Peritoneal carcinomatosis from digestive tract cancer: new management by cytoreductive surgery and intraperitoneal chemohyperthermia

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Peritoneal carcinomatosis is a common manifestation of digestive-tract cancer and has been regarded a terminal disease with a short median survival. Over the past decade, a new locoregional therapeutic approach combining cytoreductive surgery with intraperitoneal chemohyperthermia (IPCH) has evolved. Because of its limited benefits, high morbidity and mortality, and high cost, this comprehensive management plan requires accurate patient selection. Quantitative prognostic indicators are needed to assess a patient's eligibility for combined treatment, including tumour histopathology, classification of carcinomatosis extent, assessment of completeness of cytoreduction, and determination of the extent of previous surgery. Patients with pseudomyxoma peritonei and those with peritoneal dissemination of digestive-tract cancer have shown promising survival. Complete cytoreduction with no visible disease persisting is a requirement for long-term benefit. In Japan and Korea, use of IPCH as prophylactic treatment in potentially curative gastric-cancer resection has shown improved survival and lower peritoneal recurrence rates. IPCH combined with cytoreductive surgery seems to be an effective therapeutic approach in carefully selected patients, and offers a chance for cure or palliation in this condition with few alternative treatment options.

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In the past, carcinomatosis from digestive-tract cancer (figure 1) was thought to be a terminal disease; most oncologists regarded it a condition only to be palliated. Published work about the natural history of this condition is not extensive. However, results of three studies[1–3] have shown a median survival of about 6 months. Palliative systemic chemotherapy has shown encouraging tumour response rates, but with no improvement in survival.[2,4,5] In the 1980s, a renewed interest in peritoneal-surface malignant diseases developed through new multimodal therapeutic approaches. Previously unexplored treatment options such as peritonectomy,[6] intraperitoneal injection of the anticancer drug OK432,[7] intracavitary immunotherapy,[7] intraperitoneal chemohyperthermia (IPCH),[8,9] and early postoperative intraperitoneal chemotherapy,[10] were also investigated.

Promising results have been reported for comprehensive cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. This new management plan can be used for palliative treatment of carcinomatosis that is not accessible to complete macroscopic cytoreduction. It is the only plan that has shown curative results for carcinomatosis in phase II and a few phase III trials. Although these data were viewed with great scepticism for many years, many patients with carcinomatosis survived in the long term.[8,11–14]

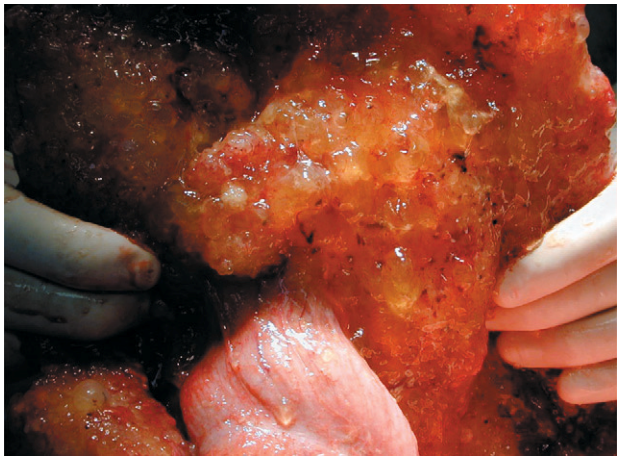

Figure 1. Intraoperative pictures showing stage 4 disease with massive involvement of the greater omentum by a mucinous tumour.

Here, we discuss the natural history of digestive carcinomatosis, the clinical techniques for quantitative assessment of the disorder, and the therapeutic approach of cytoreductive surgery and peritonectomy procedures combined with IPCH.

Natural history

The primary peritoneal malignant disorders such as malignant mesothelioma and papillary serous carcinoma are rare. By contrast, peritoneal dissemination from digestive cancers is common. In colorectal cancer, despite advances in early detection of the primary tumour, carcinomatosis is detected in about 10% of patients at the time of primary cancer resection.[2,3] 10–20% of patients being investigated for

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Table 1. Histopathological features of epithelial mucinous tumours of appendiceal, colonic, and small bowel

Feature	DPAM	PMCA
Primary site	Appendix	Appendix, colon, small intestine
Primary diagnosis	Mucinous adenoma usually when a mucocoele	Mucinous adenocarcinoma
Surgical appearance	Mucinous tumours and mucinous ascites with redistribution	Carcinomatosis with variable mucinous ascites, redistribution is prominent with large volume of ascites
Peritoneal tumour	..	..
Cellularity	Scant	Moderate to abundant
Morphology	Abundant extracellular mucin containing simple to focally proliferative mucinous epithelium. Single layer of cells	Moderate to abundant extracellular mucin containing extensively proliferative mucinous epithelium or mucinous glands, clusters of cells, or individual cells consistent with carcinoma
Cytological atypia	Minimum	Moderate to marked
Mitotic activity	Rare	Infrequent to frequent
Lymph-node involvement	Almost never	Moderate
Liver metastases	Almost never	Very infrequent
Parenchymal organ invasion	Rare (except ovary)	Frequent

DPAM, disseminated peritoneal adenomucinosis; PMCA, peritoneal mucinous carcinomatosis. Hybrid tumours show less that 5% of PMCA within DPAM. Mucinous carcinomas divided into three grades by maintenance or loss of glandular architecture.

potentially curative resection of gastric cancer will have peritoneal seeding at the time of abdominal examination, and half of patients with gastric cancer will present with peritoneal carcinomatosis.[15] The mechanisms causing carcinomatosis are multifactoral and include peritoneal dissemination of free cancer cells as a result of serosal involvement of the primary tumour,[16] implantation of free cancer cells caused by the presence of adhesion molecules,[17] and presence of cancer cells in lymph fluid or venous blood retained within the peritoneal cavity.

Three main prospective studies have been done to document the clinical features and natural history of carcinomatosis from non-gynaecological malignant disorders. In 1989, Chu and colleagues[1] recorded an overall median survival of 6 months in 100 patients with miscellaneous non-gynaecological carcinomatosis. A decade later, a French multicentric prospective study[1] of 370 patients showed an overall median survival of 3·1 months: 5·2 months for colorectal cancer, 3·1 months for gastric cancer, 2·1 months for pancreatic cancer, and 1·5 months for carcinomatosis from an unknown primary cancer. In 2002, Jayne and colleagues[3] did a retrospective analysis of 3019 patients with colorectal cancer. 13% of patients were identified with peritoneal carcinomatosis, and the median survival of patients with synchronous disease was 7 months. All these studies identify the inability to reliably diagnose carcinomatosis, either with the primary malignant tumour or with recurrent cancer, as a major diagnostic shortcoming. In current surgical practice, patients with carcinomatosis from digestive-tract cancer have a poor prognosis and are usually referred for systemic chemotherapy. Unfortunately, in these patients, long-term survival is rarely, if ever, achieved.[18,19]

Assessment of prognosis

Quantitative prognostic indicators have been used successfully in several surgical disciplines and serve as guidelines to select patients who are most likely to respond to treatment. Often, the major value of the quantitative prognostic assessment is to exclude patients who have little or no chance of benefiting from expensive, high-risk management protocols. Several specialised teams have identified a series of clinical assessments to select patients for cytoreduction plus perioperative chemotherapy.[20]

Histopathology

Accurate assessment of the biological aggressiveness of a malignant disease is essential to plan treatment. Mucinous epithelial tumours of appendiceal origin that show peritoneal dissemination have been extensively investigated, and a histopathological classification has been published.[21] Patients are scored by the morphology of the mucinous tumour—as adenomucinosis, mucinous, or a hybrid. This classification depends on the histological character of malignant cells (differentiation), the glandular morphology, the stroma on which the epithelial cells are based, the presence or absence of signet-ring cells, and evidence of tissue invasion (table 1). The survival of patients treated by cytoreductive surgery and intraperitoneal chemotherapy is strongly affected by the histological type of the tumour.[8] Non-invasive mucinous tumours have repeatedly been found to respond more definitively to cytoreductive surgery and intraperitoneal chemotherapy than to invasive mucinous tumours.[17]

Gilly staging of peritoneal carcinomatosis

Gilly staging was described in 1994 and takes into account the size and distribution of malignant granulations (table 2). Its two main advantages are simplicity and reproducibility. The usefulness of this technique was shown in a prospective study of 370 patients from nine treatment centres who had had surgery for peritoneal carcinomatosis from

Table 2. Gilly staging of peritoneal carcinomatosis

Stage	Description
Stage 0	No macroscopic disease
Stage 1	Malignant granulations less than 5 mm in diameter. Localised in one part of the abdomen
Stage 2	Malignant granulations less than 5 mm in diameter. Diffuse to the whole abdomen
Stage 3	Localised or diffuse malignant granulations 5–20 mm in diameter
Stage 4	Localised or diffuse large malignant masses (more than 2 cm in diameter)

non-gynaecological malignant disorders.[1] Patients with peritoneal carcinomatosis stage 1 and 2 (malignant granulations <5 mm) survived significantly longer than those with stage 3 and 4 tumours (malignant granulations ⩾5 mm; figure 1). However, a shortcoming of this staging system is that it does not clearly indicate the potential resectability of carcinomatosis. Stage 2 disease could consist of diffuse peritoneal carcinomatosis with nodules of less than 5 mm that are non-resectable. Conversely, stage 3 and 4 disease could include diffuse and localised peritoneal carcinomatosis with nodules of 5 mm or greater that are resectable. Despite this limitation, the Gilly staging system has been proved to be an important prognostic indicator in several clinical trials.[1,9,22,23]

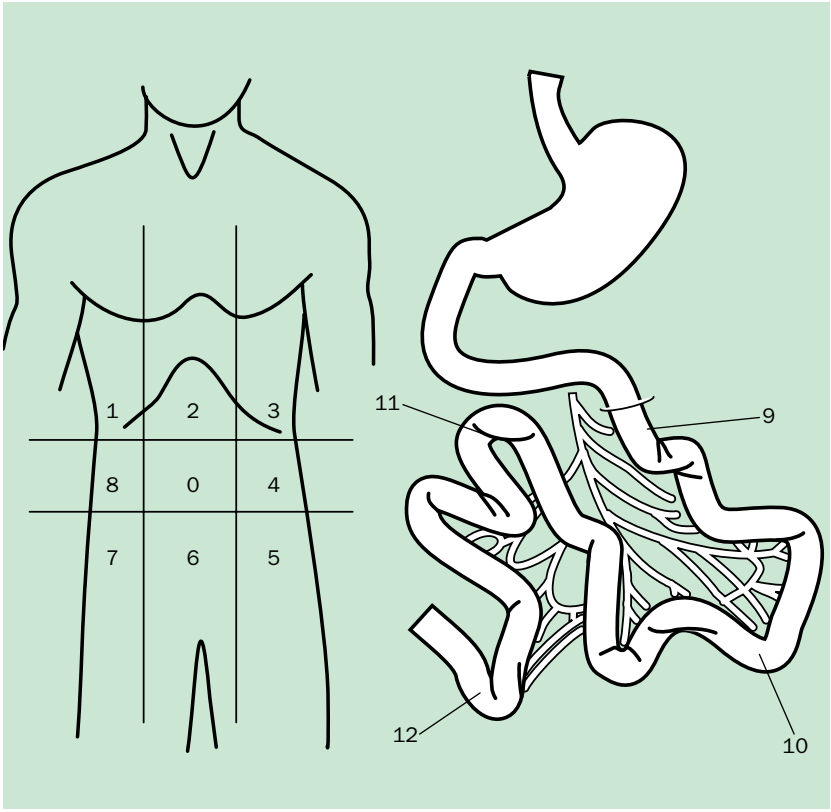

Figure 2. Peritoneal Cancer Index (PCI). The abdomen and the pelvis are divided into 12 regions. The lesion sizes of the largest implants are scored (0 through 3) in each abdominopelvic region. They can be summed as a numerical score, which varies from 1 to 39.

Japanese Research Society for Gastric Cancer

In Japan, carcinomatosis from gastric carcinoma is classified by the Japanese Research Society for Gastric Cancer[24] as follows: P0, no implants to the peritoneum; P1, cancerous implants to the region directly adjacent to the stomach peritoneum (above the transverse colon) including the greater omentum; P2, several scattered metastases to the distant peritoneum and ovarian metastasis alone; and P3, numerous metastases to the distant peritoneum. This classification has been used in some Japanese studies as an accurate quantitative prognostic indicator.[25,26] For example, Fujimoto and colleagues[27] reported significantly lower survival in patients with P3 carcinomatosis than in those with P2 or P1 classification after treatment combining cytoreductive surgery and IPCH.

Peritoneal Cancer Index (PCI)

The PCI is more precise assessment of carcinomatosis quantification and distribution than the Gilly staging system, and was described by Jacquet and Sugarbaker.[28] It assesses quantitatively the distribution and implant size of the cancer throughout the abdomen and pelvis (figure 2). The abdomen and the pelvis are divided by lines into nine regions (AR 0–8). The small bowel is then divided into another four regions. Regions 9 and 10 define the upper and lower portions of the jejunum, regions 11 and 12 define the upper and lower portions of the ileum. The lesion size of the largest implants is scored in each abdominopelvic region. Implants are scored as lesion size 0 through 3 (LS-0 to LS-3). LS-0 means no implants are seen throughout the region; this measurement is made after a complete lysis of all adhesions and the complete inspection of all parietal and visceral peritoneal surfaces. LS-1 refers to implants that are visible up to 0·5 cm in greatest diameter. LS-2 identifies nodules greater than 0·5 cm and up to 5 cm. LS-3 refers to implants 5 cm or greater in diameter. This method quantifies the extent of disease within each region of the abdomen and pelvis, and they can be summed as a numerical score (which varies from 1 to 39) for the peritoneal cavity as a whole.

The PCI method also allows an estimate of the probability of a complete cytoreduction.[17] The PCI score that would serve as a threshold for favourable versus poor prognosis has been reported for several tumour types. For colorectal carcinomatosis, Elias and colleagues[12] reported that the survival results were significantly better when the PCI was lower than 16 than when 16 or higher. Sugarbaker[17] suggested that carcinomatosis from colon cancer with a PCI of greater than 20 should be treated only with palliative intent, and that IPCH is seldom indicated.

Simplified PCI

At the Netherlands Cancer Institute, the size of the tumour is recorded on standardised forms indicating large (>5 cm), moderate (1–5 cm), small (<1 cm), or no involvement in seven abdominal regions: I-pelvis; II-right lower abdomen; III-greater omentum, transverse colon, spleen; IV-right subdiaphragmatic region; V-left subdiaphragmatic region; VI-subhepatic and lesser omentum region; VII-small bowel and small-bowel mesentery.[29] This assessment has been referred to as the Simplified PCI, or SPCI. The system has

been used for staging of colorectal and appendiceal cancer and can be used to predict outcome after cytoreductive surgery and IPCH. According to the Dutch group, patients with a high SPCI have greater morbidity and mortality when combined treatment is used than in patients with low SPCI.

Previous surgical score (PSS)

Previous surgeries might modify the pathobiology of the peritoneal-surface malignant tumour. Wound sites induced by surgical trauma have been shown to promote implantation of tumour cells.[30] Once implanted in the wound sites and contained by avascular scar tissue, tumour cells can become resistant to further chemotherapy.[31] Treatment for patients with carcinomatosis that has progressed deep in the peritoneal surface is jeopardised because peritonectomy with a tumour-free deep surface is no longer possible. Therefore, the number of interventions and the extent of the surgical procedures should be taken into account before deciding on cytoreduction with IPCH. A scoring system of previous surgical interventions, the PSS, has been established by Sugarbaker's team.[28] The number of abdominopelvic regions is, by convention, additive for all previous surgical procedures. In this regard the PSS is a composite of all previous surgeries and seems to be an important quantitative prognostic factor. For patients with pseudomyxoma, a PSS of 0–2 (fewer than five abdominal regions previously dissected) was associated with a 25% improved survival compared with those with PSS of 3 (extensive previous cytoreduction with more than five abdominal regions dissected).[32]

Assessment of complete cytoreduction

The size of tumour nodules remaining after cytoreduction has been shown to predict prognosis by estimating the possibility of cancer eradication by IPCH. Results of several studies[12,13,33,34] have shown a direct relation between the completeness of cytoreductive surgery and survival for carcinomatosis from all primary cancer locations. The Lyon group[13] has successfully used complete (R0–R1) or incomplete (R2) cytoreduction to assess the completeness of surgical clearance of cancer. Confirming an R0 resection is difficult in patients with carcinomatosis; thus, R0 and R1 can be grouped together because the outcome of these two groups is very similar.[9,22,35]

Jacquet and Sugarbaker[28] used the completeness of cytoreduction score (CC score) to assess surgical clearance of carcinomatosis. A CC-0 score indicates that no peritoneal seeding was exposed during the complete exploration; CC-1 that tumour nodules persisting after cytoreduction are less than 2·5 mm in diameter; CC-2 that nodules are between 2·5 mm and 25 mm in diameter; and CC-3 score that nodules are greater than 25 mm in diameter or a confluence of unresectable tumour nodules at any site within the abdomen and the pelvis. CC-2 and CC-3 cytoreductions are regarded incomplete. The CC score should be modified according to the chemoresponse of the tumour to intraperitoneal chemotherapy. The more resistant the cancer is, the smaller the implant needed for a CC-1 score.

In both non-invasive and invasive peritoneal-surface malignant disease, the CC score is a major prognostic indicator. It has been used to accurately predict prognosis of pseudomyxoma peritonei and colorectal carcinomatosis.[32,36]

Rationale for locoregional treatment

IPCH

Intraperitoneal administration of anticancer drugs has many pharmacokinetic advantages and gives high response rates within the abdomen compared with other treatments because the peritoneal plasma barrier provides dose-intensive therapy. High concentrations of anticancer drugs can be in direct contact with tumour cells, with reduced systemic concentrations and lower systemic toxicity.[37] Heat has been shown to be cytotoxic in vitro at 42·5°C.[38] Hyperthermia at 42°C has been shown to enhance the antitumour effects of agents such as oxaliplatin, mitomycin, doxorubicin, and cisplatin, by augmenting cytotoxicity and increasing the penetration of drugs into tissue.[17,36,39,40] This notion of thermal enhancement of drugs with hyperthermia lead to a new locoregional treatment being developed: IPCH. The amount of hyperthermia varies, but most teams aim for an homogeneous intraperitoneal temperature of 42–43°C.[17,37,41]

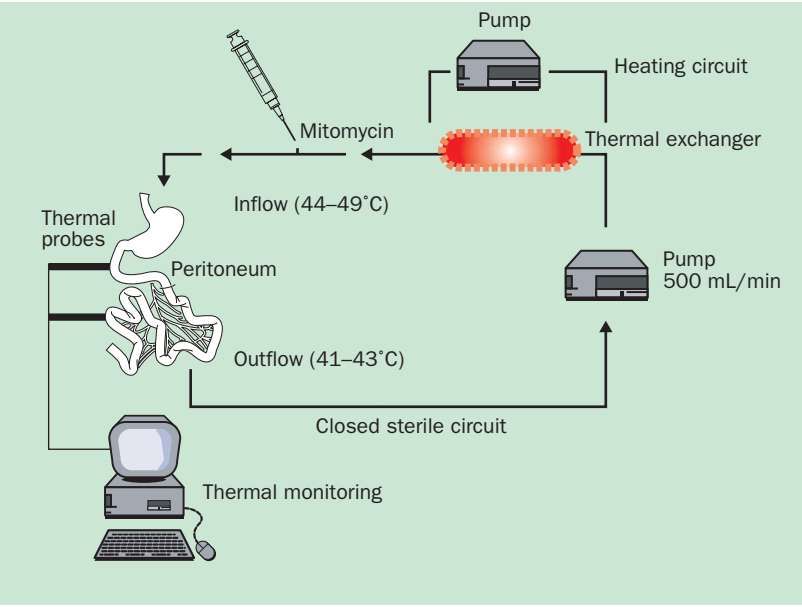

Figure 3. Lyon closed-circuit IPCH device.

Cytoreductive surgery and peritonectomy

Reducing tumour volume has always been judged an important factor in achieving tumour response to chemotherapy,[12,13] and has been reported for ovarian cancer.[42,43] The combination of cytoreductive surgery and peritonectomy procedures with IPCH could act as a dose-intensification device, leading to

better results. From a theoretical perspective, cytoreductive surgery is used to treat macroscopic disease, and IPCH to treat microscopic residual disease; the end result is complete eradication of disease with a single procedure.[13] Intraperitoneal chemotherapy penetrates into peritoneal carcinomatosis nodules by only 2–5 mm, even when combined with heat.[17,37,44] Thus, the goal of cytoreductive surgery for curative intent is to achieve maximum reduction of tumour volume. Only in pseudomyxoma peritonei has long-term survival been reported without a macroscopic complete resection or without a sufficient reduction in tumour volume.[32]

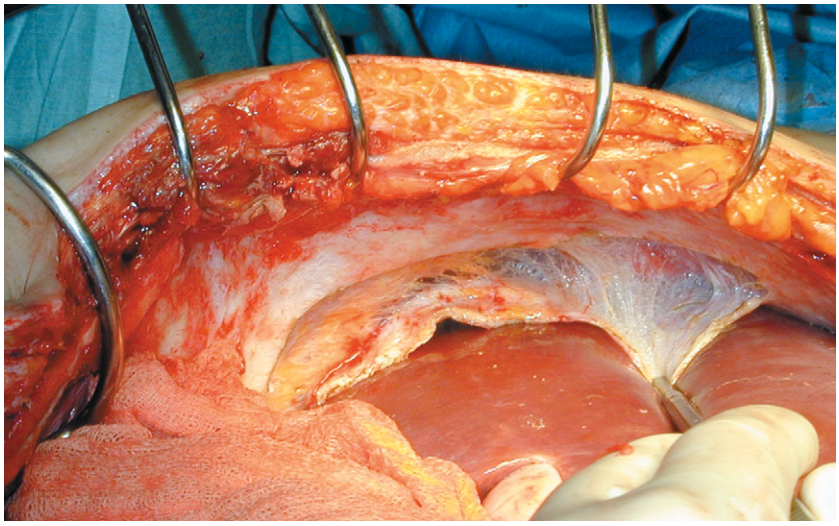

Figure 4. Parietal peritonectomy or stipping of the peritoneum under the right diaphragmatic cupula.

IPCH technique

Devices

Several different IPCH devices have been described.[45] Constant hyperthermia is obtained by a closed continuous circuit, with pump, heater, heat exchanger, and real-time temperature monitoring. Figure 3 illustrates the Lyon closed circuit. Open circuits (without recirculation and reheating of the instillate) should be avoided.[41]

Elias and colleagues[45] did a prospective phase II trial testing seven different techniques in 32 patients. They found that complete closure of the abdominal wall before the perfusion restricted the volume of the perfusion, decreased spatial diffusion of the instillate, and resulted in lack of thermal homogeneity. Use of a peritoneal-cavity expander allowed an immediate thermal homogeneity, but the expander isolated the abdominal wall from the instillate, resulting in early parietal peritoneal recurrence. Use of an open abdominal-cavity technique with the skin edges raised by a retractor placed above the patient was identified as the best technique in terms of thermal homogeneity and spatial diffusion.[45]

The open abdominal-cavity technique has advantages but can pose an environmental hazard in the operative room, even though no evidence exists that vapour coming from an open cavity has toxic effects. The closed abdomen technique has been refined with modelling studies to optimise thermal homogeneity,[46] but as yet there is no in vivo evidence that complete spatial diffusion of the instillate can be achieved.[45] Intraperitoneal chemotherapy with positive pressure has been reported to enhance the penetration of drugs into tissue.[47] A consensus about the ideal technique is not yet available.

Duration, perfusate, and drugs

The volume of perfusate used in the different protocols is calculated according to the body surface area. Most teams have used isotonic perfusate, since hypotonic solution can cause intraperitoneal haemorrhage.[48] Pharmacokinetic studies done at the Washington Cancer Institute showed that use of hypertonic carrier solution enhanced the exposure of peritoneal surfaces and of residual tumour cells to anticancer drugs.[49,50]

The duration of the procedure varies according to investigators from 30 min to 120 min. An increased drug concentration in the instillate with a shorter bathing duration would probably give similar pharmacokinetic results to a longer bathing duration with decreased drug concentration. The best duration is not known and depends on the protocol used.[41]

The rationale behind choice of drug is based on the intraperitoneal pharmacokinetics of the agent. The most frequently used regimens are mitomycin alone, cisplatin alone, or a combination of both.[37,41] Other agents have been used in few phase I-II studies: oxaliplatin,[48] doxorubicin, tumour necrosis factor (TNF) α, carboplatin, and gemcitabine.[17,37,51] No standard dose (instillate concentration) has been defined for most of these regimens because the variables differ between teams—eg, drug dose, total volume of instillate, duration of intraperitoneal chemotherapy, temperature, and dynamic flow. Each variable modifies the pharmacokinetics of the drug used.[41] Experimental and clinical studies have focussed on new agents and their potential effect on IPCH. Hyperthermia enhances the antitumour effect of oxaliplatin in vitro by augmenting its cytotoxicity,[52] and in vivo by increasing its penetration into tissue.[53] This drug has already been tested in combination with heat in clinical practice.[54] Irinotecan, another promising drug in metastatic colorectal cancer, has also been tested in vitro in combination with heat.[55] Melphalan, a well known chemotherapeutic agent, shows excellent thermal enhancement when used at 41·5°C.[56]

Cytoreductive surgery and peritonectomy

To be effective, IPCH must be preceded by comprehensive cytoreductive surgery to remove as much tumour as possible. The objective is to clear the entire abdominal cavity of all macroscopic detectable disease. Procedures for cytoreductive surgery and peritonectomy have been described extensively by Sugarbaker.[6] When the tumour involves visceral

peritoneal surfaces, organ resections (splenectomy, large bowel or small-bowel resection) are needed. When it involves parietal peritoneal surfaces, parietal peritonectomy or stripping of the peritoneum is needed (figure 4). Although large portions of stomach or large bowel can be sacrificed without serious consequences in terms of nutrition, only small portions of small bowel can be resected. Frequently, implants on small-bowel surfaces are the major limitation to complete or sufficient cytoreduction.[17,37]

The combination of extensive surgery and intraperitoneal chemotherapy needs to be done in specialised centres involved in management of peritoneal-surface malignant tumours, as is the case in France. Surgeons must be competent in the visceral and parietal peritonectomy procedures needed for treatment of carcinomatosis. They must also know about chemotherapeutic agents and their toxic effects during the perioperative period.

Indications

IPCH after cytoreductive surgery has been used with palliative or curative intent as well as prophylactic treatment for gastric cancer in some Japanese and Korean studies. A consensus for its indications has been established within peritoneal-surface-malignancy treatment centres but has not been validated by large prospective studies.

Patient selection

In Europe, this combined management seems to be reserved for patients younger than 70 years who have not had cardiorespiratory or renal failure, especially when extensive cytoreductive surgery has to be combined with IPCH.[13,37,41] Glehen and colleagues[13] recommend a routine preoperative cerebral CT scan and echocardiography.

Carcinomatosis selection

Irrespective of carcinomatosis origin, IPCH is indicated when carcinomatosis is amenable to effective cytoreductive surgery allowing either a macroscopic complete resection, or a small residual tumour volume, with residual cancer nodules of less than 5 mm.[9,12,13,17]

In cases of carcinomatosis synchronous with the primary tumour, results of a comparative retrospective study[36] suggested that patients should be treated with cytoreductive surgery followed by IPCH at the time of primary-tumour removal. This management plan avoids the theoretical risk of cancer dissemination through sites of peritonectomy and resection. Prospective studies are needed to confirm these findings.

Use of IPCH as a palliative therapeutic method for patients with malignant ascites is less clear. Results of two studies[57,58] have suggested that IPCH improved the quality of life of patients with malignant ascites. In a study by Loggie and colleagues,[22] IPCH controlled ascites effectively in 70% of patients with gastric cancer. A phase II clinical trial[59] done at Wake Forest University School of Medicine used cytoreductive surgery with IPCH in 109 patients treated for various diagnoses. The assessment of quality of life at four timepoints over 1 year was done in 64 patients, and showed that survivors tolerated the treatment well and returned to their baseline quality of life within 3 months.[57] McQuellon and collegues[60] reported a good quality of life in 17 long-term survivors after the combination of cytoreductive surgery with IPCH, suggesting that despite the morbidity associated with cytoreduction and IPCH, patients still feel the procedure is worthwhile. Prospective studies are needed to investigate the toxic effects and benefit of this therapeutic approach.

Contraindications

Because of their poor prognosis and difficulty in locoregional control, carcinomatosis of pancreatic or hepatobiliary origin are not suitable for IPCH. Extra-abdominal metastases or massive retroperitoneal lymph-node involvement are also an absolute contraindication.[37,41] An aggressive locoregional treatment cannot be envisaged with non-controlled systemic disease. Liver metastases are a classic contraindication for this combined therapeutic approach, but are controversial, especially when resectable metastases are discovered at the time of cytoreduction.[8,13]

Table 3. Postoperative mortality and morbidity of IPCH combined with cytoreductive surgery

Primary tumour	Patients	IPCH device	Drug	Cytoreductive surgery	Mortality (%)	Morbidity (%)	Ref
Digestive cancers	83	Closed wall	10 mg/L mitomycin	Limited	3·6	10	9
Colon, rectum	64	Miscellaneous	Mitomycin±cisplatin	Extended	9·3	NA	12
Gastric cancer	18	Closed wall	Mitomycin+etoposide+cisplatin	Extended	1·2	NA	14
Digestive cancers	35	Closed wall	10 mg/L mitomycin	Extended	2·8	NA	23
Miscellaneous	109	Closed wall	10 mg/L mitomycin	Extended	8·0	36	33
Miscellaneous	207	Closed wall	Mitomycin±cisplatin	Limited to extended	3·2	24·5	61
Colon, appendix	60	Closed wall	10 mg/L mitomycin	Extended	5·0	35	62
Digestive cancers	183	Open wall	10·0–12·5 mg/m^2 mitomycin	Extended	1·5	27	63
Colon, rectum	29	Open wall	35 mg/m^2 mitomycin	Extended	0	17 of reoperations	64
Pseudomyxoma peritonei	46	Open wall	15–40 mg/m^2 mitomycin	Extended	9·0	39	64

NA, not available.

Table 4. Survival results in patients treated with IPCH after cytoreductive surgery

IPCH device	Patients	Drug	Cytoreductive surgery	Median survival (months)	Follow-up (months)	1-year survival (%)	3-year survival (%)	5-year survival (%)	Ref
Colorectal origin									
Open wall	56	Mitomycin–cisplatin	Extended (R0 resection)	36·0	56	..	47	..	12
Closed wall	40	5 mg/L mitomycin	Extended	14·0	52	60	25	..	33
Open wall	29	35 mg/m^2 mitomycin	Extended	..	38	82	23	..	34
Open wall	99	Mitomycin	Extended	..	..	..	..	..	36 (overall)
	44			24·0	40	..	..	..	36 (R0)
	55			12·0	12	..	..	..	36 (R2)
Closed wall	53	10 mg/L mitomycin	Limited to extended	12·8	59	..	..	..	66 (overall)
				32·0	..	78	..	25	66 (stage 1 or 2)
				10·7	..	41	..	..	66 (stage 3 or 4)
Gastric origin									
Closed wall	83	Mitomycin, cisplatin, etoposide	Extended	..	46	43	..	11	14 (overall)
	28			14·0	..	61	..	17	14 (R0)
	55			7·0	..	30	..	2	14 (R2)
Closed wall	6	10 mg/L mitomycin	Extended	9·0	..	..	..	..	23
Closed wall	19	5 mg/L mitomycin	Extended	10·0	52	37	16	..	33
Closed wall	48	10 mg/L mitomycin	Extended	16·0	..	54	41	31	28
Closed wall	49	10 mg/L mitomycin	Limited to extended	10·3	99	48	..	16	67 (overall)
				19·0	..	71	..	30	67 (stage 1 or 2)
				6·6	..	32	..	0	67 (stage 3 or 4)
Closed wall	17	Mitomycin, cisplatin, etoposide	Extended	11·0	15	44	..	..	68
Pseudomyxoma									
Open wall	46	15–40 mg/m^2 mitomycin	Extended	..	12	81	..	..	64
Open wall	385	Mitomycin	Extended	..	38	..	..	60	32 (overall)
205 patients	250			..	..	..	..	80	32 (R0)
treated by IPCH	135			..	..	..	..	20	32 (R2)
Open wall	36	Mitomycin, cisplatin	Extended	48·0	..	..	..	66	69

R0, complete macroscopic resection; R2, incomplete macroscopic resection.

For some teams, extensive and invasive carcinomatosis is a contraindication for use of IPCH when cytoreductive surgery cannot achieve sufficient downstaging.[12,13,23,51] The quantitative indicators including volume, distribution, and histopathology of the tumour that were developed by all peritoneal-surface-malignancy treatment centres are useful methods for prediction of prognosis. However, these quantitative indices need to be standardised and validated.

Morbidity and mortality

The main morbidities associated with IPCH combined with cytoreductive surgery are caused by complications of surgery: anastomotic leakages, intraperitoneal sepsis or abscesses. In view of variations in surgical treatment, IPCH devices, and carcinomatosis origin, the analysis of reported studies is difficult (table 3).[61–64]

Postoperative mortality

Mortality after surgery varies from 0% (in studies with a small number of patients) to 9·3%, and is greater than 5% in half the studies reported (table 3). In an univariate analysis,[65] mortality was linked significantly with patient age and the intraperitoneal temperature. Age was the only significant factor in a multivariate analysis.

Surgical complications

The most frequent surgical complications, affecting up to a third of patients in the largest studies, are represented by anastomotic leakages, digestive-tract perforations, and pancreatitis. Results of three multivariate analyses[61–63] have showed that the independent factors of morbidity were duration of surgery, extent of carcinomatosis, the number of anastomoses done, and sex. Cytoreductive surgery seems to be the major cause of these complications, but IPCH might

also be responsible. The extent and stage of the carcinomatosis has also been reported as an important predictive factor of morbidity.[12,64] Patients with stage 3 or 4 carcinomatosis are more likely to present with complications than are patients with stage 1 or 2 disease.

Morbidity from IPCH

The main morbidity from IPCH is haematological toxic effects, which are reported to arise in 8–31% of patients. Renal toxic effects, when IPCH is delivered with cisplatin, have also been reported. The lack of homogeneity of chemotherapy protocols restricts interpretation of published results.

Survival

Colorectal carcinomatosis

The survival results reported by many investigators show the importance of residual tumour volume after cytoreductive surgery (table 4). With a median follow-up of more than 4 years, Elias and colleagues,[12] who treated 56 patients with complete cytoreductive surgery followed by early postoperative intraperitoneal chemotherapy or IPCH, reported 3-year and 5-year survival rates of 47% and 27%, respectively. All phase II studies reported median survival of longer than 2 years for patients treated with complete macroscopic cytoreductive surgery or with residual tumour nodules of less than 5 mm after cytoreduction. The results of the randomised Dutch trial[70] comparing IPCH with mitomycin and cytoreductive surgery to intravenous chemotherapy alone (5-fluorouracil, leucovorin) for treatment of carcinomatosis from colorectal origin showed that 2-year survival was 43% in the IPCH group versus 16% in the control (p=0·014); the trial was stopped for ethical reasons.

Gastric carcinomatosis

The main studies reporting treatment of carcinomatosis from gastric cancer are Japanese (table 4). Studies done in western countries have been small and the median survival rates have not exceeded 1 year. However, Sayag and colleagues[22] reported a 3-year survival of 41% for patients with stage 1 or 2 carcinomatosis. In a large study of 85 patients, Yonemura and colleagues[14] reported a median survival of more than 1 year for patients treated with complete cytoreductive surgery, with five patients surviving to 5 years. In a smaller study with shorter follow-up, Fujimoto and colleagues[28] also showed promising survival results. The prognosis for gastric carcinomatosis treated with the combined therapeutic approach (cytoreductive surgery plus IPCH) seems to be worse than for colorectal carcinomatosis.

Pseudomyxoma peritonei

The largest experience has been reported by the Washington Cancer Institute (table 4). Some of the early patients they included were treated without IPCH, but with early postoperative intraperitoneal chemotherapy alone. The natural history of this disease is not extensively documented,[71,72] but the prognosis is better than that for gastric or colorectal carcinomatosis.

The main prognostic indicators of pseudomyxoma peritonei are the histopathological grade, the completeness of cytoreductive surgery and the PSS.[32] For patients treated with complete cytoreductive surgery or for patients with grade I disease, the 5-year survival was more than 80%. In Europe, with a smaller number of patients and shorter follow-up, the same results were reported with a similar comprehensive therapeutic approach.[64,69]

Search strategy and selection criteria

References were selected from our own collections. We identified additional references by searching MEDLINE and PubMed using the search terms "carcinomatosis", "intraperitoneal chemotherapy", and "hyperthermia". We also searched references from relevant articles and the abstracts of international conferences. Only reports published in French or English and published between January, 1963, and December, 2003, were selected.

Adjuvant IPCH for gastric cancer

Over the past decade, four randomised studies from Japan and Korea have investigated use of IPCH as adjuvant treatment after potentially curative gastric-cancer resection. The oldest study found no significant difference in survival between the group treated with surgery followed by IPCH and the group treated with surgery alone.[73] This finding was probably because of the small number of patients included. The three other studies were positive. Fujimoto and colleagues[74] included 141 patients and showed that IPCH significantly reduced the rate of peritoneal recurrence (p<0·001). They also reported that IPCH significantly improved survival rates (p=0·03), without any detrimental effect in the immediate postoperative course. Yonemura and colleagues[11] randomised 139 patients into three groups (surgery alone, surgery and IPCH, surgery and intraperitoneal chemotherapy without hyperthermia). The 5-year survival was 61% in the group treated with IPCH compared with 43% and 42% in the other groups. This difference was more noticeable in the patients with lymph-node involvement and serosal involvement. A study by Huang and colleagues[65] confirmed a significant reduction in peritoneal recurrence and improvement of survival when patients were treated with surgery followed by IPCH.

These studies underline the potential benefit of IPCH in prevention of peritoneal carcinomatosis from gastric cancer. As is the case for lymph-node resection, it is difficult to transpose the results of Japanese studies to western countries. Future studies are needed in Europe or USA to investigate the true role of IPCH as adjuvant treatment for gastric cancer.

Conclusion

IPCH in combination with cytoreductive surgery and peritonectomy procedures is still under investigation for treatment of carcinomatosis from digestive-tract cancer. The IPCH techniques, the surgical procedures, and the indications are not yet standardised. The survival results of many prospective studies are promising despite high morbidity, which emphasises the importance of careful patient selection. IPCH has a potential role as adjuvant treatment for potentially curative gastric-cancer resection.

Conflict of interest

None declared.

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