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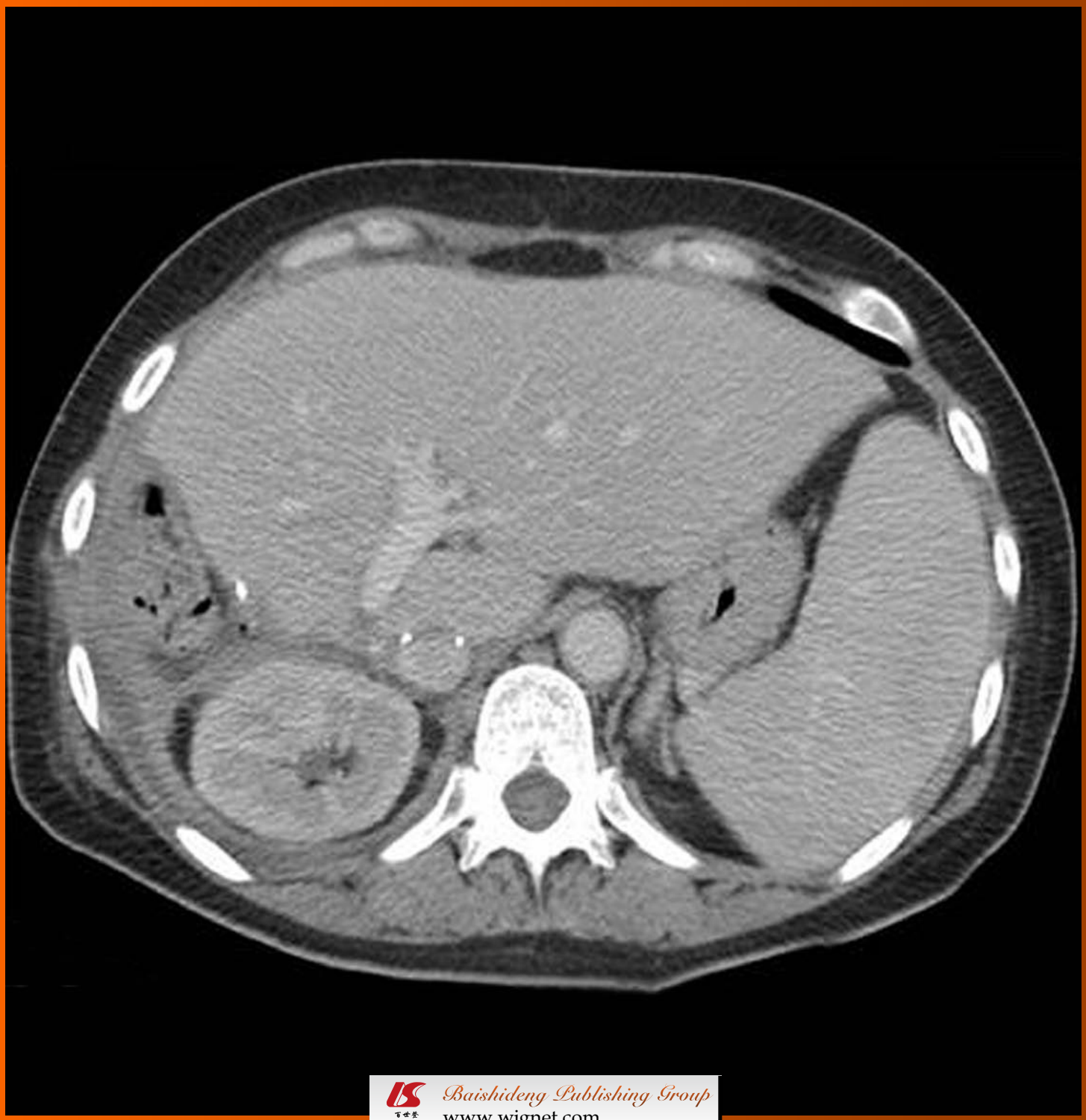

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EDITORIAL

Interval routine appendectomy following conservative treatment of acute appendicitis: Is it really needed?

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Abstract

Conservative management of acute appendicitis (AA) is gradually being adopted as a valuable therapeutic choice in the treatment of selected patients with AA. This approach is based on the results of many recent studies indicating that it is a valuable and effective alternative to routine emergency appendectomy. Existing data do not support routine interval appendectomy following successful conservative management of AA; indeed, the risk of recurrence is low. Moreover, recurrences usually exhibit a milder clinical course compared to the first episode of AA. The role of routine interval appendectomy is also questioned recently, even in patients with AA complicated by plastron or localized abscess formation. Surgical judgment is required to avoid misdiagnosis when selecting a conservative approach in patients with a presumed "appendiceal" mass.

Key words: Appendicitis; Surgery; Antibiotics; Interval appendicectomy; Plastron; Abscess

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INTRODUCTION

Since the first publication on acute appendicitis (AA) by Fitz *et al*[1] in 1886, surgical management of AA has been considered as a classical dogma for over one century. Emergency appendectomy has the advantage of immediate resolution of a surgical problem, which is dealt with by a single admission, at a time when the benefit is most apparent to the patient and his/her family; this approach eliminates the problem of possible recurrences of AA and the initial uncertainty about the effectiveness and the outcome of conservative treatment. Despite the fact that appendectomy still remains the "gold standard" in the management of AA, during the last two decades there has been an increasing body of evidence suggesting that conservative management is a valuable alternative to surgery in selected patients with suspected AA, which can be used as the first line therapy for AA. This approach has

been shown to be effective in many recent publications (including clinical trials and meta-analyses). The main advantage of the conservative approach is the elimination of the early and late morbidity (and mortality, albeit low) of an abdominal operation and general anesthesia. The effectiveness of this approach has been increased by the availability of new efficient antibiotics[2].

In evaluating the role of conservative management of AA, it is important to consider the need for interval appendectomy. Obviously, if routine interval appendectomy is required, then conservative management of AA would seem unattractive as a therapeutic option for most cases since its main advantage (e.g., avoidance of surgery) is eliminated. On the other hand, if interval appendectomy is not routinely needed, then conservative management of AA would be the treatment of choice in a large percentage of patients with suspected AA. The aim of this review is to critically summarize currently available data regarding the role of interval appendectomy in the management of patients with AA who were conservatively treated.

CONSERVATIVE MANAGEMENT OF AA: HOW EFFECTIVE IS IT?

Success and recurrence rates are the two main end points when evaluating the effectiveness and long-term results of conservative management of AA. Many recent studies have shown that conservative treatment is effective in a high percentage of patients with AA. Success rates range in the literature between 68% and 95%[2-8]. Recurrences following conservative management may be observed in about 5%-14% of patients[9-13]. Recently, Kaminski *et al*[14] reported a 5% recurrence rate with a median follow-up of 4 years in 864 patients treated with antibiotics alone. Interestingly, recurrent episodes exhibited a milder clinical course than the first episode[14]. Dixon *et al*[15] reported a similar low incidence of recurrent appendicitis and found that subsequent attacks were less frequent and less severe. As expected, the identification of factors associated with a high risk of recurrence of AA would be of great interest for the clinician since, when present, the effectiveness of conservative management of AA is diminished. These risk factors should be taken into consideration when selecting patients for conservative or surgical management and include retained fecal stones, increased (> 4 mg/dL) CRP levels, elevated percent bands, partial small bowel obstruction on admission, *etc*.[7,16-22]. In the presence of these "risk factors", emergency appendectomy should be strongly considered.

INTERVAL APPENDECTOMY FOLLOWING SUCCESSFUL CONSERVATIVE MANAGEMENT OF UNCOMPLICATED AA: IS IT NECESSARY?

Although there are some groups suggesting routine interval appendectomy for all patients who have had nonsurgical treatment of an episode of AA, in clinical practice most surgeons question its routine use. The basic question which should be answered is the following: is the risk of surgery and general anesthesia justified by the risk of recurrent AA? The clinician should keep in his/her mind that appendectomy is associated with a small, albeit significant, morbidity and even mortality, despite being considered a "routine" surgical procedure. Indeed, following emergency appendectomy, mortality ranges from 0.07% to 0.7% in patients without and 0.5% to 2.4% in patients with perforation[23-25]. Operative mortality increases in the presence of co-morbidity (e.g., heart and lung diseases, morbid obesity, *etc*.) and in aged patients (< 0.1% in patients younger than 40 years, 2.6% in septuagenarians, 6.8% in octogenarians and 16.4% in nonagenarians)[24]. Morbidity rates range between 10% and 20% for AA without perforation and reach up to 30% for perforated appendicitis[2,9,26]. Common complications after appendectomy include wound and (more rarely) intraabdominal septic complications, adhesive small bowel obstruction (a long term complication requiring surgery in about 1.5% of patients by 30 years)[4,27]. Even the less invasive laparoscopic appendectomy is also associated with its one morbidity and even mortality rates.

Interval appendectomy could, however, be justified if the risk of recurrence was too high. However, the risk of recurrence is low (see above) but increases in the presence of the "risk factors" mentioned above. Moreover, recurrences are usually characterized by a milder clinical course than the primary attack[15]. Therefore routine interval appendicectomy is probably not warranted following successful management of uncomplicated AA, given the low risk of recurrent appendicitis and the potential early and late complications of an elective operation[8,28-30].

INTERVAL APPENDECTOMY FOLLOWING SUCCESSFUL CONSERVATIVE MANAGEMENT OF COMPLICATED AA: IS IT ROUTINELY NECESSARY?

Occasionally, a patient's defense mechanisms may restrict and enclose the inflammation, resulting in the formation of an inflammatory mass (phlegmon or plastron) of a contained (circumscribed) abscess. Typically, these inflammatory changes are observed some days (usually more than 4 d) after the onset of symptoms and more commonly in children (especially < 5 years)[2,10].

Patients with plastron formation

Emergency surgery in these cases is not warranted; indeed, under these circumstances surgery may be technically demanding because of the distorted anatomy and the difficulties of closing the appendiceal stump because of the inflamed tissues. The risk of injury of adjacent organs (i.e., intestinal loops) is increased due to the presence of inflammatory changes and adhesions[13,30]. Moreover, the overstimulation of an already primed inflammatory sys-

tem, with extensive stimulation of the cytokine cascade, may further complicate the postoperative course[11,31]. As a result, immediate surgery in these patients is associated with over a 3-fold increase in morbidity compared with conservative management[2]. Occasionally, the exploration ends with an ileocecal resection or a right-sided hemicolectomy (in about 3% of patients) due to technical problems or a suspicion of malignancy because of the distorted inflamed tissues[2,32]. For these reasons, in patients with AA complicated by inflammatory mass (plastron) formation, the classical and recommended initial treatment is conservative with antibiotics[33]. Interval appendectomy is traditionally performed about 6 wk after the episode of AA to prevent recurrences and remove the offending organ to permanently resolve infection[33,34]. During this time of about 6-8 wk, the local inflammatory changes usually have subsided, the edematous and inflamed bowel has recovered and the patient is appropriately prepared[32-35]. However, the need for interval appendectomy after a successful nonsurgical treatment has recently been questioned as the risk of recurrence is relatively small[12,35-37]. This issue remains highly debated, with others proposing either delayed (i.e., appendectomy during the same admission, mainly to diminish sick leave) or routine interval appendectomy[38-40].

Patients with localized abscess formation

Non-operative management has been proposed for the management of patients with localized abscess formation due to perforated appendicitis[11]. Antibiotic therapy is successful in about 93% of these patients; in about 20% of them, image-guided percutaneous drainage of the abscess will eventually be required[2]. Interestingly, Nadler *et al*[7] suggested that patients with a phlegmon on imaging tests as opposed to an abscess are more likely to respond to conservative treatment and that the presence of a phlegmon reflected improved host defenses. These authors also suggested that the need for abscess drainage increases the failure rate, perhaps because of inadequate source control[7]. To date, the role of interval appendectomy in these patients has not been adequately evaluated.

POTENTIAL PROBLEMS, CONCERNS AND DISADVANTAGES OF OMITTING INTERVAL APPENDECTOMY

Some authors have stated that in patients with AA treated conservatively without interval appendectomy, there is a risk (about 2%) of missing pathological findings, such as Crohn's disease or neoplasms (most commonly, appendiceal carcinoids)[2,41]. Immediate surgery with a right sided hemicolectomy, if needed, to avoid this problem, proposed by some authors as the definitive treatment in patients with complicated AA, is too aggressive an approach[42-44] and has not been adopted by most surgeons. Nowadays, the availability and wide use of modern diagnostic tools (including computed tomography and interval colonoscopy) in selected patients have diminished the risk of misdiagnosis. Most colon cancer cases occur in patients over the age of 40 years. Therefore, patients older than 40 years should be followed-up with colonoscopy or computed tomography to exclude malignancy, especially when initial symptoms were atypical or in the presence of other suspicious findings (for example, anemia).

The risk of recurrence of appendicitis is a concern in patients with AA treated conservatively and without interval appendectomy. These patients should be counseled about the possibility of a recurrence of appendicitis and encouraged to seek medical attention early should symptoms recur. Most surgeons would advocate appendectomy (emergency or interval) in patients with multiple (> 2) recurrences. Personal preferences of the patient should also be taken into consideration in the process of management decision-making.

In conclusion, interval appendectomy is not routinely required in patients treated conservatively for AA. The risk of recurrence is low; moreover, potential recurrences usually have a mild clinical course. Interval (or emergency) operation should be considered in selected patients (for example, in the presence of "risk factors" indicating a high probability of recurrence, such as the presence of a retained fecalith) or following multiple (> 2 or 3) episodes of AA. Patients with AA complicated by plastron or localized abscess formation should be treated conservatively initially; image-guided percutaneous drainage may be required to achieve drainage in patients with localized abscess. Despite that interval appendectomy is still performed by the majority of surgeons around the world, there is evidence that, even in these cases, interval appendectomy could be avoided. Currently, the lack of a sufficient body of evidence precludes firm recommendations. Surgical judgment is required to avoid misdiagnosis if such a conservative approach is adopted; further diagnostic evaluation may be required in selected patients (for example in patients > 40 years with anemia and a presumed "appendiceal" mass) to exclude malignancy. Personal preferences and specific conditions (for example, people living in remote or isolated areas without easy access to health facilities) should also be taken into consideration when deciding about the optimal management of each patient with AA (complicated or not).

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REVIEW

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.

Key words: Carcinomatosis; Peritoneal; Paracentesis; Peritovenous shunts; HIPEC

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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 *at 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 differentiating 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.

Peritovenous 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 Peritovenous 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 homogenously 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 Phas 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 ℃. 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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BRIEF ARTICLE

Resection and reconstruction of the inferior vena cava for neoplasms

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Abstract

AIM: To evaluate the results of an aggressive surgical approach of resection and reconstruction of the inferior vena cava (IVC).

METHODS: The approach to caval resection depends on the extent and location of tumor involvement. The supra- and infra-hepatic portion of the IVC was dissected and taped. Left and right renal veins were also taped to control the bleeding. In 12 of the cases with partial tangential resection of the IVC, the flow was reduced to less than 40% so that the vein was primarily closed with a running suture. In 3 of the cases, the lumen of the vein was significantly reduced, requiring the use of a polytetrafluoroethylene (PTFE) patch. In 2 of the cases with segmental resection of the IVC, a PTFE prosthesis was used and in 1 case, the IVC was resected without reconstruction due to shunting the blood through the azygos and hemiazygos veins.

RESULTS: The mean operation time was 266 min (230-310 min) with an average intraoperative blood loss of 300 mL (200-2000 mL). The patients stayed in intensive care unit for 1.8 d (1-3 d). Mean hospital stay was 9 d (7-15 d). Twelve patients (66.7%) had no complications and 6 patients (33.3%) had the following complications: acute bleeding in 2 patients; bile leak in 2 patients; intra abdominal abscess in 1 patient; pulmonary embolism in 2 patients; and partial thrombosis of the patch in 1 patient. General complications such as pneumonia, pleural effusion and cardiac arrest were observed in the same group of patients. In all but 1 case, the complications were transient and successfully controlled. The mortality rate was 11.1% (n = 2). One patient died due to cardiac arrest and pulmonary embolism in the operation room and the second one died 2 d after surgery due to coagulopathy. With a median follow-up of 24 mo, 5 (27.8%) patients died of tumor recurrence and 11 (61.1%) are still alive, but three of them have a recurrence on computed tomography.

CONCLUSION: There are a variety of options for reconstruction after resection of the IVC that offers a higher resectable rate and better prognosis in selected cases.

Key words: Resection; Reconstruction; Inferior vena cava

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INTRODUCTION

Involvement of the inferior vena cava (IVC) has traditionally been considered as a contraindication for resection of advanced liver and retroperitoneal tumors because of the poor long-term prognosis and high surgical risks. The development of innovative surgical techniques, such as total hepatic vascular exclusion, veno-venous bypass and *ex vivo* hepatic resection, and the progress of liver transplantation has made a curative surgical approach to tumors involving both the liver and the IVC possible. The resected IVC can be primarily be repaired or reconstructed with synthetic or autogenous grafts.

MATERIALS AND METHODS

From January 2008 to September 2010, 18 patients required resection of the IVC for malignancies presented in Table 1. There were 7 (38.9%) male patients and 11 (61.1%) female patients. The mean age of the patients was 58.8 years old (range 49 to 70). Tumor development was predominantly extracaval in 15 patients (83.3%) and 3 patients with leiomyosarcoma of the IVC. In most of the cases, the IVC was resected due to colorectal cancer (CRC) liver metastases (n = 8), infiltration of hepatocellular carcinoma (n = 2), cholangiocarcinoma (n = 1), gall bladder cancer (n = 1) and pheochromocytoma of the right suprarenal gland (n = 1). In 2 of the cases, there were infiltration and thrombosis of the IVC by renal cell carcinoma of the right kidney.

Clinical presentation

The most common presenting symptom was pain in the upper abdomen in 12 patients. Edema of the lower extremities was observed in only 2 patients (11.7%), due to rich collaterals, and one patient (5.8%) presented with Budd-Chiari syndrome, with hepatomegaly, ascites and jaundice.

Preoperative imaging

Abdominal Doppler ultrasound and angio-computed tomography (CT) were performed in all patients (100%). Ascending cavography by the femoral route was performed in 6 patients (33.3%) and selective arteriography of the celiac trunk in 3 patients (16.7%). Trans-esophageal echocardiography was performed in 4 patients (22.2%) in whom intracardiac extension was suspected. All the patients were thoroughly examined and preoperatively staged.

Surgical procedures

Surgery was performed through a superior midline and bilateral subcostal incision. In 2 patients with involvement of the suprahepatic IVC, an additional midline thoracotomy and pericardiotomy was used. A staging laparoscopy was performed in 3 patients. After mobilization of the liver, intraoperative Doppler ultrasound was performed. The approach to caval resection depended on the extent and location of tumor involvement. The supra- and infra-hepatic portion of the IVC was dissected and taped. Left and right renal veins were also taped to control the bleeding. In the cases of CRC metastases and liver resection, hepatic parenchyma was divided using the Ultrasonic Surgical Aspirator and bipolar pincettes. The parenchyma transection was performed with inflow occlusion (Pringle maneuver) in 8 of the cases. Central venous pressure was kept at or below 5 cm H_2O during parenchymal transection to minimize blood loss. Total vascular exclusion of the liver was performed in 5 of the patients. Warming therapy was applied to 16 patients to minimize intraoperative hypothermia.

In one of the cases with cancer of sigmoid colon (T3N1M1H3) and liver metastases in Sg 2, 3, 4, 6, 7, 8, we performed resection of primary cancer combined with metastasectomies in the left liver and ligation of the right branch of the portal vein in the first operation. In the second operation, we performed a right hepatectomy with partial tangential resection of the IVC and resection of metastasis of segment 3.

In 12 of the cases with partial tangential resection of the IVC, the flow was reduced to less than 40% so that the vein was primarily closed with a running suture (66.7%) (Figure 1).

In 3 of the cases, the lumen of the vein was significantly reduced, requiring the use of a polytetrafluoroethylene (PTFE) patch (16.7%). In 2 (11.1%) of the cases with segmental resection of the IVC, a PTFE prosthesis was used and in 1 case, the IVC was resected without reconstruction due to shunting the blood through the azygos and hemiazygous veins.

One of the patients with leiomyosarcoma of the IVC presented with edema of the lower extremities and Budd-Chiari syndrome. In this case, a resection of the retrohepatic vena cava with partial resection of Sg 8, thrombectomy from the middle and right hepatic veins was performed. For the reconstruction of the IVC, a PTFE prosthesis was used (Figure 2).

RESULTS

The mean operation time was 266 min (230-310 min) with an average intraoperative blood loss of 300 mL (200-2000 mL). The patients stayed in the intensive care unit for 1.8 d (1-3 d). Mean hospital stay was 9 d (7-15 d). Twelve patients (66.7%) had no complications and 6 patients (33.3%) had the following complications: acute bleeding in 2 patients; bile leak in 2 patients; intra abdominal abscess in 1 patient; pulmonary embolism in 2 patients; and partial thrombosis of the patch in 1 patient.

In one of the cases with PTFE patch reconstruction, we found a thrombosis at the place of the patch on the second postoperative day, which was successfully treated with anticoagulation therapy (Figures 3 and 4).

In the patient with advanced cholangiocarcinoma, we first performed ligation of the right branch of the portal vein due to insufficient liver volume in the left liver. One

Table 1 Patients with resection of the inferior vena cava

Diagnose	Sex	Age (yr)	Operation	Vascular resection
CRC metastases	F	65	Right hepatectomy	Tangential
CRC metastases	F	61	Right hepatectomy	Tangential
CRC metastases	M	65	Right hepatectomy	Tangential
CRC metastases	M	52	Sg Ⅴ, Ⅵ, Ⅶ	Tangential
CRC metastases	F	56	Right hepatectomy	Tangential
CRC metastases	F	70	Right hepatectomy	Tangential
CRC metastases	F	61	Metastasectomy	Tangential
CRC metastases	F	63	Right hepatectomy	Tangential
HCC	F	65	Right hepatectomy	Tangential
HCC	M	62	Sg Ⅶ and Ⅷ	Segmental + PTFE
Cholangiocarcinoma	F	51	Right hepatectomy	Tangential + patch
Gall bladder cancer	F	68	Sg Ⅳ, Ⅴ and Ⅵ	Tangential
Leiomyosarcoma	F	62	Right hepatectomy	Tangential + patch
Leiomyosarcoma	M	57	Partial Sg Ⅷ	Segmental + PTFE
Leiomyosarcoma	M	49	Resection	Tangential
Renal cell carcinoma	M	63	Right nephrectomy	Tangential
Renal cell carcinoma	M	62	Right nephrectomy	Segmental
Pheochromocytoma	F	28	Right suprarenalectomy	Tangential + patch

CRC: Colorectal cancer; HCC: Hepatocellular carcinoma.

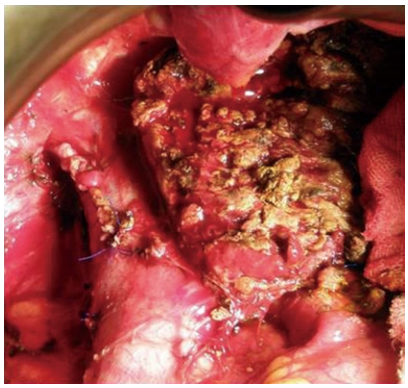

Figure 1 Partial tangential resection with a running suture of the inferior vena cava.

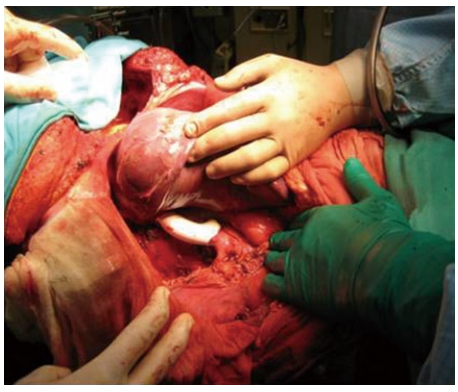

Figure 2 Polytetrafluoroethylene reconstruction of the inferior vena cava.

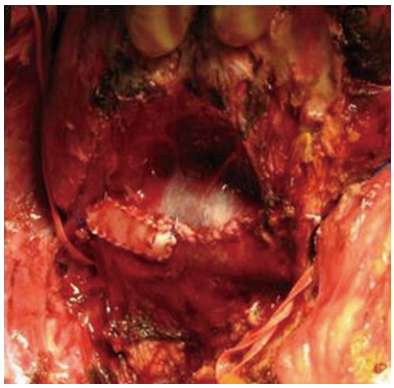

Figure 3 Reconstruction with a patch.

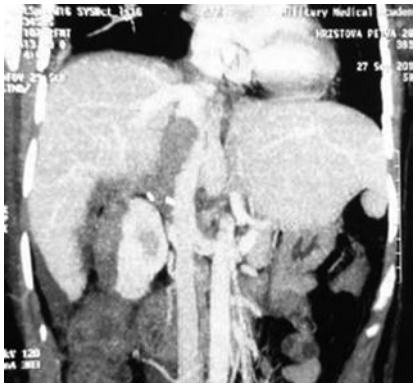

Figure 4 Thrombosis at the side of the patch on the second postoperative day.

month later, a right hemihepatectomy with partial tangential resection of the IVC was performed. Six months later there is no evidence of recurrence (Figures 5 and 6).

General complications, such as pneumonia, pleural effusion and cardiac arrest, were observed in the same group of patients. In all but 1 case, the complications were transient and successfully controlled. The mortality rate was 11.1% (n = 2). One patient died due to cardiac arrest and pulmonary embolism in the operation room and the second one died 2 d after surgery due to coagu-

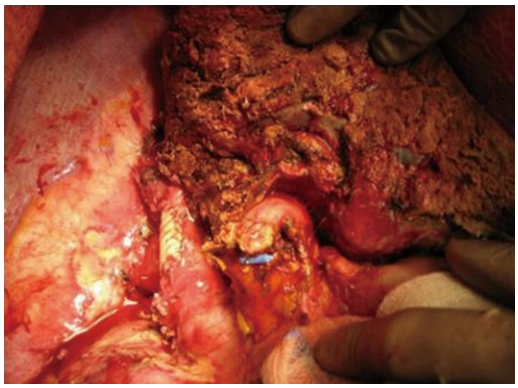

Figure 5 Reconstruction with a patch.

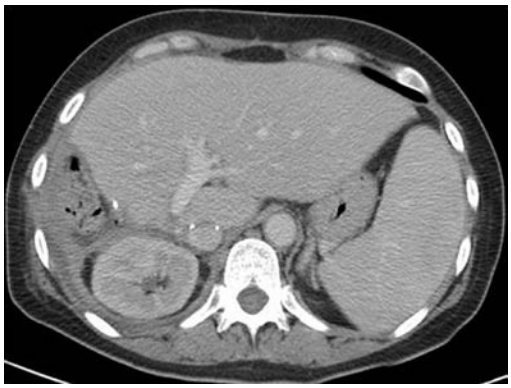

Figure 6 No evidence of recurrence six months later.

lopathy. With a median follow-up of 24 mo, 5 (27.8%) patients died of tumor recurrence and 11 (61.1%) are still alive, but three of them have a recurrence on CT.

DISCUSSION

For patients with CRC liver metastases, liver resection offers the only potential for cure[1]. The ultimate goal in hepatic resection of colorectal metastases is to obtain negative histological margins. In the past, patients with involvement of the IVC were considered poor candidates for surgical management. Untreated patients, however, have a median survival of less than 12 mo[2]. Chemotherapy alone does not offer a curative option with few 5 years survivors reported[3]. Resection of liver tumors that involve the vena cava has become possible with lessons learned from liver transplantation. This aggressive surgical approach offers hope for patients with hepatic tumors involving the IVC, who would otherwise have a dismal prognosis. This procedure can be performed under total hepatic vascular exclusion, with or without veno-venous bypass, and by *ex vivo* resection[4]. Control of blood flow through the IVC is essential to facilitate resection and reconstruction. When involvement of the IVC is minimal (< 60° circumferentially and < 2 cm longitudinally), control may be simply achieved by applying a side clamp to the IVC. In our series, we used such an approach in 14 of the cases. When the estimated narrowing of the vein is less than 20%-40%, the IVC can be repaired primarily by a lateral suture[5].

More extensive involvement of the IVC requires the use of a patch or segmental resection with graft replacement. In such cases, TVE may be used[6-9]. This may be achieved by applying vascular clamps to the IVC below and above the liver, with concomitant interruption of hepatic blood inflow using a Pringle maneuver[10]. This approach is further facilitated by the tolerable prolonged periods (60-90 min) of continuous warm hepatic ischemia in patients with normal livers[8,11,12]. Attention should be paid to patients with cirrhotic livers, where the ischemic time is much shorter and the risk of bleeding is higher.

In 2 of our patients we used total graft replacement. The material of choice is PTFE[13-15]. TVE may significantly reduce cardiac output as a result of decreased venous return, possibly resulting in hemodynamic instability[16]. Systemic veno-venous bypass may restore venous return and cardiac output, but we did not use this in our group of patients. A proper anticoagulation therapy was used in all of the patients.

Leiomyosarcomas of the IVC are extremely rare, documented in the surgical literature mostly as case reports rather than organized series. Usually they have a slow growth so symptoms may be absent in the beginning. However, even with extensive caval involvement, severe venous obstructive symptoms are not often seen, probably because of the development of extensive venous collaterals, which maintain adequate flow around the level of obstruction[17]. The segment of the IVC between the renal veins and the hepatic veins is the most commonly affected location for all primary vascular tumors[18-20]. Resection with negative margins is the treatment of choice[18]. If negative margins can be achieved, extended venous resection does not influence local recurrence rate or long-term outcome[21]. Radical resection of the tumor *en bloc* with the affected segment of the vena cava has been shown to be a feasible option with improved survival in multiple studies[17-20,22,23]. However, such patients have a poor prognosis and over half of them who undergo radical resection develop tumor recurrence; the 5-year survival rate ranges between 31% and 62%[24]. Poor prognostic factors include suprahepatic location, presence of Budd-Chiari syndrome, intraluminal tumor growth and IVC occlusion[25]. Adjuvant therapy has not been shown to have a significant effect[18].

Caval management after IVC resection is controversial. Options include primary repair, autologous patching, ligation or reconstruction with a prosthetic graft. Extensive venous involvement and large tumor size often preclude short segment resection with simple repair or patching. Ligation of the IVC is favored by some and has been shown to be well tolerated and generally safe, especially in those with preoperative IVC thrombosis[18,22]. However, there is a risk of late complications such as pain, swelling and skin breakdown from severe lower extremity edema. Long-term anticoagulation may be necessary in these patients. Suprarenal IVC tumor involvement

treated with IVC ligation can place a patient at serious risk for renal insufficiency. Restoration of flow to the right renal vein by reimplantation (or pelvic kidney autotransplantation) is mandatory to maintain right kidney function, but optional for the left renal vein because of the left kidney's considerable collateral drainage through the adrenal, inferior phrenic, gonadal and paravertebral vessels[26]. Kieffer *et al*[19] used a proximal pressure reading of 30 mm Hg or more in the IVC as an indication for caval reconstruction and found reconstruction to be necessary in most cases. PTFE is the most commonly used prosthetic material and has been shown to be a suitable replacement for the IVC with excellent long-term patency[19,20,23,27,28]. Infection and graft thrombosis are the 2 major complications of this type of reconstruction but both are rare. Graft thrombosis may or may not have any clinical importance and methods used to decrease its incidence include the use of ring-reinforced PTFE to prevent compression, short-term anticoagulation and placement of an arterio-venous fistula to augment flow[19].

PTFE graft infection after IVC replacement has been shown to be a rare occurrence in several large series[19,20,23,27]. The treatment is usually conservative but in some cases the graft must be removed.

Direct extension of renal cell carcinoma into the vena cava has been found in 4% to 10% of patients undergoing nephrectomy to treat cancer[29,30]. The prognosis of RCC with IVC tumor thrombosis is difficult to predict due to a wide variety in clinical behavior[31]. Although involvement of the IVC in renal cancer is generally not a vascular invasion by the neoplastic process but mostly an intraluminal extension of the tumor mass, such intravascular growth implies a heightened biological behavior of the tumor. Early pulmonary metastases are found in most cases.

Resection of intrahepatic cholangiocarcinoma with a negative microscopic margin improved survival. Thus, concomitant hepatic and IVC resection may provide a potentially curative operation. This aggressive surgical approach may offer hope for patients with intrahepatic cholangiocarcinoma involving the IVC[32,33].

In conclusion, it is apparent that application of combined resection of the liver and IVC expands the role of liver resection for malignancy and will benefit selected patients[34-36]. *En bloc* resection can be accomplished safely and confers an increase in survival for lesions often considered unresectable. There are a variety of options for replacement of the IVC if it cannot be primarily reconstructed. The use of various graft materials for reconstruction of the hepatic great vessels offers a higher resectable rate and better prognosis in selected cases. Such an operation should be performed in a specialized center where surgeons are familiar with both aspects of complex hepatobiliary surgery and liver transplantation.

COMMENTS

Background

Involvement of the major vessels has traditionally been considered as a contraindication for resection of advanced liver and retroperitoneal tumors because of the poor long-term prognosis and high surgical risks.

Research frontiers

The development of innovative surgical techniques, such as total hepatic vascular exclusion,veno-venous bypass and *ex vivo* hepatic resection, and the progress of liver transplantation has made a curative surgical approach to tumors involving both the liver and inferior vena cava (IVC) possible.

Innovations and breakthroughs

The surgical removal of the tumor with clear margins is the only potential for cure. The advances in surgery and perioperative care lead to a more aggressive approach to malignancies involving major vessels which should be replaced by different kinds of allogen artificial grafts.

Applications

The use of vascular grafts after block resection of tumor and major vessels should be performed in specialized HPB and Transplant centers. The type of the graft depends on the hospital protocol and personal preferences of the surgeon.

Terminology

Allograft is organ or tissue from one individual to another of the same species with a different genotype, including cadaveric or living related. A suitable vein is not always available and in this situation an artificial graft should be used.

Peer review

The authors presented resection and reconstruction of the IVC for tumors. They conclude that the technique of combined resection of the liver and IVC is safe, expands the indication, and increases survival.

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CASE REPORT

Lymphoma presenting as a necrotic colonic mass

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Abstract

Primary colonic lymphomas represent a rare minority among the colonic neoplasms. Their correct pre-operative identification is crucial for the design of treatment. We herein describe a case of a colonic lymphoma presenting as a necrotic colonic mass and we discuss the current evidence about the presentation, diagnosis and treatment of lymphomas isolated to the colon.

Key words: Colonic lymphoma; Necrotic colonic mass

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INTRODUCTION

Colonic lymphomas represent a rare entity, comprising less than 1% of colonic neoplasms. Their correct treatment is still an issue of debate as the rarity of this disease precludes randomized clinical trials. In this report, we describe a case of a colonic lymphoma presenting as a necrotic colonic mass and we emphasize the correct identification of colonic lymphomas and the current evidence with regard to their treatment.

CASE REPORT

A 70-year-old female presented with a 6-mo history of vague abdominal pain. The patient also complained of constipation, fatigue and night sweats but no nausea, vomiting, weight loss or melena. The patient's medical history included breast cancer status post lumpectomy 10 years ago and splenic lymphoma status post splenectomy 6 years ago. Her last colonoscopy was 6 years ago and was normal. The abdomen was soft, tender to palpation over the left lower quadrant with no rebound or guarding. An 8-10 cm abdominal mass was palpable at the left lower quadrant. The laboratory results showed a white cell count of 13 000 per cubic millimeter and a carcino-embryonic antigen level of 0.7 ng/mL. Abdominal computed tomography (CT) with oral and intravenous contrast medium showed a necrotic mass 8.7 cm × 9.4 cm at the left lower quadrant, encasing the distal descending and proximal sigmoid colon, with associated adenopathy in the retroperitoneum and left sided hydronephrosis secondary to ureteral obstruction by the mass (Figure 1A and B, arrows). A colonoscopy was consistent with a large necrotic and ulcerated mass in the sigmoid colon (Figure 2).

Biopsies obtained during the colonoscopy were consistent with B-cell lymphoma. The patient underwent surgical exploration and proximal colostomy with the plan to follow up with systemic chemotherapy and surgery after the conclusion of the chemotherapy.

DISCUSSION

Primary colonic lymphomas account for only 0.2%-0.6% of colon cancers[1-5] and 10%-20% of the gastrointestinal

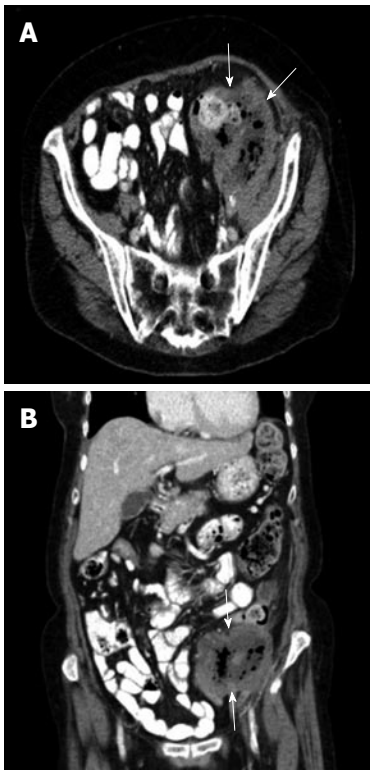

Figure 1 Axial (A) and coronal (B) computed tomography scan images of the colonic mass.

lymphomas, with the stomach by far the most common site[1,6]. Colonic lymphomas are found more frequently in males in their sixth and seventh decade of life[1,3,5]. Inflammatory bowel disease and immunosuppressive states like HIV are known risk factors[1,5]. The most frequent presentation is abdominal pain and weight loss, whereas an abdominal mass, as in our case, is often palpable[1-3,5]. The most commonly involved site is the cecum, likely because of the abundance of lymphoid tissue in the ileocecal region[1-5]. The predominant type is non-Hodgkins B cell lymphoma[1,3,4].

In our case, the lymphoma presented as a necrotic colonic mass on computerized tomography. In general, the CT appearance of lymphomas can be that of either a discrete mass, focal induration or diffuse colonic invasion[7]. The presence of extensive abdominal and/or pelvic lymphadenopathy places the lymphoma at the top of the differential diagnosis. Even in the absence of lymphadenopathy, imaging characteristics such as location at the cecum, demarcation from the peri-colonic fat with no invasion of surrounding viscera and the presence of perforation in the absence of desmoplastic reaction should raise the suspicion of a lymphoma[7]. The role of colonoscopy and biopsy is crucial for the correct preoperative diagnosis.

Most of the tumors present in an advanced stage and the reported 5-year survival is thus relatively poor, ranging between 27%-55%[1-6]. Most of the reported series use a combination of surgery and chemotherapy[3]. Although the exact role of chemotherapy cannot be defined due to the rarity of the disease and the lack of randomized trials, some authors support that it is associated with a survival benefit[1,4]. In the presence of a colonic perforation, which may occur during the chemotherapy, the mortality is high[4]. In the report by Lai *et al*[4], the four patients who were operated emergently for perforation died within 30 d post-operatively. In our case, we elected to offer a proximal colostomy, given the extent of the disease, and to proceed with chemotherapy. We plan to resect the remnant tumor and restore the continuity of the GI tract after completion of the chemotherapy.

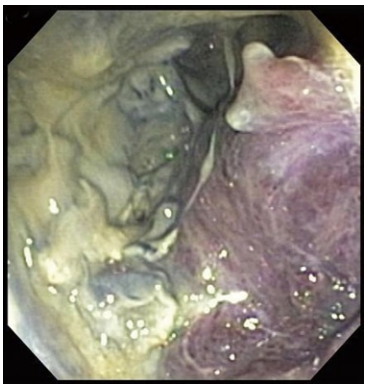

Figure 2 Endoscopic appearance of the colonic mass.

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Events Calendar 2012

January 19-21, 2012
Gastrointestinal Cancers Symposium 2012
San Francisco, CA, United States

January 25-29, 2012
Alpine Liver and Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel,
Madonna di Campiglio, Italy

February 1-4, 2012
Society Of Laparoendoscopic Surgeons AsianAmerican Multi-Specialty Summit 2012 (SLS 2012)
Honolulu, HI, United States

February 4, 2012
Radio ENT 2012
Bangalore, India

February 14-16, 2012
7th Annual Academic Surgical Conference
Las Vegas, NV, United States

February 22-24, 2012
BTS 15th Annual Congress
Glasgow, United Kingdom

February 20-25, 2012
Minimally Invasive Surgery Symposium 2012
The Grand America Hotel,
Salt Lake City, UT, United States

March 7-10, 2012
Society of American Gastrointestinal and Endoscopic Surgeons Annual Meeting 2012 (SAGES 2012)
The San Diego Convention Center,
San Diego, CA, United States

March 9-10, 2012
Kieler Arthroskopiekurs Kniegelenk
Kiel, Germany

March 29- April 1, 2012
Endovienna 2012 - 5th World Congress for Endoscopic Surgery of the Brain Skull Base & Spine combined with The First Global Update on Fess, The Sinuses & The Nose
Vienna, Austria

March 7-11, 2012
American Hepato-Pancreato Biliary Association Annual Meeting 2012 (AHPBA 2012)
Eden Roc Resort, 4525 Collins Avenue,
Miami Beach, FL, United States

May 19-22, 2012
The 2012 Digestive Disease Week
San Diego, CA, United States

May 18-19, 2012
The American Pancreas Club Scientific Meeting
San Diego, CA, United States

June 1-5, 2012
48th American Society of Clinical Oncology Annual Meeting
Chicago, IL, United States

June 17-20, 2012
Digestive Disorders Federation Conference - Combined meeting of BSG, AUGIS, BAPEN & BSL
Liverpool, United Kingdom

June 20-23, 2012
44th meeting of European Pancreatic Club
Prague, Czech Republic

June 27-30, 2011
ESMO 14th World Congress on Gastrointestinal Cancer
Barcelona, Spain

July 1-5, 2012
10th World Congress of the International Hepato-Pancreato-Biliary Association joined with the European HPBA Congress
Paris, France

September 15-16, 2012
Current problems of gastroenterology and abdominal Surgery
Kiev, Ukraine

September 19-21, 2012
32nd Congress of the European Society of Surgical Oncology (ESSO)
Valencia, Spain

September 28 - October 2, 2012
37th European Society for Medical Oncology (ESMO) Congress
Vienna, Austria

November 4-7, 2012
8th National Cancer Research Institute Conference
Liverpool, United Kingdom

November 14-16, 2012
Pancreatic Society of Great Britain and Ireland Meeting 2012
Cameron House Hotel, Glasgow

December 8, 2012
IASGO 2012 - 22nd World Congress of the International Association of Surgeons, Gastroenterologists and Oncologists
Bangkok, Thailand

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GENERAL INFORMATION

World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240), is a monthly, open-access (OA), peer-reviewed journal supported by an editorial board of 336 experts in gastrointestinal surgery from 35 countries.

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In the interests of transparency and to help reviewers assess any potential bias, *WJGS* requires authors of all papers to declare any competing commercial, personal, political, intellectual, or religious interests in relation to the submitted work. Referees are also asked to indicate any potential conflict they might have reviewing a particular paper. Before submitting, authors are suggested to read "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Ethical Considerations in the Conduct and Reporting of Research: Conflicts of Interest" from International Committee of Medical Journal Editors (ICMJE), which is available at: http://www.icmje.org/ethical_4conflicts.html.

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Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

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2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

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Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as

χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1948-9366/g_info_20100312191949.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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