Palliative Treatments

23

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23.1 Introduction

During the last two decades, cytoreductive surgery associated with hyperthermic intraperitoneal chemotherapy (CRS plus HIPEC) has received increasing attention as a promising treatment for peritoneal carcinomatosis (PC) from several primary tumor types. However, many patients with advanced disease have no indications to be treated either by this procedure or by any other systemic therapy. Chronic pain, development of malignant ascites (MA), and bowel obstruction are often reported by the majority of those patients, with detrimental physiological and psychological status affecting quality of life (QoL) and leading to very poor prognosis [1–6]. Even if still controversial, CRS plus HIPEC may play an important role in palliative treatment, especially when associated with a less invasive approach to obtain the best results with limited morbidity and mortality.

23.2 Malignant Ascites and Palliative HIPEC

MA is a condition in which fluids originating from and containing cancer cells accumulate in the peritoneal cavity. Pathogenesis is multifactorial, and several factors such as tumor burden, portal pressure, oncotic pressure, lymphatic resorption, and increased microvascular permeability play a role in its onset [7, 8]. In general, ascites complicating an intra-abdominal malignancy accounts for 10 % of all ascites [9]. The presence of MA is estimated to occur in ~ 90 % of

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patients with PC, with a reported median survival of 5.7 months, being better for ovarian carcinoma (OC) (median 30 weeks) and worse for gastrointestinal (GI) adenocarcinomas (10 weeks) [10]. Furthermore, in 52–54 % of patients, MA represents the first sign of an intra-abdominal malignancy [11, 12]. Cytologic examination results of peritoneal fluid are still a controversial issue: some authors report it to be highly sensitive (up to 97 %) [13], whereas a more recent study reports it should not be considered as conclusive for a definitive diagnosis [14]. Onset of MA affects QoL and carries poor prognosis. Most symptoms reported are due to progressive abdominal distension that causes abdominal pain, dyspnea, anorexia, hemorrhagic complications, bowel obstruction, and systemic disorders such as protein depletion and hydroelectrolyte disorders [15, 16].

Standard treatments include salt-restricted diets, diuretics, repeated paracentesis, permanent drains, and peritoneal venous shunts in resistant cases [17]. Their real efficacy in treating ascites and improving QoL is difficult to assess due to scarce reports and knowledge about the natural history of MA formation [18]. Due to the lack of randomized controlled trials, no treatment can be considered the standard of care. Nevertheless, traditionally, paracentesis is the most frequently used (98 %) and the most effective (89 %) procedure [19]. It is considered simple and safe, providing at least temporary symptom relief in 93 % of patients [20, 21] However, benefits are time limited (often within 72 h) [18], and potential complications such as bowel perforation, hypotension, and peritonitis can occur in a small but significant number of patients. Peritoneal–venous shunt is used to reduce the need for repeated paracentesis in patients with rapid ascites formation and poor response to diuretics and diet. It provides ascites control in 75–78 % of patients, but the operative mortality rate is high (10–20 %) [22] and complications are frequent [10]. Diuretics when administered in high doses [20, 21] appear to be effective in 43–44 % of patients but with relevant systemic side effects. New treatments are emerging, mainly directed to intraperitoneal (IP) delivery of chemotherapeutic drugs or biological agents, but no definitive selection criteria, guidelines, or results (ascites reduction, QoL evaluation) are yet available [23].

In the last two decades, CRS plus HIPEC has gained increasing attention as a promising treatment in patients with PC from various primary tumor types. Administering chemotherapy directly to the tumor site can achieve higher tissue concentration than can systemic treatments, and association of hyperthermia enhances tissue penetration of cytotoxic agents, with lower systemic absorption and therefore less toxicity [24–32]. Hyperthermia increases drug tissue penetration up to 5 mm and directly inhibits cellular mechanisms of replication and repair [18]. HIPEC can be administered by an open or closed technique: the open technique is believed to achieve homogeneous distribution of thermal energy; the closed technique accounts for increased intra-abdominal pressure, which is believed to drive deeper drug penetration. In patients with PC with symptomatic MA who are not candidates for CRS, HIPEC can be administered by laparoscopy to provide ascites control. The advantages are less pain, lower mor-

bidity and mortality rates, shorter hospitalization, and maintaining the possibility of performing a minimal adhesiolysis to achieve homogeneous drug spatial distribution. In the literature, laparoscopic HIPEC for MA palliation is reported in small retrospective studies as having a high rate of success, low morbidity, and no mortality (Table 23.1) [33–39]. Drugs and procedural duration vary depending upon primary tumor type and other parameters, such as tumor burden, ascites volume, patient's general condition, previous chemotherapies, drug resistance, and personal experience of care providers. No clear data are available on the effects on QoL after laparoscopic HIPEC, although some studies reported a generic improvement in performance status [34, 35]. Literature data report control of MA in almost 100 % of patients, with no improvement in survival rates. A large study by Randle et al. on the efficacy of CRS plus HIPEC in MA management demonstrated that HIPEC alone is highly effective in long-term MA control in patients with macroscopic residual disease after surgery, although, again, the treatment does not provide any survival advantages [40]. This is also reported by other studies, regardless of primary tumor and drugs used, and the reason for these results is not clear. Drugs such as doxorubicin seem to produce sclerosis of the peritoneal surface, preventing capillary extravasation and inducing peritoneal adhesions [41]. Cisplatin and mitomycin-C do not seem to cause this same activity [42, 43] and have a direct cytotoxic effect on cancer cells, occluding lymphatic vessels and producing capillary permeability mediators; however, evidence of these results is merely experimental [44].

New drugs and new IP administration modalities are being studied: Kobold et al. reviewed current evidence suggesting that IP administration of the antivascular endothelial growth factor (VEGF) antibody, bevacizumab, might prevent local fluid accumulation [45–48]. Other studies considered the possibility drug delivery using a nebulized aerosol driven throughout the abdominal cavity by the pneumoperitoneal pressure [pressurized IP aerosol chemotherapy (PIPAC)]. Tempfer et al. applied compassionate treatment to 18 patients affected by unresectable PC from platinum-resistant OC, primary malignant peritoneal (PMP), and fallopian-tube cancers: Ten underwent PIPAC only; in eight, CRS was associated. Cisplatin at 7.5 mg/m^2 and doxorubicin at 1.5 mg/m^2 were perfused for 30 min at 37°C. In eight patients, PIPAC was repeated up to six times. Treatment was well tolerated and achieved an objective tumor response in six of eight patients who underwent more than one PIPAC treatment, although the rate of ascites control was not reported [49]. These results match with other, similar studies, on CRC, GC, and appendiceal cancers, suggesting PIPAC is a feasible and promising new modality of IP drug delivery [50, 51].

In conclusion, in patients with PC and MA who are not candidates for CRS, laparoscopic HIPEC can be safely and effectively administered, achieving satisfactory results, good MA control, and improved QoL. Other benefits are short hospitalization and very low morbidity and mortality rates, but there is no survival benefit. New drugs and new perfusion modalities are being studied to improve these promising results.

Table 23.1 Laparoscopic HIPEC for malignant ascites

Study [Reference]	No. (PSM origin)	Drugs	Operative time (min)	HIPEC duration (min)	Hospital stay (days)	Mortality	Morbidity	Ascites resolution	Median survival (months)
Chang et al. 2001[33]	2 (1 MPM, 1 BL)	CDDP	282	90	3–8	0	No	50 %	-
Facchiano et al. 2008 [34]	5 (GI)	MMC + CDDP	-	60–90	23	0	1 (delayed GI emptying)	100 %	3
Patriti et al. 2008 [35]	1 (PM)	CDDP + DOXO	-	60	7	0	No	100 %	6
Valle et al. 2009 [36]	52 (15 GI, 11 colon, 13 ovarian, 8 breast lobular)	CDDP + DOXO	147	90	2.3	0	3 (2 wound infection, 1 deep vein thrombosis)	94 %	3
Ba et al. 2010 [37]	16 (GI)	5-FU + OXA	80	90	NR	0	1 (grade 2 bone marrow suppression)	100 %	5
Graziosi et al. 2009 [38]	1 (PM)	CDDP + DOXO	-	60	7	0	1 (hyponatremia)	100 %	11
De Mestier et al. 2012 [39]	2 (1 GI, 1 OC)	MMC + CDDP	120	25	-	0	-	100 %	7 GI, 3 OC
Di Giorgio 2013 (unpublished)	13 (4 GI, 1 PMP, 8 OC)	MMC, 5-FU + OXA CDDP	157	60	5	0	No	92.3 %	8 OC, 4 GI, 2 PMP

HIPEC, hyperthermic intraperitoneal chemotherapy; *PSM*, peritoneal surface malignancy; *GI*, gastrointestinal; *BL*, breast lobular; *PM*, pulmonary mesothelioma; *OC*, ovarian cancer; *MPM*, malignant peritoneal mesothelioma; *PMP*, pseudomyxoma peritonei; *CDDP*, cisplatin; *MMC*, mitomycin-C; *DOXO*, doxorubicin; *OXA*, oxaliplatin; *5-FU*, 5-fluorouracil

23.3 Palliative Surgery and Managing Bowel Obstruction in Peritoneal Carcinomatosis

Malignant bowel obstruction is a common event in patients with locally advanced cancers, reaching an incidence of 28 % in GI cancer and 51 % in OC [1, 2]. Symptoms are related to the level of obstruction and usually include severe abdominal pain and distension, nausea, vomiting, and inability to pass gas and stool [52]. In patients with advanced or end-stage digestive or gynecological cancers, the onset of bowel obstruction may be insidious, evolving over several weeks and presenting spontaneous remissions between acute relapses [53]. Malignant bowel obstruction may have both mechanical and functional origin: the former is related to direct compression or infiltration by tumor masses of bowel loops, and the latter is related to impaired intestinal motility, resulting from tumor infiltration of mesenteries, nerves involved in intestinal motility, massive ascites, or chronic opioid therapies. Computed tomography is the gold standard for diagnosing malignant bowel obstruction, as it has a specificity and sensitivity > 90 % [54]. CT can exclude nonneoplastic causes of obstruction, which can occur in 15–30 % of patients with carcinomatosis and are mostly related to adhesions, hernias, and eventration [55, 56]. It can also identify the presence of a surgical emergency, such as perforation, volvulus, or strangulation, all of which are surgical indications even for palliative care. Decision making is very difficult in these patients. Medical conservative treatment is often not effective to relieve symptoms, and major surgical procedures should be avoided in patients who have limited life expectancy and who are poor surgical candidates because of malnutrition and underlying disease [57]. A large review by Laval et al. proposed recommendations and practical clinical guidelines to guide decision making, reserving surgery for patients with nonneoplastic mechanical obstruction, emergency situations, and limited obstruction with no indications to endoscopic prosthesis. Conservative medical management is preferred for patients with single stenosis suitable for endoscopic treatment, in poor general condition, or with extensive carcinomatosis, multiple areas of stenosis, or mesentery-root invasion. Age, comorbidities, nutritional status, previous radiotherapy, and level of obstruction are also identified as poor prognostic factors for surgical treatment [52] (Table 23.2).

Conservative management of patients with malignant bowel obstruction includes fasting, intravenously delivered rehydration, total parenteral nutrition, nasogastric tube (NGT) placement, and antiemetic, antisecretory, analgesic, and corticosteroid drug administration. Antisecretory drugs, which reduce digestive secretions such as octreotide, are particularly important in relieving patient distress; if vomiting does not stop, a venting gastrostomy rather than long-term NGT may be considered [52]. Endoscopic prosthesis must be preferred to surgery when technically possible due to its lower morbidity and mortality rates; PC must not be considered a contraindication to stent placement in patients with a single-site bowel obstruction [58]. Complications are rare and include perforation (0.5–4 %) and stent migration (8–12 %) and obstruction (0.5–10 %).

Table 23.2 Prognostic factors influencing surgical treatment of malignant bowel obstruction in unresectable peritoneal carcinomatosis

- Advanced age
- Presence of comorbidities
- Poor performance status
- Extent of peritoneal carcinomatosis; particularly, presence of multiple levels of obstruction
- Small-bowel rather than large-bowel obstruction
- Previous abdominal or pelvic radiotherapy

Technical failure is more frequent in long-standing stenosis [59].

A surgical approach should be carefully considered when conservative treatment fails or is not possible. Surgical procedures include ostomies (colostomy, ileostomy, jejunostomy), small- or large-bowel resections and/or bypass, and lysis of either malignant or inflammatory adhesions. Surgical strategy is determined upon intraoperative findings, and no standard guidelines are available. Several studies demonstrated benefits in symptoms relief with resumption of oral intake after palliative surgery for malignant bowel obstruction in 32–100 % of patients [60–66]. QoL measures are not reported by any available study. The literature reports that perioperative morbidity and mortality and rates are high, ranging from 7 % to 44 % and from 6 % to 32 %, respectively [60–62, 65, 67–69]. A frequent complication, occurring in from 6 % to 47 % of patients, is reobstruction [61–63, 66, 69]. Furthermore, duration of symptom relief may be short [66, 69] and hospital stay considerable in relation to patients life expectancy, which ranges from 1 to 94 days [70]. When obstructive symptom resolution is achieved and is long lasting, survival advantage may be significant, rising from 26 to 36 days to 154 to 192 days in some series [62, 71]. Table 23.3 summarizes the most relevant experiences and results in surgical treatment of malignant bowel obstruction in patients with PC. Authors experience is detailed in Table 23.4: overall median survival was 96.1 days (OC 100.3 days, GI cancer 83.5 days, CRC 104.5 days), and mean hospital stay was 9.6 days (range 6–14). Operative mortality occurred in two patients (17 %): one died after reoperation for bleeding, and reobstruction occurred in one, who died after 28 days.

23.4 Conclusions

In conclusion, palliative surgery may resolve obstructive symptoms and allow oral intake resumption and the patient to return home, even if for a short time; however, it has high mortality and morbidity rates. Moreover hospital stay may be long, affecting the quality of the remainder of the patient's life. Therefore, surgical palliation can be a valid option but should be carefully considered, taking into consideration patient preferences and compliance ability and providing complete information about risks and benefits.

Table 23.3 Malignant bowel obstruction in peritoneal carcinomatosis: outcomes (%) of palliative surgery

Study [Reference]	No.	Primary	Symptom relief	30-day mortality	Morbidity	60–90 days reobstruction
McCarthy [60]	12	OC 7, GI 5	75	25	25	NR
Turnbull et al. [61]	89	GI 84, HPB 5	74	13	43	38
Lau and Laurentz [62]	30	GI 30	57–63	17	27	47
Van Ooijen et al. [71]	59	GYN 46, GI 8, HPB 1, other 4	34–76	NR	NR	15
Blair et al. [67]	63	GI 44, HPB 5, other 14	45	21	44	NR
Legendre et al. [72]	109	GYN 37, GI 46, other 26	61	NR	NR	NR
Abbas and Merrie [68]	79	GI 34, GYN 19, other 25	NR	10	35	NR
Piver et al. [73]	60	OC 60	NR	17	31	NR
Lund et al. [63]	25	OC 25	32	32	32	38
Rubin et al. [74]	52	OC 52	65–87	17	15	NR
Bais et al. [75]	19	OC 19	68	11	32	21
Jong et al. [64]	53	OC 53	68	32	NR	40
Pothuri et al. [76]	64	OC 64	58	6	22	6
Mangili et al. [65]	47	OC 47	59	22	33	NR
Chi et al. [66]	14	OC 14	100	NR	7	29–36
Kim et al. [77]	23	OC 23	48	NR	13	NR
Kolomainen et al. [69]	90	OC 90	66	18	27	17
Di Giorgio (unpublished)	12	OC 6, GI 6	100	17	25	8

OC, ovarian carcinoma; *GI*, gastrointestinal; *GYN*, gynecological; *HPB*, hepatobiliary; *Other*, kidney, bladder, breast, gastrointestinal stromal tumor, melanoma, prostate, lung, sarcoma, unknown; *NR*, not reported

Table 23.4 Palliative surgery for malignant bowel obstruction in peritoneal carcinomatosis: personal experience

Patient no.	Primary tumor	PCI (mean = 26)	Surgical procedure	Morbidity	Hospital stay (days) mean = 9.6	Survival (days) Mean = 96.1
1	GI	24	Mesenteric implants resections	None	14	94
2	OC	27	Left colostomy	None	6	112
3	OC	28	Adhesiolysis	Reobstruction	13	28
4	OC	26	Right ileostomy	None	13	163
5	OC	30	Adhesiolysis	Bleeding	12	12
6	Colic	28	Left colostomy	None	7	127
7	GI	26	Gastroenteric anastomosis	Wound infection	11	73
8	Colic	29	Mesenteric implants resection	None	6	82
9	Colic	25	Gastroenteric anastomosis	Pleural effusion	12	159
10	Colic	24	Colic resection	None	10	50
11	OC	29	Right ileostomy	None	5	173
12	OC	27	Right ileostomy	None	6	114

OC, ovarian carcinoma; *GI*, gastrointestinal

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