI, PET, laparoscopy and serum tumour markers were helpful but non-essential.[32] At the National Cancer Centre of Singapore (NCCS), patients are selected based on history, physical examination and PET-CT (since PET scans became available). Diagnostic laparoscopy is often unnecessary as patients have commonly undergone a recent laparoscopy or laparotomy prior to their referral to the centre. Tumour markers are also obtained pre- and postoperatively in all cases. Biologic markers have emerged showing prognosticative efficacy,[33] including prediction of response to chemotherapeutic agents[34] but have not been shown to accurately predict surgical resectability of metastases.

The indications for consideration of CRS and HIPEC include:

1) documented peritoneal carcinomatosis or PMP
2) absence of extra-abdominal metastases
3) absence of liver parenchymal metastases
4) ECOG performance status of <2
5) informed consent

Patients who satisfy these conditions should be referred to a multi-disciplinary cancer conference for discussion

by a panel of specialists that includes surgical and medical oncologists, radiologists and pathologists.

Technical Aspects of Cytoreductive Surgery

The goal of aggressive CRS is to remove all macroscopic peritoneal disease. The procedure has been well-described by Sugarbaker[35] and can be categorised into 1) right subdiaphragmatic and parietal peritonectomy, 2) left subdiaphragmatic and parietal peritonectomy, 3) greater omentectomy with splenectomy, 4) lesser omentectomy and stripping of the omental bursa, 5) pelvic peritonectomy with salpingo-oopherectomy in women, and resection of other involved organs, such as uterus and ovaries, gallbladder, stomach, distal pancreas, colon and limited small bowel if necessary.[36] Multi-visceral resection does not appear to affect the morbidity of the procedure and should be performed if a complete cytoreduction can be achieved as a result.[37]

The Fifth International Workshop on Peritoneal Surface Malignancy reached a consensus on the technical aspects of this surgery and this is reported by Kusamura et al.[38] A partial parietal peritonectomy with resection of only macroscopically involved surfaces is felt to be acceptable, except in peritoneal mesothelioma, for which complete cytoreduction should be attempted, with electrovapourisation of small mesenteric nodules of <2.5 mm. Fashioning of bowel anastomoses should be conducted after HIPEC. Protective stomas should be fashioned as per the individual surgeon's discretion.

Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

The advantage of intraperitoneal chemotherapy includes the ability to achieve a significantly higher concentration of chemotherapy in the locoregional environment, with a phase I study documenting a median peak peritoneal concentration of 1116 times that of the plasma level of chemotherapy.[39] When this chemotherapy is instilled intra-operatively and/or in the early postoperative period, the direct tumour effect is enhanced as adhesions resulting in loculation have not been formed and equal distribution of the chemotherapy throughout the peritoneal cavity can be encouraged. The addition of heat increases the potential of the chemotherapy as temperatures over 43 degrees celcius have a direct cytotoxic effect, in addition to acting synergistically with the agent.[40] The choice of chemotherapeutic agents used is dependent on the origin of the tumour, with mitomycin C and 5FU/ doxorubicin, and paclitaxel and cisplatin commonly used for HIPEC and EPIC of gastrointestinal and ovarian tumours, respectively.[41,42]

Morbidity and Mortality

CRS carries significant morbidity and mortality in the range of 40% to 60% and 5% to10%, respectively.[43,44] Even in single centres with years of experience and high case volumes, the rates are still reported to be 27% and 2.7%, respectively.[45] Surgical complications include anastomotic breakdown, abscess, prolonged ileus, as well as deep vein thrombosis and pulmonary embolism, cardiac and cerebrovascular events. Adverse events have been shown to be related to the stage of peritoneal disease, duration of the operation, number of bowel anastomoses and blood loss.[46] Morbidity can ensue from the intraperitoneal chemotherapy and in-dwelling catheters and surgical drains and is dependent on the type of chemotherapeutic agent used. Common side effects include nausea and vomiting, myelosuppression, chemical peritonitis with abdominal pain and distension and leakage of chemotherapy, which may require additional suturing over catheter or drain exit sites. Median intensive care unit stay, blood transfusion requirement, time to feeding, and total hospitalisation duration of 1 day, 1 unit, 4 days and 12 days, respectively, have been reported.[41]

Conclusion

Cytoreductive surgery, combined with intraperitoneal chemotherapy, has been shown to improve survival in selected patients with peritoneal-based malignancies. This benefit remains significant even in the face of improved survival with modern chemotherapy.[7] Biologic factors of the disease and completeness of resection are important prognostic factors. As this aggressive therapy carries with it significant risks of morbidity and mortality, it is crucial that each individual case is presented and discussed at a multi-disciplinary cancer conference, in order to identify the benefit-cost ratio for each patient. At present, patients with good performance status, low volume of peritoneal disease and absence of extra-abdominal and liver parenchymal metastases can be considered.

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