Review

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Massive neoplastic ascites

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Abstract: Peritoneal metastases frequently occur in primary or recurrent abdominal malignancy and are often associated with massive ascites, which determines severe abdominal bloating, respiratory distress, and poor quality of life in patients with few months of life. After the failure of traditional medical therapies, simple drainage is effective in providing temporary symptom relief but does not provide a durable solution. Several treatment options are available, but no standard treatment strategy has been established, and none of the treatments consistently showed the ability to extend life expectancy. This review focuses on outcomes and adverse events of simple drainage, catheter placement, intraperitoneal therapy, peritoneovenous shunting, hyperthermic intraperitoneal chemotherapy, early postoperative intraperitoneal chemotherapy, pressurized intraperitoneal aerosol chemotherapy, and cell-free and concentrated ascites reinfusion therapy. The choice between the available options for durable symptom management requires both care and caution in weighing risks and benefits according to the patient's life expectancy.

Keywords: Ascites; Peritoneal carcinosis; Peritoneovenous shunt; Simple drainage

Introduction

Peritoneal metastases are often associated with massive ascites, defined as the presence of ascites diffusely accumulated from the pelvis to the subdiaphragm on computed tomography. Massive ascites determines severe abdominal bloating and respiratory distress and reduces the patient's quality of life (QoL), often leading to discontinuation of anticancer treatment.[1] Peritoneal metastases with massive ascites frequently occur in recurrent abdominal malignancy, such as gastrointestinal and ovarian cancer, but it can also be determined by a primary peritoneal malignancy. The primary treatment of massive ascites is dealing with the underlying neoplastic process using standard chemotherapy or recent more invasive and personalized procedures,[2] but the management of the fluid accumulation per se is done with the purpose of improving the comfort, physical activity, and QoL of these patients.[3] When the traditional methods of treatment, such as sodium and fluid restriction and diuretics, are unsuccessful, several treatment options are available, but no standard treatment strategy has been established and none of the treatments consistently showed the ability to extend life expectancy. This review focuses on outcomes and adverse events of the available treatments for patients with massive neoplastic ascites.

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Simple drainage

Paracentesis can be safely performed with a small amount of 1–3 liters, providing prompt but temporary symptoms relief, with the option of catheter placement when puncture occurs frequently.[1] This procedure involves considerable patient discomfort and there is concern that even a small amount of drainage may lead to loss of precious proteins and deterioration of nutritional status and that a large amount of drainage may lead to acute circulatory failure or renal failure. Moreover, in cases of massive ascites retention, small drainage not only has a poor symptom-relieving effect but also causes restorage in a short period of time. In conclusion, simple drainage is considered as the first-line treatment for massive ascites according to its low complexity and feasibility in all hospitals, with success rate in approximately 90% of patients. Complications, including pain, perforation, hypotension, drainage of protein and electrolytes, secondary peritonitis, and bleeding, are rare (approximately 5%) with less than 0.5% related mortality.[1] Although there is little data regarding the optimal volume of ascites to be drained, 5 liters are believed to be safe to avoid complications.[1]

Concerning catheter placement for ascites drainage, tunneled peritoneal catheters offer low rates of catheter malfunction and leakage of ascites, cellulitis, and peritonitis[4]; central venous catheters inserted intra-abdominally for ascites drainage show mechanical problems, including leakage, catheter dislodgment, or malfunctioning[5]; permanent peritoneal ports show leakage to subcutaneous tissue and infection in less than 20% of patients.[6]

Intraperitoneal therapy

In association with simple drainage, intraperitoneal administration of triamcinolone acetonide may be recommendable despite the lack of scientific evidence due to difficulty in conducting controlled trials in end-of-life care. Other agents employed intraperitoneally included interferon-α, tumor necrosis factor-α, matrix metalloproteinase inhibitors, nonpathogenic infectious agents, and vascular endothelial growth factor inhibitors, all

failing to show a significant benefit over paracentesis alone.[7] Intraperitoneal chemotherapeutic administration can be associated with drainage to give prolonged survival especially in stage III epithelial ovarian cancer, with a complication rate below 30%.[8] The most promising intraperitoneal antitumoral agent is catumaxomab, a trifunctional nonhumanized mouse/rat monoclonal antibody that targets epithelial cell-adhesion molecule and CD3 on T cells and has an Fc-γ receptor that activates receptors on accessory cells such as natural killer cells, dendritic cells, and macrophages.[7,9–11] Catumaxomab was approved for intraperitoneal treatment of malignant ascites in the European Union in 2009.[10] Phase II/III trials showed positive results in terms of puncture-free survival and quality of life for ovarian and other cancer-type patients.[7,9,12,13] The complication rate resulted in less than 25%[8,11] and the most common adverse effects of intraperitoneal catumaxomab were related to cytokine release and included pyrexia, nausea, and vomiting. Serious adverse effects included ileus, infection, pleural effusions, anastomotic leak, and gastrointestinal bleeding.[11] In conclusion, intraperitoneal antitumor therapy should be undertaken in healthier patients with massive ascites.

Peritoneovenous shunting

Peritoneovenous shunt (PVS) is a connection between the peritoneal cavity and the systemic venous circulation via a shunting tube placed subcutaneously connected with a one-way pressure valve. The pressure difference between the two ends of the shunt allows the drainage of ascitic fluid from the high-pressure peritoneal cavity toward the low-pressure central venous system. In the last 5 decades, superior vena cava was preferentially used for the drainage but, at the beginning of the experience, a saphenous vein access to the inferior cava vein (and the right atrium) has been utilized.[14] At present time, PVS can be performed by an exclusive surgical team, by an exclusive interventional radiologist team, or preferably by a combination of both, but originally the procedure was proposed by surgeons. After unsuccessful attempts in 1910 due to thrombotic occlusion of the system,[15,16] first Smith in 1962[14,17] proposed a PVS technique utilizing a manually compressible modification of the Spitz-Holter valve and a saphenous vein access. Subsequently, in 1967, Hyde et al.[18] proposed a similar technique utilizing a different manual compressible pump and the saphenous access. A milestone was represented by the pressure-actuated valve ideated by Leveen in 1974,[19] in which small silicone struts allow a theoretical critical opening pressure between 3 and 5 cm of water and the positioning of a peritoneal tube with side holes (26 French of diameter) and a central venous tube (at least 11 French of diameter) were required (Figure 1A, B). Another type of valve, named Denver valve, which was first ideated for hydrocephalus,[20] was employed for the treatment of nonmalignant and malignant ascites.[21,22] The shunt comprises of two silastic tubes connected via a compressible pump (Figure 1C). The shunt catheter is available in two sizes, 11.5 French (F) and 15.5 F.[23] The compressible pump is either single valved or double valved, which opens upon a pressure difference of more

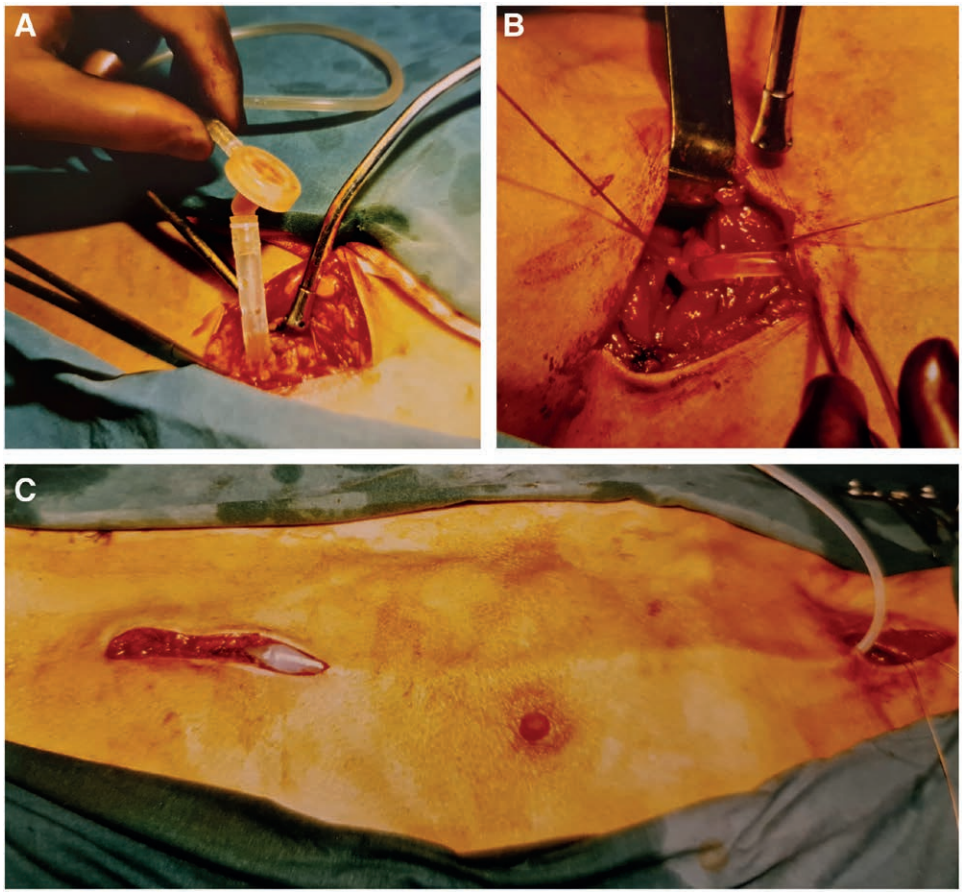

Figure 1. Peritoneovenous shunts. A, Leveen valve; the 26 French peritoneal tube with side holes has been inserted in the peritoneal cavity and the pressure-actuated valve still needs to be positioned between the anterior and the posterior sheaths of the right rectus abdominis muscle. B, The 11 French central venous tube of the Leveen valve has been inserted in the right internal jugular vein. C, Denver valve; the compressible valve has been placed over a firm noncompressible area of the rib cage; the 15.5 French peritoneal tube with side holes has been inserted in the peritoneal cavity; the 15.5 French central venous tube of the Denver valve still needs to be positioned in the internal jugular vein.

than 3 cm of water across the two ends of the shunt. The flow rate depends upon the size of the shunt and compression pump valve. Compared to the double-valved shunt, the single-valve shunt has a higher flow rate for both the shunt catheter sizes. The 15.5 F double-valve shunt, however, is most widely used as it is least likely to get occluded or cause reflux.[24] At the present time, the Leveen valve is not commercially available, and recent experiences are based on the use of the Denver valve that is manually compressible and implantable by interventional radiologists.[3,25,26] Tokue et al.[27] proposed an external PVS as an alternative for patients who could not tolerate a subcutaneously tunneled catheter.

A review of 31 published series, including 968 PVS, found that 70% were effective in palliating symptoms.[28] The operative risk of mortality related to PVS ranged between 3% and 22% (Table 1). Approximately 20% of patients experienced a complication such as transient peri-procedural fever, disseminated intravascular coagulation (DIC), infection, and tumor embolization to extra-abdominal sites.[29,41]

PVS is indicated under the following conditions: (1) patients having a life expectancy of more than 1 or 3 months with malignant ascites unresponsive to medical treatment and to large volume paracentesis; (2) patients who are not candidates for serial therapeutic paracentesis due to extensive abdominal surgical scars; and (3) unavailability of physicians to perform serial therapeutic paracentesis. PVS is contraindicated in patients with end-stage renal failure on dialysis, septicemia, uncorrectable coagulopathy, morbid obesity, and patients with septation of the peritoneal cavity due to previous infection or surgery.[25] PVS is absolutely contraindicated in bloody ascites, renal failure, history of varicose vein bleeding, grade 3-4 esophageal varices, congestive heart failure, respiratory failure with pulmonary edema, liver failure (total bilirubin >2.0 mg/dL), coagulation disorders (platelet count <50 × 10 or international normalized ratio [INR] >2.0), history of peritonitis or spontaneous bacterial peritonitis, poor performance status, hypoalbuminemia (serum albumin <2.5 g/dL), and evidence of nonsterile ascites. Relative contraindications are: patients with compensated congestive heart failure, loculated ascites, peritoneal disease, massive pleural effusion, nonbleeding varices, portal hypertension, simultaneous gastrointestinal surgery, and positive cytology for malignant cells in ascitic fluid.[29] Souter et al.[32] reported that viable cancer cells are disseminated after peritoneovenous shunt operations; they also demonstrated that these cells may be extracted from both ascitic fluid and blood and can be grown in vitro. However, few reports of massive tumor emboli have been published while the implantation of tumor cells adjacent to the distal aperture of the venous limb of tubing has been frequently reported.[36]

Some studies have shown that patients with breast and ovarian cancers had the best response to PVS, whereas patients with gastrointestinal tract cancers did poorly.[28] Complications from PVS are common and include peritoneal infection, variceal bleeding, superior vena cava thrombosis, pulmonary edema, disseminated intravascular coagulation, scar tissue formation, shunt fracture, occlusion, displacement or leakage, pneumothorax, and pneumoperitoneum. The most common complication of PVS is shunt occlusion, ranging from 4.8% to 48% (Table 1). Causes of shunt occlusion include shunt lumen obstruction due to thrombosis, intra-abdominal fat, fibrin clot, catheter kink, fibrin sheath formation around the intravenous catheter, and encapsulation by the omentum around the intra-abdominal catheter.[42] It must be noted that after a short training, the compression procedures of the Denver valve are mainly entrusted to the patient himself. DIC has been reported in a range from 2% to 27% of cases (Table 1); this condition may be due to the presence of activating factors such as tissue factors that initiate thrombogenesis.[43,44] Mortality in the

Table 1.

Comparison of PVS complication rates.

Authors	Year	No. points	L; D/s/p	DIC (%)	DVT (%)	Occlusion (%)	Thrombocytopenia (%)	Lung edema (%)	Infection (%)	Other (%)	Perioperative mortalitya (%)
Oosterlee[22]	1980	20	13; 7/7/0	0	nr	35.0	0	5.0	nr	nr	5.0
Cheung and Raaf [29]	1982	22	19; 3/3/0	27.3	nr	22.7	0	13.6	18.2	9.0	0
Lund and Newkirk[21]	1979	35	0; 35/35/0	2.9	8.6	14.3	nr	2.9	2.9	11.4	22.9
Gough[30]	1984	17	16; 1/1/0	11.8	nr	23.5	0	0	11.8	nr	nr
Tempero et al[31]	1985	26	26; 0	15.4	nr	7.7	14.0	15.4	3.8	34.0	0
Souter et al[32]	1985	33	17; 16/16/0	0	15.1	48.0	0	9.1	nr	33.3	3.0
Roussel et al[33]	1986	36	36; 0	0	11.1	36.1	5.6	0	8.3	nr	nr
Sonnenfeld and Tyden[34]	1986	27	9; 18/18/0	0	nr	29.6	0	3.7	nr	nr	11.0
Smith et al[35]	1989	50	12; 38/38/0	6.0	nr	32.0	0	12.0	4.0	10.0	0
Edney et al[36]	1989	45	25; 20/20/0	2.2	nr	22.2	15.6	13.3	0	nr	6.7
Gough and Balderson [37]	1993	42	16; 26/26/0	0	0	21.4	nr	nr	nr	nr	2.4
Personal experienceb	1997	22	20; 2/2/0	0	0	9.0c	9.0	0	4.5	4.5	9.0
Zanon et al[38]	2002	42	0; 42/32/10	0	9.5	4.8	0	4.8	2.4	nr	4.8
Orsi et al[39]	2002	8	0; 8/0/8	0	0	0	0	0	0	12.5	0
Seike et al[40]	2007	20	0; 20/0/20	5.0	10.0	10.0	0	5.0	5.0	15.0	5.0
Sugawara et al[26]	2011	133	0; 133/0/133	5.3	2.3	8.3	9.0	7.5	12.0	1.5	4.5
Yarmohammadi and Getrajdman[24]	2017	28	0; 28/0/28	7.0	7.0	21.4	nr	3.5	3.6	0	0
Tamagawa et al[3]	2020	35	0; 35/0/35	14.3	5.7	22.8	17.1	8.6	2.8	8.6	5.7

[a]Mortality in the first week after PVS procedure.

[b]Not published.

[c]Both occlusions in Denver valve after discharge from the hospital.

D indicates Denver valve; DIC, disseminated intravascular coagulation; DVT, deep venous thrombosis; L, Leveen valve; nr, not reported; p, percutaneous placement of the Denver valve; s, surgical placement of the Denver valve.

first week after PVS placement varies from 2.4% to 22.9% (Table 1). Although many reports on PVS have been published, most of them are small-scale studies. According to a relatively large multicenter study of 133 cases,[26] the symptom relief rate was 83%, the time to onset of effect was 2 days (1–9 days), and the duration of symptom relief was 26 days (maximum 330 days). Median survival of personal experience including patients with peritoneal surface malignancies from ovarian, breast, liver, lung, stomach, uterus, and primary peritoneal cancers, resulted in 60 days. In conclusion, based on the relatively high incidence of complications and mortality, PVS is not the first-line treatment for massive ascites and may be indicated only in selected patients.

Hyperthermic intraperitoneal chemotherapy

Hyperthermic intraperitoneal chemotherapy (HIPEC) without cytoreductive surgery (CRS) has been proposed for the treatment of massive neoplastic ascites. In trials of CRS-HIPEC for curative intent, it was noted that malignant ascites decreased even in cases where cytoreduction was not achieved (R2 resection), prompting the hypothesis that HIPEC itself could reduce malignant ascites.[45,46] Palliative HIPEC through the placement of abdominal catheters can be performed by open surgery, laparoscopic approach, or brightness-mode ultrasonography.[45,47,48] Palliative HIPEC can be performed in the operating room and followed by two more sessions in the intensive care unit on postoperative days 1 and 2.[47] High rates of ascites remission (83%–100%), increase in Karnofsky performance scores, and increase of puncture-free survival have been reported, but these data should be judged as inconclusive because the studies had very small sample size.[45,47–50] Adverse effects associated with alone palliative HIPEC for malignant ascites include nausea, vomiting, abdominal pain, abdominal wall metastases, peritoneal inflammation, neutropenia, and bone marrow suppression.[47] Palliative HIPEC without CRS for the treatment of massive ascites has been performed in patients with peritoneal metastases from ovarian and other cancers in Italy,[45,48] United States,[46] and China.[47,49–52] In 2020, the Chicago Consensus Working Group recommended laparoscopic HIPEC for the management of malignant ascites in patients who are not candidates for curative-intent CRS/HIPEC.[53] In the last 2 years, however, palliative HIPEC for massive ascites, with or without palliative CRS, has been reported in the United States,[54] Spain,[55] and Italy[56] for very small series of patients. In conclusion, there is low evidence to strongly recommend palliative HIPEC without CRS for the exclusive treatment of massive ascites.

Early postoperative intraperitoneal chemotherapy

Early postoperative intraperitoneal chemotherapy (EPIC) is the administration of chemotherapeutic agents from postoperative day 1 to day 5 through an abdominal inflow and outflow drain(s) inserted during an initial procedure.[57] To date, there are several time periods for intraperitoneal chemotherapy delivery.[58] The time period most frequently used in practice is intraoperative administration, usually delivered by a hyperthermic solution (HIPEC). A second time-period delivery procedure is the aforementioned EPIC. A third time period for intraperitoneal chemotherapy delivery, characterized by instillation at body temperature, ranges from several weeks to months following the surgical procedure; this method of chemotherapy delivery is referred to as normothermic intraperitoneal chemotherapy (NIPEC). A fourth time period for intraperitoneal chemotherapy is before the surgical procedure, using a bidirectional approach (neoadjuvant intraperitoneal and systemic drugs) named NIPS. A fifth postoperative time period for intraperitoneal chemotherapy, named sequential postoperative intraperitoneal chemotherapy (SPIC), is a combination of EPIC followed by NIPEC for 6 months.

In the EPIC administration technique, uniform contact of peritoneal surface and chemotherapy solution cannot be assumed; consequently, it is recommended to turn the patient from the extreme right side to the extreme left side, together with intermittent Trendelenburg position. During EPIC, augmentation of chemotherapy cytotoxicity by heat is not required mainly because the drugs are instilled for long time periods (usually 24 hours) and cell-cycle-specific drugs are appropriate (such as 5-fluorouracil, paclitaxel, pegylated liposomal doxorubicin, pemetrexed, cisplatin, gemcitabine, and docetaxel). However, cisplatin hyperthermic EPIC for 1 hour has been the object of a recent Chinese study for the treatment of massive ascites in patients with ovarian and gastric cancers, reporting significant ascites reduction and limited adverse events.[52] There are some other older studies[59,60] reporting that EPIC may be beneficial in malignant mesothelioma patients with the disadvantage of a discrete rate of postoperative complications (approximately 40%). In conclusion, evidence is very low to recommend EPIC for the treatment of massive ascites but, according to the expert opinion of Sugarbaker,[58] a future perspective may be represented by an integration of laparoscopic palliative CRS plus HIPEC, followed by EPIC and NIPEC.

Pressurized intraperitoneal aerosol chemotherapy

Although Tempfer[61] reported that pressurized intraperitoneal aerosol chemotherapy (PIPAC) has a limited effect on ascites volume in patients with ovarian cancer and Winkler et al[62] suggested that PIPAC should not be recommended for the treatment of massive ascites, a recent prospective single-center registry study showed a significant decrease of ascites after the first three Cisplatin plus Doxorubicin PIPAC procedures in 108 patients with peritoneal metastases or primary peritoneal cancers.[63] An initial experience with taxane-PIPAC in 47 patients with peritoneal metastases reported a 35.4% rate of ascites reduction.[64] A recent systematic review on 53 studies reported ascites reduction after PIPAC in seven studies.[65] In conclusion, despite the aforementioned recent reports, to date, there is not enough evidence to recommend PIPAC for massive neoplastic ascites.

Cell-free and concentrated ascites reinfusion therapy

To minimize the negative consequences of paracentesis, approximately 5 decades ago, a procedure was proposed that involved the drainage of the ascitic fluid and the use of an extracorporeal circuit including a filtration unit to separate the cellular components (blood cells, cancer cells, bacteria, etc.) from proteins, electrolytes, water, etc. Cellular components were removed while proteins, electrolytes, and water were submitted to a concentration process in another filtration unit, before being reinfused in the patient.[66] This procedure was named cell-free and concentrated ascites reinfusion therapy (CART). In relation to serious side effects, such as high fever and septic shock due to toxic substances such as inflammatory cytokines, endotoxins, and high molecular weight mucus, CART was little used up until about 10 years ago, when an improved CART system has been proposed to solve the technological problems (filtration pressure, filtration membrane obstruction, etc.) that generated toxic substances.[67] In recent years, CART has been actively used in combination with chemotherapy for peritoneal dissemination cases with a large amount of ascites especially in Japan.[68,69] In conclusion, CART is effective in improving symptoms, such as abdominal bloating or loss of appetite, and can be safely

performed. CART is recommendable for palliation in patients with massive cancerous ascites, but further clinical trials are required to demonstrate its efficacy in association with systemic chemotherapy.

Conclusions

Massive neoplastic ascites often become symptomatic in patients with only a few weeks of life but can have a significant detrimental impact on QoL. After the failure of traditional medical therapies, simple drainage is effective in providing temporary symptom relief but does not provide a durable solution. The choice between the available options for durable symptom management requires both care and caution in weighing risks and benefits according to the patient's life expectancy.

Conflict of interest statement

The author declares that they have no conflicts of interest with regard to the content of this report.

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