Pattern and prognostic factors in patients with malignant ascites: a retrospective study

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Received 10 August 2006; revised 3 November 2006 and 11 December 2006; accepted 15 December 2006

Background: Malignant ascites is a manifestation of end stage events in a variety of cancers and is associated with a poor prognosis. We evaluated the pattern of cancers causing malignant ascites and factors affecting survival.

Patients and methods: Patients coded with the International Classification of Diseases-9 coding system for malignant ascites over a 2-year period were reviewed. The clinicopathological data and patients’ survival were compared among cancer groups.

Results: There were 209 patients (140 females and 69 males), median age being 67 (30–98) years. The commonest cancer was ovarian followed by gastrointestinal (GI) cancers. Fifty-eight per cent of the patients had symptoms related to the ascites. Liver metastases were significantly commoner in the GI cancers \((P = 0.0001)\). Fifty-four per cent of our patients presented with ascites at the initial diagnosis of their cancer. Paracentesis was given to 112, diuretics to 70 and chemotherapy to 103 patients. The median survival following diagnosis of ascites was 5.7 months. Ovarian cancer favoured longer survival while low serum albumin, low serum protein and liver metastases adversely affected survival. The independent prognostic factors for survival were cancer type, liver metastases and serum albumin.

Conclusion: The identified independent prognostic factors should be used to select patients for multimodality therapy for adequate palliation.

Key words: cancers, chemotherapy, malignant ascites, paracentesis, prognostic factors, survival

introduction

Malignant ascites is a manifestation of end stage events in a variety of cancers and is associated with significant morbidity. It accounts for about 10% of all cases of ascites and usually caused by ovarian, endometrial, breast, oesophageal, gastric, colorectal, lung, pancreatic and primary peritoneal carcinomas [1–3]. It is known that about 50% of patients with malignant ascites present with ascites at the initial diagnosis of their cancer [4, 5]. The onset and progression of malignant ascites is associated with deterioration in quality of life (QoL) and a poor prognosis. There are, however, no generally accepted evidence-based guidelines for evaluation and treatment of this condition. There are also no clinical predictors that identify cancer patients who will develop this distressing entity; hence there are no preventive measures for its development.

There are different approaches to the treatment of malignant ascites from symptomatic relief with simple drainage procedures to chemotherapy and debulking surgery aimed at treating the underlying cancer. It is envisaged that QoL and possibly the survival of patients with malignant ascites may be improved with increasing availability and use of appropriate and potent combination chemotherapy.

The objectives of this study were to determine the pattern of cancers causing malignant ascites, treatment modalities offered and factors affecting survival.

patients and methods

The medical records of all patients coded for malignant ascites using the International Classification of Diseases-9 coding system from January 2003 to December 2004 at the Nottingham City Hospital were reviewed. The patients included in this study had clear documentation of ascites of malignant origin in their clinical notes. The development of ascites in patients with history of either intra-abdominal or extra-abdominal malignancy in the absence of liver cirrhosis and other causes of nonmalignant ascites was accepted as being malignant. Malignant origin of the ascites in these patients was usually confirmed by one or more of cytological examination, imaging, laparoscopy or laparotomy.

The data collected included demographics, cancer entity, time interval between the diagnosis of the primary cancer and that of the ascites, symptoms of ascites, method of diagnosis of ascites, laboratory parameters at diagnosis, the presence of metastases at diagnosis of ascites, treatment of ascites and survival.

Statistical analysis was by the SPSS version 13.0 (SPSS, Chicago, IL, USA) using Mann–Whitney \(U\)-test and log-rank test with \(P\) value <0.05 considered significant.

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**results**

There were 209 patients with malignant ascites during this period with 140 (67%) females and 69 (33%) males. The median age at diagnosis of the ascites was 67 (30–98) years. The cancer types causing the ascites are shown in Figure 1. The proportion of patients developing ascites from each main cancer group expressed as a percentage of the total number of patients registered at the tumour specific multidisciplinary team meetings include 18.3% for gastric cancer, 4.0% for oesophageal cancer, 3.7% for colorectal cancer, 36.7% for ovarian cancer, 3.0% for breast cancer and 21% for pancreatobiliary cancers. One hundred and twenty-two (58%) of the patients presented with symptoms related to the ascites including abdominal swelling (55%), abdominal pain (53%), nausea (37%), anorexia (36%), vomiting (25%), fatigue (17%), dyspnoea (11%), early fullness (6%), weight change (5%), ankle swelling (3%) and heartburn (1%). The median time interval between the diagnosis of the cancer of origin and that of the ascites was 0.87 (0–341) months. In fact, 54% of patients had their ascites at first diagnosis of their cancer and the median of 0.87 (not zero) months represents a delay in diagnostic investigations in a few patients. Forty-one per cent of the patients had their ascites diagnosed clinically and those with subclinical ascites, diagnosis was made at laparoscopy, laparotomy or with imaging investigations [computed tomography (CT) and ultrasound scans].

The sites of metastases at diagnosis of the ascites as demonstrated by diagnostic imaging techniques included peritoneal (181 patients), liver (36 patients), bone (26 patients) and lung (16 patients). Liver metastases was commonest in patients with cancers of gastrointestinal (GI) origin at 45%, followed by breast cancer 32%, unknown cancer 11%, ovarian cancer 7% and ‘other’ cancer 5%. The difference in the incidence of liver metastases in the tumour groups is statistically significant ($P = 0.0001$). Bone metastases were most common in patients with a breast primary. Immunocytochemistry of the ascites was positive in 140 (67%), suspicious in 10 (4.8%), negative for cancer cells in 12 (5.7%) and was not carried out in 47 (22.5%). There was no metastasis detected in 10 patients on imaging techniques. Of these cytology was positive in five, suspicious in two, negative in one and not done in two patients.

The median total serum protein and albumin at diagnosis of the ascites in the 209 patients were 61 (30–78) g/l and 28 (15–43) g/l, respectively. There is a significant correlation between the presence of liver metastases and low total serum protein ($P = 0.018$) but no relationship was found with low serum albumin ($P = 0.390$).

The most common treatment offered for the ascites was serial paracentesis in 112 (53.6%) patients with mean of two (1–7) drainages required. Sixty-three out of 209 (30%) patients had the initial drainage of their ascites either at laparoscopy or laparotomy with only 15 out of 63 patients requiring further paracentesis. Forty-nine out of 209 (23.4%) patients had no need for a drainage procedure. These patients who had drainage at surgery or required no drainage at all during their hospital episode had subclinical ascites that were either diagnosed radiologically or incidentally found at laparoscopy or laparotomy. None of the patients in this series had either continuous catheter drainage or peritoneovenous shunt placement. Diuretics were used in 70 patients with spironolactone, an aldosterone antagonist used in 56 (80%), frusemide in six (8.6%) and combination of both in eight (10.4%). Diuretics tended to be used in patients with liver metastasis (55/56). Intravenous or oral single or combination chemotherapy was given in 103 (49.3%) patients (41 ovarian, 35 GI, 11 breast, 12 ‘other’ cancers and four unknown primary). The commonest chemotherapy in ovarian cancer was a carboplatin-based regimen. Intraperitoneal (i.p.) cisplatin was used in one patient. The remaining 50.7% of the patients were entered into the palliative care pathway and had only symptomatic control of their malignant disease process.

Follow-up was until death or at least 17 months after diagnosis of ascites. There were 23 patients who were still alive at the end of the study (follow-up range 17–52 months). The overall median survival after the diagnosis of malignant ascites was 5.7 (95% confidence interval 3.54–7.93) months. Eighty-eight out of 209 patients had subclinical ascites and these had a slightly longer median survival than patients with clinical ascites (7 versus 5 months) but this did not reach a statistical significant level ($P = 0.159$). Patients with ovarian cancer had better survival than those with other cancer groups ($P = 0.0001$). Patients with ascites of GI cancer origin, other cancers and those with unknown primary had the worst survival (Figures 2 and 3).

Levels of serum albumin and total protein at diagnosis of ascites significantly affected survival. Low serum albumin (<30 g/l) and low serum total protein (<60 g/l) are both associated with poor overall survival ($P = 0.0001$ and $P = 0.025$, respectively). The presence of liver metastases was associated with worse survival in all cancer groups ($P = 0.016$). Females survived longer than the males ($P = 0.0001$) but this is due to better prognosis with ovarian and breast cancer groups. There was improved survival in those patients who had chemotherapy ($P = 0.0001$). Multivariate Cox regression analysis showed cancer type, low serum albumin levels and the presence of liver metastasis to be independent prognostic factors for overall survival.

**discussion**

Symptomatic malignant ascites is a significant problem in the palliative care setting and associated with a progressively
deteriorating QoL and a poor prognosis. It is, however, believed that with better understanding of the pathophysiology of malignant ascites, better diagnostic evaluation and the use of multimodality therapy, the QoL and survival of these patients may be improved. There are few studies evaluating the natural history of malignant ascites and the prognostic factors relating to survival [4, 6–8] and some authors [6, 7] in different series have demonstrated the predominance of ovarian cancer causing ascites in the patient’s population studied.

Parsons et al. [5] carried out a 2-year retrospective review from this centre over a decade ago in which they showed that ovarian cancer was the commonest cause of ascites with far better prognosis than patients with GI cancers. We wanted to see whether there had been any changes in relation to pattern of cancer causing ascites, treatment options, prognostic factors and survival in the last 10 years. Again, the commonest cancer of origin leading to malignant ascites in our series was ovarian representing 25% of the total patient population. Of the total cancer cases seen by each multidisciplinary team in our institution during the 2-year review, ovarian cancer had the highest proportion of patients who developed ascites at 37.7% followed by pancreaticobiliary cancers 21%, gastric cancer 18.3%, oesophageal cancer 4.0%, colorectal cancer 3.7 and breast cancer 3.0%. We did not encounter any case of hepatocellular carcinoma causing ascites in this series. This may be due to low incidence of primary hepatocellular carcinoma in the UK population. There is a predominance of the female patient population (140 of 209) similar to previous studies and this is accounted for by the predominance of the ovarian and breast cancer entity.

Fifty-four per cent of our patient population presented with malignant ascites at the initial diagnosis of their cancer and this is similar to the series previously reported [4, 5]. These patients were mainly the ovarian and the GI cancer groups, while patients with breast cancer tended to develop ascites due to their cancers months or years after their primary cancer had been diagnosed and treated. The number of malignant ascites due to an unknown primary cancer in the present study was less than the previous study done by Parsons et al. [5] (8.1% versus 22.6%) from this same centre and other reported incidence of 13–22% [9]. This is probably due to improvements in determination of tumour of origin by techniques such as imaging, laparoscopy and immunocytochemical analysis. In our series, 10 patients had no evidence of metastases on imaging. Seven out of the 10, however, had malignant or suspicious cytology and therefore, probably had peritoneal carcinomatosis not detected on CT. In another two patients, cytology was not carried out and in one other the cytology was negative. It may be that the cytologically negative patient also had peritoneal carcinomatosis, although Runyon et al. [3] previously showed that of their total number patients with malignant ascites, 53.3% had peritoneal carcinomatosis and all of this group had a positive cytology indicating a near 100% sensitivity of cytology in patients with peritoneal carcinomatosis.

Twelve-three of our patients are still alive after a minimum follow-up of 17 months and most of them are in the ovarian cancer group. Ovarian cancer is usually amenable to debulking surgery and has a good response to chemotherapy. Our finding that ascites of ovarian origin has a better median survival than all other cancer groups agrees with previous studies [4–8]. This also may have been responsible for the better survival seen in women compared with men. We therefore reinforce the conclusion of our previous study [5] that female patients with malignant ascites from cancer of unknown primary should be aggressively investigated in case they have an underlying ovarian cancer. Seventy-nine per cent (41 of 52) of our patients with ovarian cancer had chemotherapy which was mainly a carboplatin-based regime with a measure of response.

We have evaluated various factors that affect survival in patients with malignant ascites and our findings are in keeping with the few published articles addressing this issue [5–8]. Patients with GI cancer as well as those with an unknown primary have a very poor survival compared with the ovarian or breast cancer groups. Overall, we noticed that patients in our series had longer median survival periods in all cancer groups than reported 10 years ago. This may be explained by increasing use of aggressive multimodality therapy including combination chemotherapy (49% received chemotherapy in the current
study compared with 41% in our previous study). Furthermore, the success of chemotherapy has improved over the last 10 years in breast and ovarian cancers. The presence of liver metastases at the time of ascites diagnosis was a significant predictor of poor survival both on univariate and multivariate analyses. This finding was similar to that from previous studies [5, 6, 8]. Patients with GI cancer were, however, found to be more likely to have liver metastases followed by breast cancer unlike our previous findings [5] where patients with breast cancer had the highest proportion of liver metastases a decade ago. Patients with liver metastases in this study tended to be given diuretics on the understanding that their ascites is likely caused by the renin–angiotensin–aldosterone pathway. Diuretics have been shown to be more effective in the presence of liver metastases [2, 10, 11].

Low levels of serum albumin and total proteins are significant factors affecting survival adversely. In fact, low serum albumin is an independent prognostic factor especially in the nonovarian cancer groups. There are no other studies that have reported the prognostic roles of serum albumin and total protein in malignant ascites except our previous study [5]. The poor prognostic role is likely to be related to poor nutritional reserve, association of low total serum protein with the presence of liver metastases and impaired immune network function in this group of patients. Our findings also demonstrated that female gender is associated with longer survival and better prognosis in malignant ascites and we believe that this is due to the combined preponderance of ovarian and breast cancer groups. Patients who had chemotherapy also survived longer than those who did not receive chemotherapy but again this is likely to be multifactorial such as response of cancer and ascites to chemotherapy, the higher proportion of the ovarian cancer in the chemotherapy group and the fact that patients selected for chemotherapy are those with relatively good performance status (PS) and longer life expectancy. We did not look at PS in this retrospective study but we feel it is another important tool in the selection of patients suitable for aggressive treatment. PS is being used as part of the selection criteria for a multicentre prospective randomised therapeutic trial of the monoclonal antibody catumaxumab and we await the results of this trial with interest. The patients who had no chemotherapy (50.7%) in this series were entered into the palliative care pathway and had only symptomatic control of their malignant disease process.

Serial paracentesis was still the commonest treatment offered to patients with symptomatic malignant ascites followed by the use of diuretics. Paracentesis provides relief of symptoms for patients with malignant ascites and improves their QoL. [12]. Lee et al. [13] in a survey of Canadian physicians’ practice showed that the use of diuretics was the second preferred treatment after therapeutic paracentesis, though it was not felt to be effective in the treatment of malignant ascites. The group of patients who had drainage at surgery and required no further drainage, and those who required no drainage at all during the course of their hospital episode, were those with subclinical ascites that were either diagnosed radiologically or incidentally found at laparoscopy or laparotomy. There is no prospective study evaluating the role of diuretics and no general consensus for the use of diuretics in the treatment of malignant ascites.

Therefore, further studies are required in order to identify those patients who will benefit from this therapy. Only one patient in this study had i.p. cisplatin therapy and none of the patients reviewed had intracavitary radiotherapy, matrix metalloproteinases inhibitors or i.p. immunotherapy. There are emerging new concepts in the treatment of malignant ascites on the basis of better understanding of the pathophysiological basis of its formation [14–17]. These new agents include i.p. administration of a monoclonal antibodies (catumaxumab) against epithelial cell adhesion molecule which has shown encouraging results in a phase I/II trial [16] and is currently being investigated in a large multicenter randomised clinical trial.

**Conclusion**

The overall prognosis of patients with malignant ascites is poor and patients are typically in the palliative phase of care when they present. Patients, however, may be successfully palliated by careful selection and appropriate offer of therapy tailored towards individual patient’s characteristics and primary cancer type. The prognosis is, however, determined mainly by the origin of the primary cancer, presence of hepatic metastases and serum albumin concentration. Malignant ascites of ovarian origin has a better prognosis even in the presence of ascites while patients with malignant ascites of GI origin or unknown origin have the worst outcome.

Fifty-four per cent of our patients presented with ascites at the initial diagnosis of their cancer. The independent prognostic factors mentioned above should be used to select patients for multimodality therapy as this may offer adequate palliation, improved QoL and prolonged survival.

**References**


