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EDUCATIONAL SECTION

Cytoreduction and intraperitoneal chemotherapy for the management of peritoneal carcinomatosis, sarcomatosis and mesothelioma

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Despite new developments in multi-modality treatments, complete resection remains as an absolute requirement for cure of gastrointestinal cancer. We have reported benefits from combined treatment with complete cytoreduction and intraperitoneal chemotherapy. This has been achieved with low morbidity and mortality.

Success in the surgical management of peritoneal surface malignancy depends on the surgeon's ability to complete complex cytoreductive procedures so that only microscopic residual disease remains. This paper describes the current strategy that the surgical oncologist should pursue in the treatment of patients with peritoneal carcinomatosis, sarcomatosis and mesothelioma. Technical details required for this surgery include patient position, incision and exposure, complete lysis of adhesion, electroevaporative dissection with irrigation and suction to preserve the translucent quality of tissues, peritonectomy procedures, proper positioning of tubes and drains for intraperitoneal chemotherapy, and reconstructive surgery.

Understanding the treatment and mastery of surgical skills to manage the peritoneal surface spread of cancer has led to long-term survival of selected patients. Combination of this treatment strategy with proper patient selection has reduced the mortality and morbidity.

The success of cytoreductive surgery and perioperative intraperitoneal chemotherapy depends on a long-term dedication to achieve the full potential of a curative outcome. Our unit has continued to achieve good results over two decades as improved results of treatment have evolved.

Key words: cancer seeding; 5-fluorouracil; hyperthemia; intraperitoneal chemotherapy; electrosurgery; mitomycin C; surgical oncology.

INTRODUCTION

Peritoneal seeding is a major cause of surgical treatment failure leading to death of patients with abdominal and pelvic malignancies. Despite curative surgery, 20–30% of patients will develop local cancer recurrence.[1,2] Traditionally, locoregional cancer recurrence with peritoneal implantation has been difficult to treat; most patients undergo palliative surgical procedures or no surgery at all.

Peritoneal carcinomatosis, sarcomatosis and mesothelioma may occur either concomitantly with a primary tumour or as a recurrence in patients who have had a prior surgical resection. In the former, dissemination of cancer cells is spontaneous and dependent upon the anatomical site, the histology, size and the depth of invasion by the primary tumour. In the latter, cancer metastases may be caused by spread during surgery.[3] The dissemination of cancer on the surface of the peritoneum may occur in the absence of lymphatic and haematogenous spread.

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Peritoneal seeding is a major cause of surgical treatment failure among patients with abdominal and pelvic malignancies. Cancer cells may be shed from the serosal surfaces prior to surgery and during surgical manipulations. A positive peritoneal fluid cytology has been detected in 25–30% of resectable gastric[4–6] and colonic cancer.[7] Surgical dissection results in the release of intraperitoneal cancer cells in 50–60% of cases.[8] These cancer cells were found to be viable and possess the ability to implant.[9,10] The disruption in the peritoneal lining may also provide a fertile area for tumour implantation as healing and the inflammatory response to occur.[11] The combined use of peritonectomy and peri-operative intraperitoneal chemotherapy is aimed at the complete eradication of the disease. This new approach requires the acquisition of new technical skills to ensure safety and efficacy.

CURRENT STRATEGY FOR COMBINED TREATMENT

Intraperitoneal chemotherapy and cytoreductive surgery are divided into four major steps: electrosurgery for tumour resection and peritonectomy; hyperthermic intraperitoneal chemotherapy; reconstruction; and early post-operative intraperitoneal chemotherapy. The use of dedicated instruments and adherence to specific surgical techniques are essential to achieve optimum results.

Electrosurgical dissection

Intra-abdominal dissection is facilitated by electro-evaporative surgery using a 0.3-cm ball-tipped diathermy.[12] The electrosurgical generator is set at a very high voltage between 200–250 MW. A maximal pure cut that evaporates the tissues on contact is used for dissection; it minimizes blood loss from small vessels up to 1.5 mm in diameter. Larger vessels are electrocoagulated or ligated in continuity and divided. Heat damage can be reduced by a frequent intermittent saline irrigation at the site of dissection. Heat necrosis at the tumour's margin of resection could reduce the likelihood of cancer dissemination and local recurrence.

Chemotherapy

The selection of agents for peri-operative intraperitoneal chemotherapy is based on the drug's ability to produce a cytotoxic effect over a short time period and to show heat synergy. Mitomycin C, doxorubicin and cisplatin have a slow clearance from the peritoneal cavity.[14,15] The effects of these agents are potentiated by hyperthermia to achieve a maximum cancer cell kill. Pharmacokinetic studies of intraoperative intraperitoneal chemotherapy report an absorption of 75–90% of the mitomycin C and cisplatin within the first hour.[16,17] Despite the greatly enhanced drug cytotoxicity because of high concentrations and heat synergy, the technique is effective only in treating small volume peritoneal disease. All the patients who undergo cytoreduction surgery proceed on to post-operative intraperitoneal 5-fluorouracil. 5-fluorouracil has a rapid first-pass effect through the liver. The use of early post-operative intraperitoneal chemotherapy may be restricted by the patients co-morbidity state.

Safety

The cumulative effect on long-term, low-dose occupational risk to peri-operative personnel exposed to hyperthermic intraperitoneal cytotoxic agents remains unknown, however, research to date suggests no measurable increased risk.[18] Guidelines for the safe administration and handling to cytotoxic agents are provided by the National Cancer Institute, the Occupational Safety and Health Administration, and the Joint Commission on Accreditation of Healthcare Organization.[19] The safety of all personnel in the operating room is paramount during the administration of chemotherapy. The use of eye protection, double gloving with outer elbow-length gloves secured with sterile tape and impervious gowns are essential to protect the operator. Incorporation of a plastic cover within the sutures to the skin edge prevents droplet contamination by splashes. A smoke evacuation system is used to remove vapours from the chemotherapy in the abdominal cavity.

OPERATIVE PROCEDURE

Patient position

Careful positioning is important for the prolonged surgical procedure of 10–12 hours, to minimize pressure areas. We advocate the lithotomy position with open legs, thighs flexed at 15° on the abdomen and legs flexed 30° on the thighs. The legs are supported with St. Mark's leg holders (AMSCO, Erie, PA, USA) surrounded by alternating pressure devices (SCB Compression Boots, Kendall Co., Boston, MA, USA) and protected from decubitus lesions by egg crate foam padding. The weight of the lower extremity is on the heel and not on the calf or popliteal crease.

Exposure

A vertical incision is made from the xiphoid to the symphysis pubis to allow maximum exposure; the xiphoid process is usually excised. During re-operation, excision of old surgical scars from the skin to the peritoneum including the umbilicus, reduces the risk of recurrence

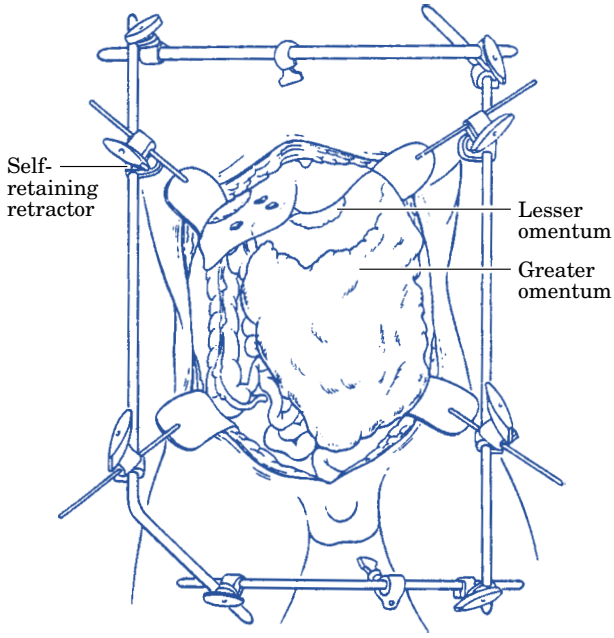

Figure 1 Abdominal incision and utilization of a self-retaining retractor.

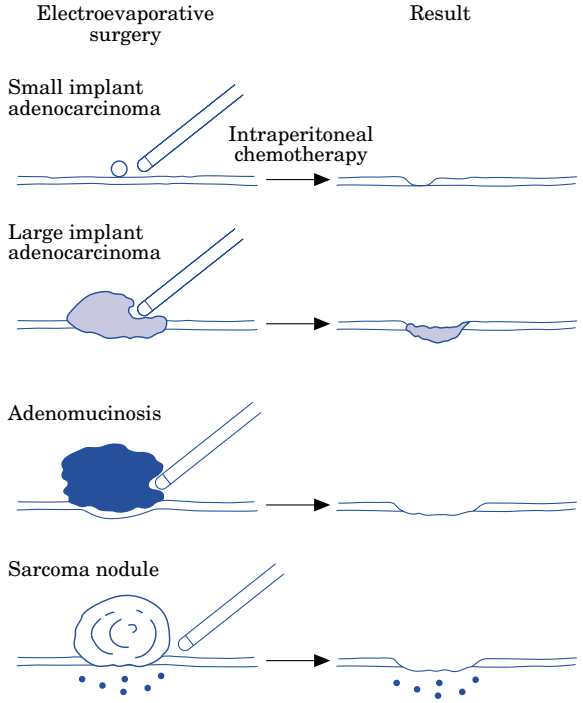

Figure 2 Effects of electro-evaporative surgery and peri-operative intraperitoneal chemotherapy on peritoneal surface malignancy.

at the sites of operation.[20,21] The Thompson self-retaining retractor (Thompson Surgical Instruments, Inc., Traverse City, MI, USA) improves the exposure, and multiple angles of retraction can be applied to gain maximum exposure for peritonectomy (Fig. 1).

Centripetal surgery

Peritoneal stripping begins at the furthest extent of the tumour and proceeds towards the deepest extent of the tumour and the major vessels. This centripetal surgery combines as many as six peritonectomy procedures into a single co-ordinated effort. It is necessary to allow optimum clearance and containment of the tumour with minimal bleeding and no damage to vital structures. Tumour manipulation may cause dislodgement of free cancer cells into the peritoneum or resection site. Care is taken to preserve the abdominal rectus muscle during peritonectomy but the posterior rectus sheath may be sacrificed.

Peritonectomy

This fundamental technique requires the removal and stripping of all tumour involving the parietal and visceral peritoneum. Small cancer deposits found on the visceral peritoneum, especially the surface of tubular structures, are individually electroevaporated. Large tumour nodules on the small bowel must be resected and all visible tumours must be removed to maximize the benefits of peri-operative intraperitoneal chemotherapy (Fig. 2).

Right and left upper quadrant peritonectomy

The falciform ligament and triangular ligaments of the liver are removed at the start of the operation. In right upper quadrant peritonectomy, peritoneum is stripped from the posterior rectus sheath in continuum. The dissection removes the peritoneum from the undersurface of the right hemidiaphragmatic muscle and fascia, and dissection extends to the bare area of the liver (Fig. 3). If the tumour is advanced and has an invasive component, peritoneal stripping of the tendinous portion of the diaphragm may result in penetration into the pleural cavity. Isolated patches of tumour on the liver surface are electrovaporated. A layer of tumour on the liver requires electro-evaporative surgical dissection beneath the Glisson's capsule to lift the tumour off the dome of the liver. In the left upper peritonectomy, the stripping away of the peritoneum will expose the left hemidiaphragm muscle and tendon, left adrenal gland, distal portion of the pancreas and the cephalad portion of the perirenal fat. Care is taken with the left gastric artery and coronary vein to protect the vascular supply of the stomach.

Greater omentectomy and splenectomy

The greater omentum is involved early in tumour dissemination within the coelomic space and its removal is important to reduce the risk of recurrence even if

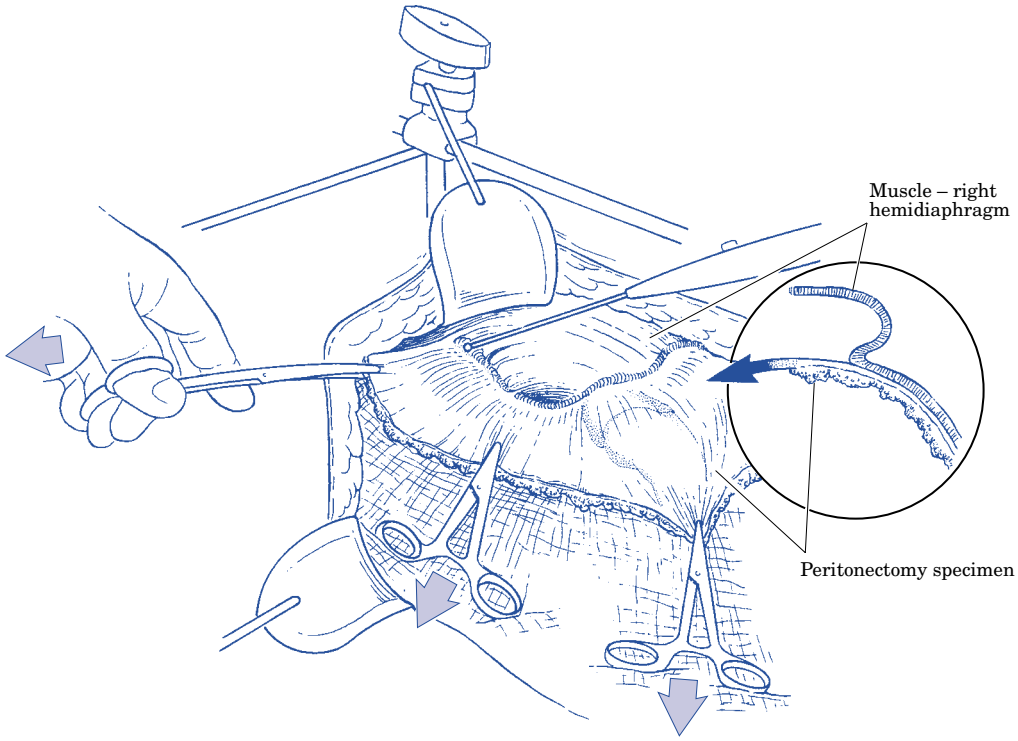

Figure 3 Right upper quadrant peritonectomy.

this structure appears normal. The greater omentum is resected to include the branches of the gastro-epiploic vessels on the greater curvature of the stomach and the short gastric vessels. All vessels are ligated and divided on the surface of the stomach. Early mobilization of the omentum improves exposure and enables an adequate visual assessment of the abdominal cavity, especially of the lesser sac. A splenectomy is performed to include the complete removal of tumour deposits on the anterior fascia of the pancreas.

Pelvic peritonectomy and rectosigmoid colectomy

Complete pelvic peritonectomy involves peritoneal stripping from the right and left caudal portions of the abdominal wall, the bladder and the iliac fossa preserving the ureters, resection of the sigmoid colon and mesosigmoid colon from the origin of the inferior mesenteric artery (Fig. 4). Stripping the peritoneum up to the duodenum and ligament of Treitz completes the peritonectomy and facilitates ligation of the inferior mesenteric artery and vein. The subperitoneal rectum and apex of vagina in women are removed en bloc including all the neoplastic tissues in the peritoneal cul-de-sac. Closure of the vagina is necessary before the intra-operative chemotherapy is initiated.

Cholecystectomy, lesser omentectomy, and stripping the floor of the omental bursa

Cholecystectomy is performed from the fundus. The structures of the porta hepatis are dissected free of tumour by a spreading clamp. Great care is taken to electro-evaporate the tumour from the anterior surface of the left caudate process and resect the gastrohepatic ligament in resection of the lesser omentum. Care is taken with the left gastric artery and vein to protect the vascular supply of the stomach.

After tumour resection, the abdominal and pelvic cavity are vigorously lavaged by many litres of warm saline solution aimed at mechanically eliminating viable cancer cells from fibrin and blood clots. The removal of fibrin and blood clots also helps reduce the risk of post-operative adhesions.

OPEN HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY

Hyperthermia optimizes the dose intensity of chemotherapy to the abdominal and pelvic surfaces. The combined use of hyperthermia and intraperitoneal chemotherapy has enhanced the cytotoxicity of the chemotherapeutic agents and increased tissue

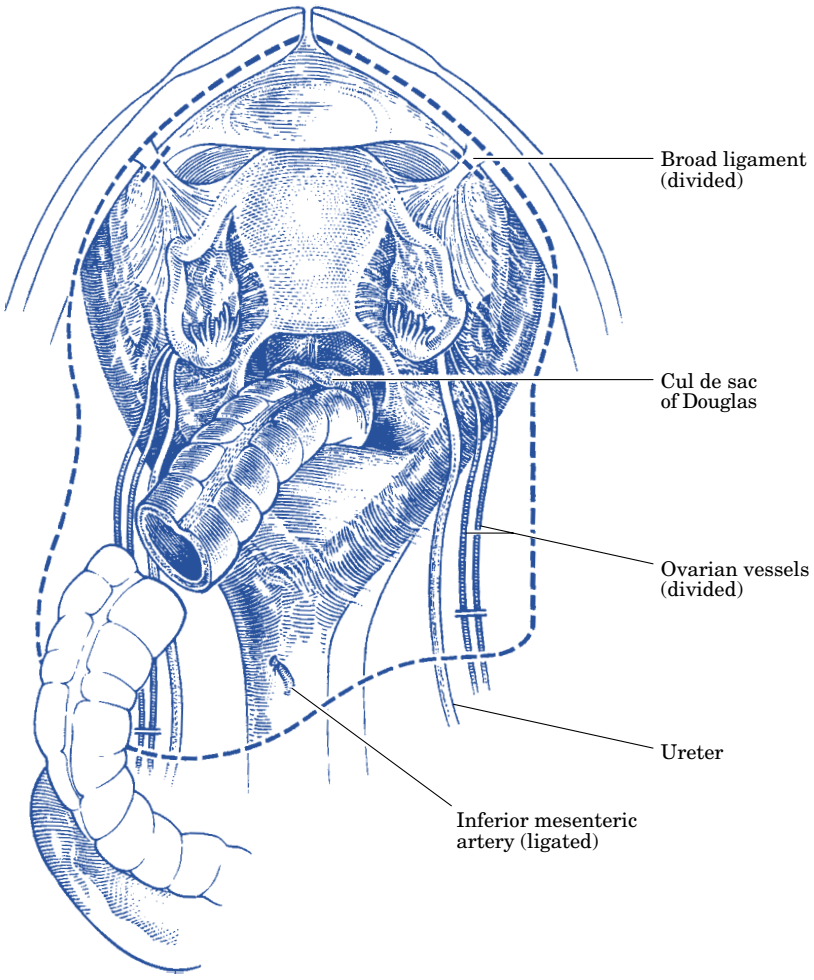

Figure 4 Line of peritoneal incision for complete pelvic peritonectomy.

penetration by chemotherapy in cancerous as compared to normal tissues.

A Tenckhoff inflow catheter (Quinton Spiral Peritoneal Catheter, Quinton, Inc., Seattle, WA, USA) and outflow drains are secured watertight with purse-string sutures on the skin of the abdomen. After priming and testing for leakages with one litre of 1.5% dextrose peritoneal dialysis solution, a total of three litres of chemotherapy solution are used to wash in the abdomen and pelvis. Care is taken to avoid spillage. The perfusate is externally heated to 44–46°C to achieve a core intraperitoneal fluid temperature of 41–42°C. Hyperthermic chemoperfusion is undertaken for a total of 90 min.

RECONSTRUCTIVE SURGERY

After performing the colorectal and other anastomoses, thoracic tubes are inserted in the right and the left pleural cavities to evacuate fluid accumulating in the chest following subdiaphragmatic resection. In gastrectomy cases a duodenal exclusion operation is performed to protect the esophagojejunal anastomosis. The jejunum is transected 20 cm distal to the ligament of Treitz. The proximal portion of jejunum is brought out to divert bile and digestive enzymes from the gastrointestinal tract. The distal portion is anastomosed with the esophagus using a circular stapler (Ethicon ILS29, Cincinnati, OH, USA). All anastomoses or ostomies are performed after the administration of intraoperative intraperitoneal chemotherapy.

Before closure the Tenchkoff catheter is placed in the left upper quadrant close to the ligament of Treitz or in the right subdiaphragmatic space. Drains are positioned in the pelvic cavity and subdiaphragmatic spaces. The abdomen is then closed in the usual fashion.

EARLY POST-OPERATIVE INTRAPERITONEAL CHEMOTHERAPY

Intraperitoneal chemotherapy is indicated following the complete resection of appendiceal, colonic, rectal, gastric

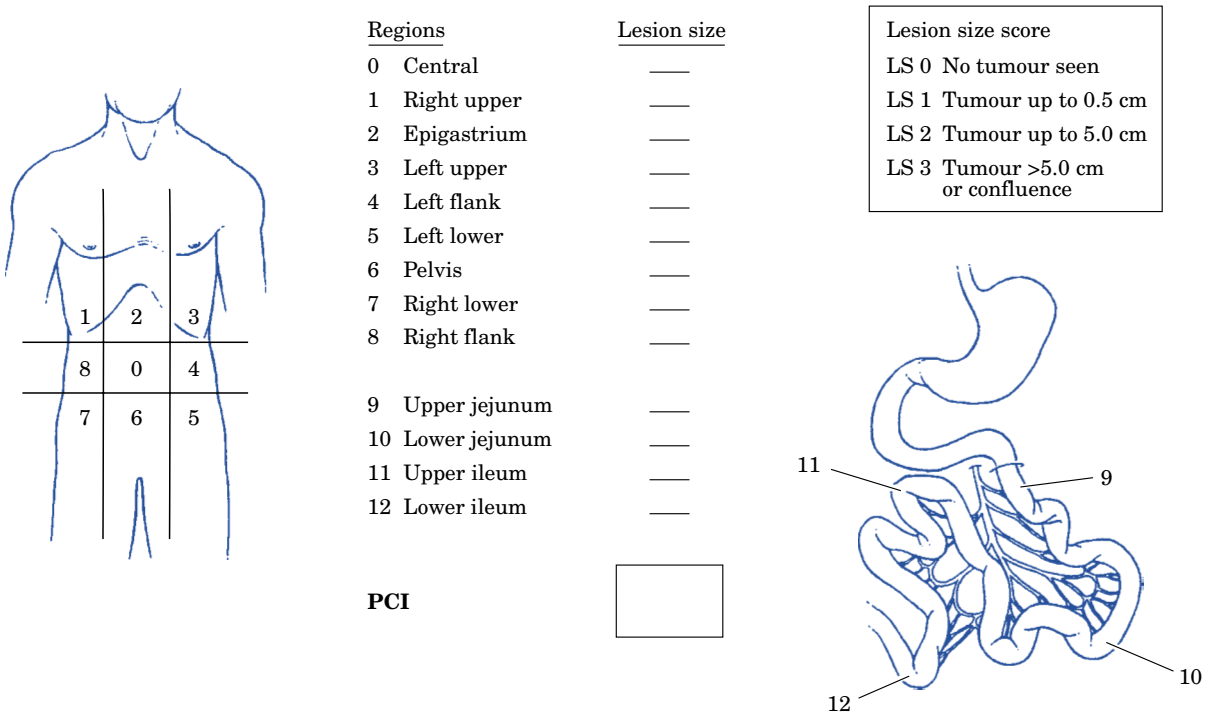

Figure 5 Peritoneal cancer index. The volume of tumour as assessed by the lesion size score is determined for the 13 abdomino–pelvic regions. The sum of these scores (0–39) is the peritoneal cancer index.

or other gastrointestinal carcinomas. Approximately 24 hours after surgery, early post-operative intraperitoneal chemotherapy is initiated and the drains are closed for 23 hours. The abdomen is then drained for 1 hour until the next chemotherapy infusion. This is repeated for 5 consecutive days.

PERITONEAL CANCER INDEX

The peritoneal cancer index is a quantitative prognostic score calculated after abdominal exploration and complete adhesiolysis (Fig. 5). The success of complete cytoreduction and long-term survival can be predicted by grading the distribution and the mass of peritoneal surface cancer.[22] It is not useful in grading minimally invasive tumours such as pseudomyxoma peritonei or cystic mesothelioma. In patients with peritoneal seeding from colon cancer, a score of 10 or less had a 5-year survival of 50%, from 11–20 a survival of 20%, and a score of greater than 20 survival of 0%.[23]

CYTOREDUCTION SCORE

Another quantitative prognostic score is the completeness of cytoreduction. For gastrointestinal cancer, the completeness of cytoreduction score has been defined as follows: CC-0, no visible peritoneal carcinomatosis remained after cytoreduction; CC-1, tumour nodules persist after cytoreduction but less than

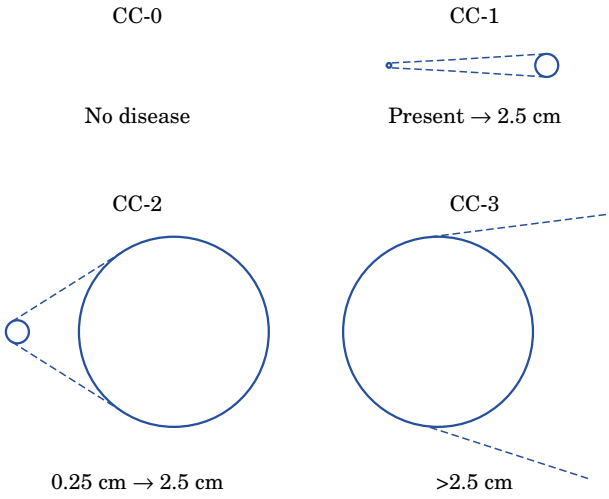

Figure 6 Completeness of cytoreduction after surgery score.

0.25 cm; CC-2, tumour of 0.25–2.5 cm; CC-3, tumour greater than 2.5 cm or a confluence of tumour unresectable at any site (Fig. 6).

Patients with complete cytoreduction have a higher chance of long-term survival, but incomplete cytoreduction rarely offers cure. In patients with peritoneal seeding from colon cancer a complete cytoreduction had a 40% 5-year survival; patients with an incomplete cytoreduction had a 0% 5-year survival.[23] It is important to note that no patient with long-term

survival have been reported undergoing surgery alone or surgery plus systemic chemotherapy.

POST-OPERATIVE COMPLICATION

Careful patient selection is crucial for the success of the peritonectomy procedure and intraperitoneal chemotherapy. The most common post-operative complication is prolonged intestinal ileus and gastric paresis. Nasogastric suction is maintained until there is evidence of bowel function such as passing gas per rectum and decreasing gastric drainage (less than 750 ml per day), especially of bile. Total parenteral nutrition is maintained until full caloric oral intake is achieved. A fifth of the patients will require parenteral feeding at home.

In the most recent study of 200 patients who had undergone cytoreductive surgery and heated intra-operative intraperitoneal chemotherapy for peritoneal carcinomatosis, peripancreatitis (7.1%) and bowel fistula (4.7%) were the most common reported major complications.[24] Peripancreatitis, a potentially life-threatening condition, occurs more frequently if the peritoneum and fat are stripped from the surface of the pancreas. A high index of suspicion for a peripancreatic collection needs to be exercised should the patient become febrile. Fluid collected from the drain placed at the superior aspect of the pancreas should be sent for assessment of lipase and amylase levels. The incidence of fistula formation, anastomotic leak, intestinal necrosis and prolonged ileus is reduced with the use of diverting and decompressing ileostomy. Overall, a quarter of the patients had grade III and IV complication. There was less than 2% (3/200) mortality rate.

SECOND-LOOK OPERATION

A second-look with closure of a diverting ileostomy or jejunostomy at 6–9 months is routinely performed in one-third of the patients. Eighty percent of the patients are found to have recurrences but have a complete redo cytoreduction in 80% of patients because of the low peritoneal cancer index.

Key Points

- Cytoreductive surgery reduces carcinomatosis to microscopic residual disease so that peri-operative intraperitoneal chemotherapy is able to eradicate cancer.
- Centripetal surgery is initiated at the furthermost extent of the tumour, it works in a retroperitoneal plane towards the centre of the abdomen and pelvis to complete an optimal cytoreduction.
- Hyperthermic intraoperative intraperitoneal chemotherapy enhances the cytotoxicity of the drugs, increases their penetration into cancerous tissue, and promotes uniform distribution.
- The two quantitative prognostic indicators useful in the assessment of outcome are the peritoneal cancer index and completeness of cytoreduction score.
- Knowledgeable patient selection is necessary in order to avoid low-benefit surgery that because of its extent carries high morbidity, mortality, and cost.
- Dedication to technical perfection with surgery and a knowledgeable management of intraperitoneal chemotherapy are essential to the development of a programme in peritoneal surface malignancy.

DISCUSSION

The successful management of peritoneal surface malignancies depends on several factors: the presence of co-morbid disease, the disease stage, tumour biology, the completeness of cancer excision and the elimination of minimal residual cancer by chemotherapy. The higher success rate associated with the treatment of cystadenocarcinoma, cystic mesothelioma and low-grade sarcomas are attributable to their expansive growth, with minimal invasion of the underlying structures. In contrast, poorer results obtained with adenocarcinomas are related to the infiltrative nature of these tumours. In all conditions, an imperfect peritonectomy will result in an early recurrence and treatment failure.

The surgical procedure for the management of peritoneal malignancies poses a steep learning curve. It is technically and physically demanding with long operative time and a risk of excessive blood loss. Furthermore, the administration of early post-operative intraperitoneal chemotherapy may be compromized by the patients' post-operative status. These factors may contribute to poor treatment outcome during the early stages of a programme in treating peritoneal surface malignancy and may deter many surgeons.[25] However, the use of electroevaporation surgery has revolutionized the radical excision of peritoneal malignancies by minimizing blood loss.

The pharmacokinetic advantages to intraperitoneal chemotherapy have been well described.[26] The success of intraperitoneal chemotherapy is dependent on the elimination of residual cancer cells following complete resection. However, the benefit of intraperitoneal chemotherapy is localized to the surface area of infusion. Drug diffusion occurs but the tissue penetration is limited to 1–2 mm from the surface.[26–28] We believe that the open technique is superior to the closed technique in allowing adequate and uniform exposure of all the abdominal and pelvic surfaces to intraperitoneal chemotherapy, as demonstrated by the dye studies. In contrast many areas are unstained with dye when the closed technique is employed, especially the lesser

omentum, the base of the mesentery, the pelvis and the suture lines. As a result, recurrence of tumour often occurs on these sites of poor chemo-perfusion.[20]

SUMMARY

Traditionally, peritoneal surface malignancy was regarded as a terminal condition for which surgery was indicated only no palliative effort. Advances in cytoreductive surgery and perioperative intraperitoneal chemotherapy have improved the surgical approach for this condition.[23,25,29–32] Also, new evidence from tumour biology research suggests that peritoneal carcinomatosis, sarcomatosis and mesothelioma may occur without systemic dissemination, which has sparked new interest in these conditions. Curative treatment for peritoneal surface malignancies requires a complete cytoreduction followed by intraperitoneal chemotherapy. The careful selection of patients for a complete cytoreduction with curative intent *vs* appropriate surgical palliation remains a crucial component of management to ensure that patients with unresectable disease receive the appropriate palliation. This paper describes the current strategy for the management of patients with peritoneal carcinomatosis, sarcomatosis and mesothelioma. The relevant technical details specific to this form of treatment include patient position, incision and exposure, electroevaporative dissection, complete lysis of adhesion, peritonectomy procedures, reconstructive surgery and intraperitoneal chemotherapy improved.

REFERENCES

1. Abulafi AM, Williams NS. Local recurrence of colorectal cancer: the problem, mechanisms, management and adjuvant therapy. *Br J Surg* 1994; **81**: 7–19.
2. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *Semin Oncol* 1999; **26**: 536–9.
3. Fortner JG. Inadvertent spread of cancer at surgery. *J Surg Oncol* 1993; **53**: 191–6.
4. Koga S, Kaibare N, Litsuka Y, Kudo H, Kumura A, Kiraka H. Prognostic significance of intraperitoneal free cancer cells in gastric cancer patients. *J Cancer Res Clin Oncol* 1984; **108**: 236–8.
5. Baba H, Korenaga D, Haraguchi M, Okamura T, Saito A, Watanabe A, Sugimachi K. Width of serosal invasion and prognosis in advanced human gastric cancer with special reference to the mode of tumor invasion. *Cancer* 1989; **64**: 2482–6.
6. Haraguchi M, Watanabe A, Kakeji Y, Tsujitani S, Baba H, Maehara Y, Sugimachi K. Prognostic significance of serosal invasion in carcinoma of the stomach. *Surg Gynecol Obstet* 1991; **172**: 29–32.
7. Zeng Z, Cohen A, Hajdu S, *et al.* Serosal cytological study to determine free mesothelial penetration of intraperitoneal colon cancer. *Cancer* 1992; **70**: 737–40.
8. Hansen E, Wolff N, Knuechel R, Ruschoff J, Hofstaedter F, Taeger K. Tumor cells in blood shed from the surgical field. *Arch Surg Oncol* 1995; **130**: 387–93.
9. Izuka Y, Kaneshita S, Taneda O, Takeuchi T, Koga S. Intraperitoneal free cancer cells and their viability in gastric cancer. *Cancer* 1979; **44**: 1476–86.
10. Tanida O, Kaneshima S, Izuka Y, Kuda H, Kigasu Y, Koga S. Viability of intraperitoneal free cancer cells in patients with gastric carcinoma. *Acta Cytol* 1982; **26**: 681–7.
11. Savalgi RS. Mechanism of abdominal wall recurrence following laparoscopic resection of colonic cancers. *Sem Lap Surg* 1995; **2**: 158.
12. Sugarbaker PH. Laser-node electrosurgery. In: Sugarbaker PH (ed). *Peritoneal carcinomatosis: principles of management.* Boston: Kluwer Academic Publishers, 1996; pp. 375–85.
13. Howell SB, Pfeifle CL, Wung WE, *et al.* Intraperitoneal cisplatin with systemic thiosulfate protection. *Ann Intern Med* 1982; **97**: 845.
14. Hayashi T, Nasu Y, Aramaki K, Johnsen T, Matsuura H. A case of peritoneal malignant mesothelioma with disappearance of ascites result of intraperitoneal instillation of mitomycin C and oral administration of UFT. *Gan To Kagaku Ryoho* 1989; **16**: 2449–52.
15. Sugarbaker PH, Cunliffe WJ, Graves T, *et al.* Phase I and pharmacologic studies with early postoperative intraperitoneal epiadriamycin. Fourth International Conference on Advances in Regional Cancer Therapy. Berchtesgaden, Germany, 1989.
16. Fernandez-Trigo V, Stuart OA, Stephen AD, Hoover LD, Sugarbaker PH. Surgically directed chemotherapy: Heated intraperitoneal lavage with mitomycin C. In: Sugarbaker PH (ed). *Peritoneal carcinomatosis: Drugs and disease.* Kluwer: Boston, 1996; pp. 51–61.
17. Stephens AD, Belliveau J, Sugarbaker PH. Intraoperative hyperthermic lavage with cisplatin for peritoneal carcinomatosis and sarcomatosis. In: Sugarbaker PH (ed). *Peritoneal carcinomatosis: Drugs and disease.* Kluwer: Boston, 1996; pp. 15–30.
18. Stuart OA, Stephens AD, Welch L, Sugarbaker PH. Safety monitoring of the coliseum technique for heated intraoperative intraperitoneal chemotherapy with mitomycin C. *Ann Surg Oncol* (in press).
19. White SK, Stephens AD, Sugarbaker PH. Hyperthermic intraoperative intraperitoneal chemotherapy safety consideration. *AORN J* 1996; **63**: 716–24.
20. Zoetmulder FAN, Sugarbaker PH. Pattern of failure following treatment of pseudomyxoma peritonei of appendiceal origin. *Eur J Cancer* 1996; **32**: 1727–33.
21. Hughes ESR, McDermott FT, Polglase L, *et al.* Tumor recurrence in the abdominal wall scar tissue after large-bowel cancer surgery. *Dis Colon Rectum* 1983; **26**: 571.
22. Esquivel JE, Sugarbaker PH. Elective surgery in recurrent colon cancer with peritoneal seeding: When to and when not to operate (Editorial). *Cancer Therapeutics* 1998; **1**: 321–5.
23. Sugarbaker PH. Successful management of microscopic residual disease in large bowel cancer. *Cancer Chemother Pharmacol* 1999; **43 (Suppl)**: S15–S25.
24. Stephens AD, Alderman R, Chang D, Edwards GD, *et al.* Morbidity and mortality of 200 treatments with cytoreductive surgery and hyperthermic intraoperative intraperitoneal chemotherapy using the Coliseum technique. *Ann Surg Oncol* 1999; **6**: 790–6.
25. Cavaliere F, Di Filippo F, Botti C, Cosimelli M, *et al.* Peritonectomy and hyperthermic antiblastic perfusion in the treatment of peritoneal carcinomatosis. *Eur J Surg Oncol* 2000; **26**: 486–91.
26. Markman M. Intraperitoneal chemotherapy for malignant diseases of the gastrointestinal tract. *Surg Gynecol Obstet* 1987; **164**: 89.
27. Los G, Verdegaal EM, Mutsaers PH, McVie JG. Penetration of carboplatin and cisplatin into rat peritoneal tumor nodules after intraperitoneal chemotherapy. *Cancer Chemother Pharmacol* 1991; **28**: 159–65.
28. Los G, van Vugt MJH, Pinedo HM. Potentiation of i.p. chemotherapy by abdominal hyperthermia in rats. 83rd Annual Meeting of the AACR. San Diego, California 1992, **33**: 2980.
29. Panteix G, Guillamont M, Cherpin L, Cuichard J, Gilly FN, *et al.* Study of the pharmacokinetics of mitomycin C in humans during intraperitoneal chemohyperthermia with special mention of the concentration in local tissues. *Oncology* 1993; **50**: 366–70.
30. Yonemura Y, Fujimura T, Nishimura G, *et al.* Effects of intraoperative chemo-hyperthermia in patients with gastric cancer with peritoneal dissemination. *Surgery* 1996; **199**: 437–44.
31. Fujimoto S, Takahashi M, Mutou T, *et al.* Improved mortality rate of gastric carcinoma patients with peritoneal carcinomatosis treated with intraperitoneal hyperthermic chemoperfusion combined surgery. *Cancer* 1997; **79**: 884–91.
32. Sayag-Beaujard AC, Francois Y, Glehen O, *et al.* Intraperitoneal chemo-hyperthermia with Mitomycin C for gastric cancer patients with peritoneal carcinomatosis. *Anticancer Res* 1999; **19**: 1375–82.

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