

Malignant ascites: A review of prognostic factors, pathophysiology and therapeutic measures

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Abstract

Malignant ascites indicates the presence of malignant cells in the peritoneal cavity and is a grave prognostic sign. While survival in this patient population is poor, averaging about 20 wk from time of diagnosis, quality of life can be improved through palliative procedures. Selecting the appropriate treatment modality remains a careful process, which should take into account potential risks and benefits and the life expectancy of the patient. Traditional therapies, including paracentesis, peritoneovenous shunt placement and diuretics, are successful and effective in varying degrees. After careful review of the patient's primary tumor origin, tumor biology, tumor stage, patient performance status and comorbidities, surgical debulking and intraperitoneal chemotherapy should be considered if the benefit of therapy outweighs the risk of operation because survival curves can be extended and palliation of symptomatic malignant ascites can be achieved in select patients. In patients with peritoneal carcinomatosis who do not qualify for surgical cytoreduction but suffer from the effects of malignant ascites, intraperitoneal chemotherapy can be safely and effectively administered *via* laparoscopic techniques. Short operative times, short hospital stays, low complication rates and ultimately

symptomatic relief are the advantages of laparoscopically administering heated intraperitoneal chemotherapy, making it not only a valuable treatment modality but also the most successful treatment modality for achieving palliative cure of malignant ascites.

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INTRODUCTION

Malignant ascites is a sign of peritoneal carcinomatosis, the presence of malignant cells in the peritoneal cavity. Tumors causing carcinomatosis are more commonly secondary peritoneal surface malignancies which include: ovarian, colorectal, pancreatic and uterine; extra-abdominal tumors originating from lymphoma, lung and breast; and a small number of unknown primary tumors. Malignant ascites accounts for approximately 10% of all cases of ascites^[1]. The presence of malignant ascites is a grave prognostic sign. While survival in this patient population is poor, averaging about 20 wk from time of diagnosis, quality of life can be improved through palliative procedures^[2]. Currently no effective anti-tumor therapy exists for peritoneal carcinomatosis. Given the uncertainty sur-

rounding the disease process and formation of malignant ascites, the therapeutic options are limited and often the goal of treatment is to target palliation of symptoms, which can include abdominal pain, dyspnea, nausea, vomiting and anorexia. In this paper, we will provide a review of the prognostic factors of malignant ascites, the pathophysiology of ascites formation, current diagnostic modalities, traditional therapeutic measures and newer therapies, including current medical and surgical treatment options.

PATHO-PHYSIOLOGY

The pathophysiology of malignant ascites is multifactorial. It is postulated that ascites formation is related to a combination of altered vascular permeability and obstructed lymphatic drainage. A careful understanding of the peritoneum, the lymphatic system and the dynamic flow of fluid are needed to elucidate the mechanisms of malignant ascites formation. Five microscopic barriers exist which prevent movement of proteins away from the intravascular space: capillary endothelium, capillary basement membrane, interstitial stroma, mesothelial basement membrane and mesothelial cells of the peritoneal lining. By means of a combination of mechanical and selective mechanisms, including tight junctions and anionic macromolecules, an effective barrier is maintained, preventing leakage of protein molecules into the peritoneal cavity. In 1922, Putnam described the peritoneal membrane as a “living membrane,” of which crystalloid solutions instituted into the peritoneal cavity equilibrated between the peritoneal cavity and the serum. The movement of colloid was not well understood, however, described as being transmitted in one direction into the serum from the peritoneal cavity, by means of some “vital (membrane) activity”, possibly phagocytosis or mechanical filtration through intercellular spaces^[3]. The relative impermeability of the capillary membrane to proteins is the basis for osmotic gradients, described by Starling’s equation of capillary forces, which states that the exchange of fluid between the plasma and interstitium is dependent on the hydraulic and oncotic pressure in each compartment. Oncotic pressure differences are the basis for fluid reabsorption from the interstitial space and prevention of edema formation.

While macromolecules, proteins and cells do not preferentially leave the intravascular space, they do accumulate in the peritoneal cavity and may return to the systemic circulation by means of the peritoneal lymphatic system. Recklinghausen first described lymphatic stomata, small openings of lymphatics that connect the body cavity and lymphatic lumen, responsible for movement of large particles into the vascular space^[4]. Fukuo *et al*^[5] demonstrated three lymphatic pathways in the abdomen using India ink injection and transmission electron microscopy. The principal pathway begins with the lymphatic stomata, entering the peritoneal lymphatics *via* networks in the diaphragm, undergoing filtration through regional lymph

nodes of the diaphragm, and eventually emptying into the thoracic duct^[5]. These mechanisms of osmotic gradients and lymphatic drainage allow for a dynamic fluid balance between the peritoneal cavity and the intravascular space, such that the osmolality of the peritoneal space is constantly changing.

As early as 1953, Holm-Nielson demonstrated that in mice with malignant ascites, India ink injected into the peritoneal cavity remained in the peritoneal cavity, suggesting lymphatic obstruction as a major factor in pathogenesis of malignant ascites^[6]. Feldman later showed that in mice inoculated with tumor cells, radioactive labeled erythrocytes injected into the intra-peritoneal space failed to return to the intravascular space as they did in normal mice due to tumor infiltrating the lymphatics, confirmed by histological evaluation, and subsequent to these events was the formation of ascites^[7]. Nagy *et al*^[8] demonstrated that radioactive albumin transport into the intravascular space was reduced after tumor injection and that this reduction preceded any significant increases in tumor burden. Additionally, radio-labeled red blood cells did not enter the intraperitoneal space at any increased rates until tumor burden had increased by at least 10 fold. Ascites fluid accumulation did not occur until late stages of tumor growth^[8]. These studies demonstrate the importance of lymphatic obstruction in tumor related ascites. Although many authors have offered theories regarding tumor metastasis, it is not clear why cancer cells preferentially localize to the peritoneal cavity rather than other sites and cause malignant ascites^[9,10].

The quality of fluid in patients with malignancy related ascites due to peritoneal carcinomatosis is distinctive, with positive cytology, high ascitic fluid protein concentrations and low serum-ascites albumin gradient^[11]. The high protein content of malignant ascites indicates that there is an alteration in vascular permeability to allow for large molecules to accumulate in the intraperitoneal space. Senger *et al*^[12] showed that vessels of the peritoneal lining of experimental animals with tumor ascites were significantly more permeable, due to the presence of a permeability factor found only in tumor ascites. When Garrison *et al*^[2] infused cell-free malignant ascites into the intraperitoneal space, an increase in edema formation in the omental vessels and an increase in the concentration of protein in the interstitial space were observed, thus implicating a tumor-induced factor that alters vessel permeability and promotes the formation of malignant ascites. This vascular permeability factor, known as vascular endothelial growth factor (VEGF), is responsible for allowing a varying degree of movement of micro and macromolecules across the vascular endothelium, in the setting of normal physiological states, in addition to pathological disease states, ranging from acute inflammation, wound healing and menstruation to tumor angiogenesis^[13]. Zebrowski *et al*^[14] showed that VEGF levels were significantly higher in malignant ascites when compared to nonmalignant ascites, and when cirrhotic ascites was exposed to VEGF, endothelial cell permeability

increased. The addition of VEGF neutralizing antibodies to malignant ascites reduced this permeability. Of note, exposure of cirrhotic ascites to cells had a similar effect on endothelial permeability, suggesting factors other than VEGF have a role in malignant ascites formation^[14]. Although not clearly a mechanism behind malignant ascites formation, ascites in cirrhotic patients has been associated with splanchnic hyperemia, thought due perhaps to tumor necrosis factor^[15,16].

Thus, it is apparent that the formation of malignant ascites is a complex, multifactorial process. The mechanism for fluid and protein accumulation in the intraperitoneal space associated with cancer appears to be secondary to a combination of impaired lymphatic drainage and increased vascular permeability. These processes are intertwined, allowing for net filtration that overwhelms the ability of the lymphatic system to drain the peritoneal space, particularly when obstructed by increasing tumor burden.

DIAGNOSIS

In 52%-54% of cases of peritoneal carcinomatosis, ascites is the first detected sign of intra-abdominal malignancy^[2,17]. The causes of intra-abdominal fluid production are many, including cirrhosis, congestive heart failure, nephrosis, pancreatitis, peritonitis, primary malignancy or hepatic metastases. It is not possible to distinguish benign ascites from malignant ascites by physical exam or radiographic techniques alone. Invasive testing is necessary to differentiate the two types. Abdominal paracentesis with ascitic fluid analyses can diagnose malignant causes of ascites production in most cases, but laparoscopic tissue sampling may be necessary. Ascitic fluid analysis consists of microscopic, chemical and cytological evaluation to help differentiate between infectious, inflammatory and malignancy induced ascites formation. In patients with peritoneal carcinomatosis, the ascites fluid has positive cytology, elevated protein concentrations and a low serum-ascites albumin gradient^[8]. While in some reports cytology is diagnostic in only 50%-60% of cases of malignant ascites, it has been demonstrated that up to 97% of patients with peritoneal carcinomatosis have positive cytology, indicating that the tumor is shedding cells into the peritoneal cavity, making it a highly sensitive test and the gold standard for diagnosing peritoneal carcinomatosis^[11,18]. In patients with peritoneal carcinomatosis and hepatic metastases, fluid cytology is positive and ascites protein concentrations are variable, but the serum-ascites albumin gradient remains elevated, with the addition of a markedly elevated serum alkaline phosphatase level (> 350 mg/dL)^[11]. The addition of tumor markers, especially CEA, CA-125 and α fetoprotein, are not reliable in diagnosing malignancy but they can aid in identifying the primary tumor causing malignant ascites. The biochemical properties of ascites fluid, including fibronectin, cholesterol, lactate dehydrogenase, sialic acid, telomerase activity and proteases, have been studied and, while clinically helpful, they have not yet been found to be reliable in dif-

ferentiating between malignant and benign ascites. Tumor and biochemical markers along with the morphological features of the cytological smear, immunohistochemical staining and clinical history are important in determining both the presence of malignancy related ascites and the primary sites of metastatic carcinomas^[19].

If the diagnostic workup does not reveal the primary source of malignancy but confirms the presence of a malignancy, a search for the tumor of origin should be pursued. In male patients with positive cytology, whose diagnostic workup remains negative despite blood tests and radiological imaging, it may not be useful to pursue further investigations because knowing the tumor of origin may not affect management or outcome. However, in female patients, if the conventional methods have failed to demonstrate the tumor of origin, laparoscopy or laparotomy should be performed for tissue diagnosis, because patients with an ovarian malignancy are responsive to tumor debulking and chemotherapy and their survival outcomes are better.

SURVIVAL

The prognostic factors associated with malignant ascites have been poorly studied, further complicating management decisions. A retrospective review of 76 patients with malignant ascites performed by Mackey *et al.*^[20], where median survival was determined to be 11.1 wk from time of diagnosis, showed that significant predictors of poor prognosis included presence of edema, depressed serum albumin and liver metastases, while prolonged survival was found in patients with ovarian cancer. Survival curves did not differ between patients with known cancers and unknown primary malignancies or between patients with ascites as the initial presentation of malignancy and patients with a known prior malignancy^[20]. In another study by Garrison *et al.*^[2], it was demonstrated that tumors originating from the female reproductive system had the longest survivals, with a mean survival of 19 wk, and foregut adenocarcinomas had the poorest survivals, with a mean survival of 10 wk from the onset of ascites. Additionally, patients with high protein concentrations within the ascitic fluid did better than those with transudative ascitic fluid^[2]. Ayantunde *et al.*^[17] showed that the presence of liver metastases and low levels of serum and ascites protein concentrations, although related, were independent prognostic factors associated with poorer outcomes. Furthermore, low protein levels are also associated with poor nutritional reserve and depressed immune function, adversely affecting this patient population. Malignant ascites thus carries a grave prognosis. Although the clinical outcome cannot be altered and survival times are limited, a successful goal of treatment is to palliate the symptoms of malignant ascites.

TRADITIONAL THERAPY

Several treatment modalities can alleviate the symptoms associated with malignant ascites. Because the natural

history of ascites formation is poorly understood, these measures and quality of life data is limited and the efficacy of existing treatments is difficult to assess. Traditional modalities for managing malignant ascites include sodium restricted diets, diuretic therapy, serial paracentesis and peritoneovenous shunting. In a survey of practice measures for managing malignant ascites, it was determined that paracentesis was most often utilized (98%) and it was perceived to be most effective (89%). Diuretics were used by 61% but were not felt to be as effective (45%)^[21].

Paracentesis

Review of the literature demonstrates a clear benefit from paracentesis in achieving symptomatic relief. Fischer described a simple, safe and effective method of inserting a 14-gauge needle with a 16-gauge catheter into the free peritoneal cavity, draining up to nine liters at a time with concurrent intravenous fluids running to prevent hypotension due to rapid vascular space depletion^[22]. The durability of paracentesis remains an issue as symptoms often return within 72 h. Theoretically, therapeutic agents could be administered *via* the catheter but this method is not used anymore due to the potential for adhesion formation and intestinal obstruction^[22]. Approximately 93% of patients show relief of nausea, vomiting, dyspnea and/or abdominal discomfort^[23,24]. Complications of therapeutic taps include pain, perforation, hypotension and secondary peritonitis. Paracentesis is effective in relieving the symptoms associated with malignant ascites but it requires repeated treatments, leads to frequent hospitalizations, depletes the patients of protein and electrolytes, and exposes the patient to a small but significant risk of peritonitis.

Peritoneovenous shunts

In 1974, LeVeen first introduced the peritoneovenous shunt to surgically treat patients with refractory ascites secondary to cirrhosis. The LeVeen shunt returns ascites fluid to the venous system *via* a one way pressure activated valve shunt mechanism that mimics physiological mechanisms. The Denver shunt, originally designed to overcome the frequent complication of shunt occlusion occurring with the LeVeen shunt, features a compressible pump chamber bearing a pressure sensitive valve, which opens when positive pressure exceeds 1 cm of water^[25]. There appears to be no particular type of Peritoneovenous shunts (PVS) shown to be more effective or superior, with complication rates similar between the two types^[26,27].

Peritoneovenous shunts are used to reduce the need for repeated paracentesis and relieve the symptoms associated with increased intra-abdominal pressure secondary to ascites and the resulting protein and fluid depletion. Patients must be carefully selected for PVS. These patients typically have failed conservative therapies and have rapid production of ascites or poor response to diuretics. Patients benefit from PVS because its use preserves serum albumin levels. Quality of life is preserved

through less frequent need for paracentesis. In 75%-78% of patients, malignant ascites is controlled by PVS and the mean duration of shunt patency is 10-12 wk^[23,24]. This treatment should be offered to patients judiciously as it does require perioperative hospitalization. Although overall days in hospital are reduced, PVS surgery carries an operative risk of mortality between 10% and 20% in an already tenuous patient^[28]. In reviewing the literature, 20% of PVS are associated with complications; these are most frequently shunt occlusion (19%-26%), pulmonary edema (9.5%-12%) and pulmonary embolism (5%-7%)^[19,20]. Other reported complications include ascitic leak from insertion site, subclinical disseminated intravascular coagulopathy (76%), clinical disseminated intravascular coagulopathy (2%), infection (5%) and gastrointestinal bleeding^[24,28]. In approximately 3%-7% of patients, tumor emboli were demonstrated at autopsy^[23,24]. Despite the direct infusion of viable malignant cells into the circulation, tumor implants were generally uncommon and if present, these metastases were clinically asymptomatic and did not affect survival^[29]. Hemorrhagic ascites and elevated ascitic fluid protein concentration are associated with higher risk of shunt occlusion and therefore are considered contraindications to PVS^[24,28]. Patients with loculated malignant effusions do not benefit from PVS. Relative contraindications for PVS include advanced congestive heart failure or renal failure because PVS is associated with volume overload. Also demonstrated as a relative contraindication is the presence of positive cytology, with 75% of complications occurring in this group, including early shunt failure, postoperative coagulopathy, infection and tumor emboli^[30].

PVS is not without risks and complications but in carefully selected patients, it can alleviate symptoms associated with malignant ascites. Patients with breast and ovarian cancer had the best response rate (> 50%), while patients with gastrointestinal malignancies did worse (10%-15% response); therefore, it is often suggested that PVS should not be implemented in patients with GI cancers^[18,28].

Diuretics

Diuretics benefit few patients with malignant ascites in a predictable fashion and when used in high doses, may cause systemic blood volume depletion, electrolyte abnormalities and renal dysfunction. Diuretics appear to be successful in achieving symptomatic relief in 43%-44% of cases reported in the literature^[23,24]. Greenway *et al*^[31] described good symptomatic control of ascites with large doses of spironolactone (150-400 mg/d) in a small group of patients who showed a clear retention of sodium and elevated plasma renin activity, with the most common side effect encountered being nausea and vomiting and no occurrences of electrolyte imbalances or renal dysfunction. It appears that patients with cancer who have ascites caused by portal hypertension secondary to hepatic metastases benefit most from diuretic therapy^[32]. When peritoneal carcinomatosis is complicated by hepatic

metastases, the quality of the ascites fluid and the mechanism of fluid production differ and can be compared to fluid production in patients with cirrhosis. In cirrhotic patients, portal hypertension is present and is associated with an elevated serum-ascites albumin gradient, secondary to the efflux of protein from the intravascular space into the peritoneal space, where the protein concentration is related to the degree of portal pressure^[33]. In both groups of patients, circulating blood volume is reduced and the renin-angiotensin-aldosterone system is activated, leading to sodium retention. Diuretics such as spironolactone serve as competitive antagonists to aldosterone, thereby decreasing the reabsorption of water and sodium in the renal collecting duct. Pockros *et al*^[32] demonstrated elevated renin levels in patients with massive hepatic metastases compared to normal renin levels in patients with ascites secondary to peritoneal carcinomatosis. Furthermore, diuretic use resulted in the mobilization of ascites fluid and approximately 1 kg/d in weight loss, without symptomatic hypotension or renal dysfunction in the hepatic metastases group compared to 0.5 kg/d in weight loss with subsequent hypotension and renal dysfunction occurring in the peritoneal carcinomatosis group^[32].

NEWER THERAPY

In the cases of primary malignancies without metastases, surgical resection with completely negative microscopic margins confers a better survival and is the basis of surgical oncology. Historically, operative intervention in cases of malignant ascites arising from peritoneal carcinomatosis was reserved for palliation of symptoms or emergent need to relieve obstruction or perforation. While clearance of tumor burden in patients with peritoneal carcinomatosis is often unachievable, investigations into aggressive cytoreductive surgery combined with intraperitoneal chemotherapy, either in the intraoperative setting with hyperthermia (known as HIPEC) or/and in the early postoperative setting (known as EPIC), has served as a premise for improving survival benefit in addition to preventing or palliating future development of malignant ascites.

With regard to gastrointestinal cancer, peritoneal recurrence of tumor will occur in up to 29% of patients^[34]. Prior to operative intervention, subclinical metastases, which escape preoperative CT scans and direct visualization during surgery, are present. These progress and spread further *via* hematogenous dissemination or lymphatic spread to distant sites of metastases and become clinically apparent months to years after resection. Tumor cells may enter the vascular or lymphatic spaces during surgical resection but these do not become clinically significant if the vessels remain intact, due to the high resistance of these endothelial lined channels to tumor proliferation, described by Weiss as the “theory of metastatic insufficiency”^[35]. These tumor cells often die without harming the host. A separate mechanism exists to potentiate tumor recurrence at the resection site and in

the peritoneum. Even after aggressive attempts at resection, tumor burden may remain at the microscopic level. The “tumor cell entrapment hypothesis” claims that local trauma during surgery is responsible for dislodging microscopic tumor emboli by tumor manipulation or lymphovascular vessel transection. These tumor cells then have the potential to implant onto the raw surfaces of neighboring peritoneum. Once this occurs, healing and restorative processes encase tumor cells within avascular intraperitoneal adhesions, precluding cancer from natural host defense mechanisms and systemic chemotherapy^[36]. This theory led to the conception of perioperative intraperitoneal chemotherapy, instilled into the abdomen up to 7 d postoperatively to target microscopic disseminated disease within the peritoneal cavity.

Direct intra-peritoneal administration of chemotherapy compared to systemic chemotherapy achieves higher tissue concentration, delivering cytotoxic agents up to 2-3 mm of the peritoneal layer without systemic absorption or toxicity^[36]. Hyperthermia offers additional cytotoxic effect by inhibiting cellular mechanisms of replication and repair and is synergistic, starting at a temperature of 39 degrees Celsius when used with chemotherapeutic agents. Hyperthermic intra-peritoneal chemotherapy is beneficial when timed directly after complete cytoreduction is first achieved, as the depth of penetration is further limited by postoperative fibrin deposition and adhesion formation. Intra-peritoneal chemotherapy can be administered *via* the open or closed techniques. The open technique is believed to distribute thermal energy homogeneously employing the properties of spatial diffusion. Closed abdominal chemotherapy allows for increased intra-abdominal pressure, which is believed to drive deeper penetration of chemotherapeutic agents without increasing the risk of exposure to the surgical team. There are no prospective trials that compare the efficacy of the open *vs* the closed techniques.

Selection criteria to determine the type of patient that will best benefit from perioperative intraperitoneal chemotherapy includes primary tumor origin, tumor biology, tumor stage, prior treatment with systemic chemotherapy or surgical resection and responses to those, patient performance status and comorbidity, and most important, effectiveness of surgical debulking. Roviello *et al*^[37] showed that postoperative complications occurred in 44% of patients undergoing cytoreductive surgery with intraperitoneal chemotherapy. These complications most commonly included wound infection, hematological toxicity, intestinal fistula and symptomatic pleural effusion requiring drainage. Reoperation was necessary in 8% of patients studied and mortality rate was 1.6%. Independent predictors of morbidity included residual tumor after resection and age. Probability of survival was higher in patients with ovarian or colorectal cancer compared to gastric cancer. Further review of the literature demonstrates morbidity rates associated with cytoreduction and intra-peritoneal chemotherapy ranging from 24.5% to 54% and mortality rates ranging from 1.5% to 4%^[38]. When complete cytoreductive surgery was possible, me-

dian survival was 32.4 mo compared to 8.4 mo in the incomplete resection group. Independent prognostic indicators associated with favorable outcomes were complete cytoreduction, treatment by a second procedure, limited peritoneal carcinomatosis, age less than 65 years, and use of adjuvant chemotherapy. Negative independent prognostic factors included the use of neoadjuvant chemotherapy, involvement of lymph nodes, presence of hepatic metastases, and poor histological differentiation^[39]. Two separate trials dedicated to the analysis of complication rates and associated morbidity point to the duration of surgery and number of resections and peritonectomy procedures as being associated with the greatest predictor of complication^[39,40].

A consensus statement was formed by seventy-five surgical oncologists regarding the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal malignancies of colonic origin. Review of the literature identified a subset of patients, in whom complete cytoreduction was achieved and combined with heated intraperitoneal mitomycin C and postoperative systemic chemotherapy. These patients had metastatic disease of colonic origin and were found to have a median survival up to 42 mo. Clinical and radiological evidence that were associated with successful complete cytoreduction (R0/R1 by the R scoring system or CC-0/CC-1 by the completion of cytoreduction score) included an Eastern Cooperative Oncology Group performance status of two or less, no evidence of extra-abdominal disease, up to three small, resectable parenchymal hepatic metastases, no evidence of biliary, ureteral or more than one site of intestinal obstruction, no small bowel involvement which included the mesentery, and a small volume of disease in the gastro-hepatic ligament. The treatment pathway to identify which patients would benefit most from surgical intervention was thus delineated. Those patients with recurrent and/or metastatic colon cancer with peritoneal involvement and a good performance status, a good response to systemic therapy, and/or limited liver involvement should be considered for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. If complete cytoreduction cannot be clearly achieved, surgical intervention should be reserved for circumstances in which palliation is the goal^[41].

Although the amount of residual disease left after attempted cytoreduction has been demonstrated to predict prognosis, categorizing a resection as complete or incomplete has become a focus of concern. Surgeons employ a variety of methodologies in determining the completeness of cytoreduction. Up to 74% of experts surveyed consider the completeness of cytoreduction (CC) score to be the best classification system for residual disease^[42]. This score proposed by Sugarbaker is based on a maximal intratumoral penetration of cisplatin (2.5 mm). This value was obtained in a controlled experimental setting using a microscope that is not used at the time of operation and does not apply to other frequently used chemotherapeutic agents. Instead, residual disease is classified using the

CC score based on remaining macroscopic disease, thus leading to observer variability.

It is known that cytoreductive surgery and hyperthermic intraperitoneal chemotherapy is associated with high morbidity. Several instruments were developed to assess quality of life in long-term survivors. In various forms, these measure physical, functional, social/family and emotional well-being. Piso *et al*^[43] performed a review of short and long-term quality of life assessments in patients undergoing cytoreductive surgery followed by intra-peritoneal chemotherapy. Review of the literature shows that while quality of life is initially impaired by surgery and postoperative complications, functional status returns to baseline, with little to no limitations in most patients, beginning at 3 mo post-treatment^[44]. There are no randomized clinical trials of cytoreductive surgery and intraperitoneal chemotherapy that also evaluate quality of life. Assessment of the quality of life in this patient population with an already limited life expectancy cannot be overlooked and should be included in clinical trials that assess the efficacy of this treatment.

A poorer overall survival has been reported in patients with non-ovarian malignant ascites and evidence of malnutrition with a median survival of 23 mo compared to 89.9% 1 year survival when ascites was absent^[45,46]. In a Phase I / II study conducted by Loggie *et al*^[46], it was demonstrated that combined treatment of radical surgical debulking and intra-peritoneal heated chemotherapy using mitomycin C was an effective means to provide palliation by preventing recurrence of ascites in up to 75% of patients for a median duration up to 7.5 mo. Radical debulking was scored as a R2 in 78% of these patients, but the association of R2 resection with the halting of ascites formation was not reported. Positive peritoneal cytology without gross ascites was observed in 35.3% of patients studied. Administration of intra-peritoneal heated chemotherapy prevented the development of ascites in all of these patients for a median duration up to 9.4 mo. Patients without positive cytology never developed ascites, suggesting that intraperitoneal administration of chemotherapy can prevent formation of malignant ascites^[46]. Patient selection criteria included absence of serious end organ dysfunction, absence of hepatic metastases, normal coagulation profile, albumin greater than 2.8 g/dL, liver function tests less than three times normal, and serum creatinine less than 2.0 mg/dL, which may account for the high success rate in this highly selected subgroup. In another Phase II trial, Bitran showed that the intraperitoneal administration of Bleomycin was successful in completely eliminating malignancy related ascites to amounts undetectable by physical exam or radiological technique in 60% of patients. Primary malignancies in this 10 patient group included gastric, ovarian and pancreatic cancers previously unresponsive to systemic chemotherapy. All patients had effective creatinine clearances greater than 70 mL/min. The effect of intraperitoneal Bleomycin lasted for a median of 8.6 mo and was overall well tolerated, with abdominal distension and pain being the most common

post procedure complaint^[47]. Schilsky *et al*^[48] used intraperitoneal cisplatin and fluorouracil without cytoreductive surgery in patients with advanced intra-abdominal cancer previously refractory to conventional systemic chemotherapy and demonstrated a favorable response to therapy in the subgroup of patients with clinically apparent malignant ascites and peritoneal tumor nodules less than one centimeter in diameter. After five cycles of intraperitoneal chemotherapy, one patient with malignant ascites and unknown primary malignancy displayed complete pathological remission, confirmed by second-look laparotomy. The six patients with intractable malignant ascites due to ovarian, colon or unknown primary malignancy received intraperitoneal chemotherapy and peritoneal fluid cytology became negative and ascites completely resolved after two or three cycles of chemotherapy^[48].

In patients with peritoneal carcinomatosis with symptomatic malignant ascites who are excluded from cytoreductive surgery, chemotherapy can be effectively administered using laparoscopic techniques with the intent to achieve palliative cure. Benefits of laparoscopy include a less painful modality to diagnose and stage malignancy, offering shorter hospitalization and less pain when compared to exploratory laparotomy. Garofalo *et al*^[49] studied patients with debilitating ascites originating from primary gastric, ovarian, breast or peritoneal mesothelioma malignancies who were not candidates for resection due to extensive peritoneal carcinomatosis. After minimal viscerolysis laparoscopically to optimize contact of chemotherapy with peritoneal surfaces, intraperitoneal chemotherapy was administered *via* a 10-mm infusion trocar and collected *via* three 5-mm suctioning drains. Drains were left in place and removed postoperatively when drainage was minimal to allow for drainage of reactive fluid and prevent formation of fluid collections and/or infected ascites. Cisplatin and doxorubicin were used for ovarian cancer, peritoneal mesothelioma or breast cancer in equivalent doses used in current standard practices for these malignancies after cytoreduction. Colorectal or gastric malignancies received mitomycin C. Average temperature of the peritoneal cavity was 42 °C. The operating table was tilted every 15 min with a total duration of perfusion time of 90 min. Resolution of ascites was observed in all cases. The mean survival of 10 of the 14 patients available for follow up was 29 wk. Neither morbidity nor mortality was associated with the procedure^[49]. In a second study, laparoscopic HIPEC using mitomycin and cisplatin achieved successful palliation of symptoms related to malignant ascites from advanced, unresectable gastric cancer, with all patients no longer requiring paracenteses. Complication rate was low, with delayed gastric emptying occurring in one patient. Mean hospital stay was 8 d. Survey of quality of life improvement was not formally studied^[50]. The largest series available to date is a multi-institutional analysis in fifty-two patients where laparoscopic HIPEC was employed using technique and chemotherapeutic agents similar to those previously described and resulted in a complete resolution of ascites

in 94% of patients. Underlying primary tumors included gastric, colon, ovarian, breast, peritoneal mesothelioma and melanoma. Median survival was 14 wk. Postoperative complications reported were two minor wound infections and one deep vein thrombosis. Mean hospital stay was 2.3 d^[51]. Laparoscopic HIPEC is a valuable treatment modality in palliating refractory malignant ascites regardless of underlying primary tumor and is not associated with major complication or treatment-related mortality, thus making it a safe and effective technique with well-demonstrated palliative cure of symptomatic malignant ascites.

Other newer treatments currently under investigation to hinder formation of malignant ascites include: intraperitoneal administration of VEGF inhibitor; matrix metalloproteinase inhibitors such as Batimastat; immunotherapeutic agents such as interferon, tumor necrosis factor, *Corynebacterium parvum* and *Streptococcal* preparation OK-432; and more recently, radioimmunotherapy utilizing monoclonal antibody therapy^[30]. Results from these methods are variable given that patient numbers are limited. While these newer therapeutic options are promising, further clinical evaluation in patients with malignant ascites is warranted.

CONCLUSION

Malignant ascites indicates the presence of malignant cells in the peritoneal cavity and is a grave prognostic sign. Survival in this patient population is poor. The formation of malignant ascites is a complex, multifactorial process involving a combination of impaired lymphatic drainage by tumor burden and increased vascular permeability by several factors, which are currently under investigation. When approaching patients with malignant ascites, the goal remains early diagnosis and treatment of symptoms associated with increased intra-abdominal pressure without the intention to cure the disease. Because the mechanisms of malignant ascites production are unclear and this is a small, heterogeneous patient population, which is often difficult to study, there are no validated guidelines for preventing or reducing the production or reaccumulation of malignant ascites. Selecting the appropriate treatment modality remains a careful process, which should take into account potential risks and benefits and the life expectancy of the patient. Traditional therapies, including paracentesis, peritoneovenous shunt placement and diuretics, are successful and effective in varying degrees. Paracentesis appears to be the most frequently employed traditional treatment modality secondary to its low associated risk and effectiveness in relief of symptoms. Peritoneovenous shunting, while most closely emulating physiological mechanisms of returning fluid to the systemic circulation, carries a 20% risk of complication in an already tenuous patient. In patients with cancer related ascites caused by portal hypertension secondary to hepatic metastases, diuretics should be considered. In these patients, the response and symptomatic control is more predictable.

Operative intervention in cases of malignant ascites arising from peritoneal carcinomatosis should no longer be reserved for emergent situations of obstruction or perforation. Early detection and attempts at complete cytoreduction combined with intraperitoneal chemotherapy have served to improve survival benefit. Direct intraperitoneal chemotherapy rather than systemic chemotherapy is implemented as it achieves higher tissue concentrations without systemic toxicity. After careful review of the patient's primary tumor origin, tumor biology, tumor stage, patient performance status and comorbidities, surgical debulking and intraperitoneal chemotherapy should be considered if the benefit of therapy outweighs the risk of operation because survival curves can be extended and palliation of symptomatic malignant ascites can be achieved in select patients. In patients with peritoneal carcinomatosis who do not qualify for surgical cytoreduction but suffer from the effects of malignant ascites, intraperitoneal chemotherapy can be safely and effectively administered *via* laparoscopic techniques with the intent to achieve palliative cure. Short operative times, short hospital stays, low complication rates and, ultimately, symptomatic relief are the advantages of laparoscopically administering heated intraperitoneal chemotherapy, making it not only a valuable treatment modality but also the most successful treatment modality for achieving palliative cure of malignant ascites. Further investigations into surveying quality of life remain to be formally studied. Quality of life assessments should be carried out in all ongoing studies, with a necessity to include this assessment in a formal randomized control clinical trial, as this is a very important factor in assessing efficacy of treatment.

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