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Review

Malignant ascites: Systematic review and guideline for treatment

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ABSTRACT

A guideline on the management of symptomatic malignant ascites by abdominal paracentesis, diuretics and peritoneovenous shunting, based on a systematic review of the literature is presented. Thirty-two relevant studies were identified. None were randomized control trials, one was a non-randomized open controlled trial, five were cohort studies or prospective uncontrolled trials, 26 studies were non-analytic studies like case series. Although paracentesis, diuretics and shunting are commonly used procedures, the evidence is weak. Available data show good, although temporary effect of paracentesis on symptom relief. Fluid withdrawal speed and concurrent intravenous hydration is not sufficiently studied. Peritoneovenous shunts can control ascites in patients with malignant ascites, but have to be balanced by the potential risks of this procedure. The available data about diuretics in treatment of malignant ascites are controversial. The use of diuretics therefore should be considered in all patients, but has to be evaluated individually.

1. Introduction

Malignant ascites is defined as abnormal accumulation of fluid in the peritoneal cavity as a consequence of cancer[1] and presents a difficult clinical problem causing discomfort and distress to many patients in the advanced stages of their disease. It accounts for around 10% of all cases of ascites and occurs in association with a variety of neoplasms, especially breast, bronchus, ovary, stomach, pancreas and colon cancer.[2] Up to 20% of all patients with malignant ascites have tumours of unknown primary origin.[3] Large amounts of ascites can cause increased abdominal pressure with troublesome symptoms like pain, dyspnea, loss of appetite, nausea, reduced mobility and problems with the body image.

Pathophysiology of malignant ascites is multifactorial and is as yet incompletely understood.[4] Ascites may result from obstruction of lymphatic drainage by tumour cells that prevent absorption of intraperitoneal fluid and protein,[5] as seen often in lymphomas and breast cancer.[6] Since the ascites of many patients with malignant ascites has a high protein content, alteration in vascular permeability has been implicated in the pathogenesis of ascites production.[7] Hormonal mechanisms are also involved. Due to decreased removal of fluid as a consequence of obstructed lymphatics, the circulating blood

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volume is reduced and this activates the renin–angiotensin–aldosterone system, leading to sodium retention. Therefore reduced sodium intake together with diuretics is often used to treat malignant ascites, but there is no consensus on effectiveness.[8] A survey by Lee and colleagues showed that paracentesis and diuretics are the most commonly used procedures in management of malignant ascites followed by peritoneovenous shunts, diet measures and other modalities like systemic or intraperitoneal chemotherapy.[8] In contrast to the treatment of underlying cancer, there is no generally accepted evidence-based guideline for the management of malignant ascites so far. Therefore the aim of this paper is to collect, critically appraise and summarize the evidence on the effectiveness of abdominal paracentesis, diuretics and peritoneovenous shunting in management of malignant asicites and to develop a guideline in order to get evidence to practice.

2. Methods

A literature search of articles published between 1966 and August 2005 was undertaken, using OVID's database interface of the following databases: OVID MEDLINE, Biological Abstracts, BIOSIS Previews, CINAHL, EMB-Reviews Cochrane Database of Systematic Reviews, EBM-Reviews ACP-Journal Club, EBM-Reviews Database of Abstracts of Reviews of Effects, EBM-Reviews Cochrane Central Register of Controlled Trials. In addition, searches were performed in NLM's PubMed (1966–August 2005) and CancerLit (1963–2002).

The database search strategy consisted of three steps. Step one identified articles about malignant ascites. Step two revealed articles about therapeutic measures for malignant ascites and step three limited the search results to human clinical trials only. The search strategy as adapted for the OVID search interface was as follows: (1) Ascites/ (2) ascit$.mp. [mp = title, original title, abstract, name of substance word, subject heading word] (3) 1 or 2 (4) exp Neoplasms/ (5) neoplas$.mp. 6. cancer$.mp. (7) carcino$.mp. (8) malign$.mp. (9) debilitat$.mp. (10) or/4–9 (11) Ascites/mo, co, pa, pp, dh, dt, su, th, et [Mortality, Complications, Pathology, Physiopathology, Diet Therapy, Drug Therapy, Surgery, Therapy, Etiology] (12) 3 and 10 (13) 11 and 10 (14) Therapeutics/ (15) therap$.mp. (16) Diet, Sodium-Restricted/ (17) diet$.mp. (18) exp Drug Therapy/ (19) drug$.mp. (20) exp Diuretics/ (21) diuret$.mp. (22) Peritoneovenous Shunt/ (23) peritoneovenous shunt$.mp. (24) Paracentesis/ (25) paracente$.mp. (26) management.mp. (27) treat$.mp. (28) Palliative care/ (29) palliative care.mp. (30) or/14–29 (31) 12 and 30 (32) 13 and 30 (33) limit 31 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv) (34) limit 33 to humans (35) limit 34 to english (36) limit 32 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv) (37) limit 36 to humans (38) limit 37 to english (39) clinical trial$.mp. (40) 31 and 39 (41) 40 not 35 (42) limit 41 to humans (43) 42 or 35 (44) 32 and 39 (45) 44 not 38 (46) limit 45 to humans (47) 38 or 46.

Hand searching was done on the reference list of pertinent articles and bibliographies of chapters on ascites in books on palliative care. Inclusion criteria for the systematic review were identified prospectively and are summarized in Table 1. As the purpose of this review was to propose a guideline on management of symptomatic ascites, also studies providing a comparatively low level of evidence, i.e., non-analytic studies like case series were included if this was the best evidence that could be obtained.

Table 1 – Inclusion criteria

Population	Adult cancer patients with malignant ascites due to cancer of any type
Intervention	Symptomatic Management of malignant ascites by Abdominal paracentesis Diuretics Peritoneovenous shunting
Outcome measure	Primary Prevention/reduction of fluid accumulation Secondary Incidence of adverse events Predictors of response

Data regarding study design, study population (including primary diagnosis and co-morbidities), intervention, side-effects and outcomes were extracted from the text, tables and figures. Due to the heterogeneity of the study designs and outcomes, meta-analysis was not performed. Hence, we prepared brief summaries when possible to synthesize the findings regarding outcome and side-effects. The level of evidence of the studies was assessed by two independent reviewers (G.B. and D.G.) according to the rigor of study design and methodology. Grading of the evidence and the recommendations in the guideline are based on the revised grading system by the Scottish Intercollegiate Guidelines Network (SIGN).[9]

3. Results

There were 32 studies identified relevant for this review. Of these, none was a randomized controlled trial. One study was a non-randomized open controlled trial, 5 were cohort studies or prospective uncontrolled trials, 26 studies were non-analytic studies like case series. The studies included heterogeneous groups of patients and there were differences in the methodology used. Some patients were still receiving systemic chemotherapy against the underlying malignancy. Most trials showed weaknesses in design. Details of the evaluated trials are summarized in Tables 2–4.

3.1. *Symptomatic management by paracentesis*

Available data show good, although temporary relief of symptoms related to the build-up of fluid in about 90% of patients managed by paracentesis. There is no consensus on fluid withdrawal speed. Several timings have been reported, varying from 30 to 90 min[10] to 24 h.[11] Possible complications of paracentesis include secondary peritonitis, pulmonary emboli and hypotension[12] (Table 2). Repeated large volume paracentesis without plasma volume expansion may be associated with significantly higher incidence of hypotension and renal impairment. In the context of benign ascites due to

Table 2 – Management by abdominal paracentesis

Author/year/ level of evidence	Study design	No. of subjects	Primary tumour	Number of paracenteses	Symptom relief	Duration of effect	Complications
Fischer (1979),[13] level 3	Case series	300	–	–	–	–	No severe hypotension under concurrent infusion with 5% dextrose
Appelqvist (1982),[11] level 3	Case series	100	Varied	127	–	–	4 died because of complications (3%): 2 died from pulmonary embolism, 1 from perforation, 1 peritonitis
Ross (1989),[57] level 3	Case series	43	Varied	109	39 (87%)	4–45 days mean 10.4 days	2 fatal hypotension (2%) 1 nonfatal hypotension (1%)
Gotlieb (1998),[10] level 3	Prospective uncontrolled trial	15	Ovary	35	100% (89% complete relief 11% partial relief)	–	No hypotension, no perforation, no peritonitis
McNamara (2000),[19] level 3	Prospective uncontrolled trial	44	Varied	48	100% in 4 symptoms (discomfort, nausea, vomiting dyspnoea) improvement of at least 2 units on a score from 0 to 10 for reading 2 h after paracentesis compared with mean score baseline	For all 4 symptoms improvement in the mean scores at 72 h compared with baseline, reaching statistical significance in discomfort, vomiting and dyspnoea	No associated adverse effects in 35 procedures (73%). 11 pts reported pain (7 requiring analgesia), 1 patient vomited soon after drain insertion
		102			Mean 94%		

Table 3 – Management by diuretics

Author/year/ level of evidence	Study design	No. of subjects	Diuretics used	Relief of ascites	Duration of effect	Renal dysfunction	Other adverse effects
Razis (1976),[58] level 2	Cohort study	12	IV furosemide 100–200 mg or IV bumetanide 3–5 mg/day	5	–	–	–
Greenway (1982),[21] level 2	Cohort study	15	Spironolactone 150–450 mg	13 (8 until death 5 at 1–4 months)	–	0	Two uncontrolled nausea and vomiting
Pockros (1992),[20] level 2	Cohort study	16	Sodium diet Spironolactone +/− furosemide (dose adjusted for weight loss of 0.5 kg/day)	3 (those with massive hepatic metastases and ↑↑ plasma renin levels)	Uncertain (study lasted 7.8 ± 3.2 days)	2 (both in the group of non-responders)	1 symptomatic hypotension (non-responder)
Gough (1993),[59] level 3	Study is not randomized open controlled trial, level 2. Concerning diuretics descriptive subgroup analysis of 68 pts, level 3	68 (38 also had shunt*)	Methylclothiazide 5 mg/day and spironolactone 50–100 mg/day	26 (12 with shunt)	15 < 8 weeks 11 > 8 weeks	–	–
Sharma et al. (1995),[60] level 3	Case report	2	Spironolactone 100–200 mg/day and furosemide 40–80 mg/day	2	One 4 months until death. One 5.5 months until lost of follow up	0	0
		Total 113		Mean 43%			

Table 4 – Management by peritoneovenous shunts

Author/year/ level of evidence	Study design	Primary tumour	No. of patients	Type of shunt	Control of ascites	Shunt block	Pulmonary oedema	Pulmonary emboli	DIC subclinial	DIC clinical	Infection	Tumour emboli at autopsy	Shunt patency
Straus (1979),[61] level 3	Case series	Varied	33	Le Veen	27	4	1	1	–	1	1	0/9	Mean 10.6 weeks
Kudsk (1980),[62] level 3	Case series	Varied	10	Le Veen	8	2	0	1	5	1	1	0/2	–
Lokich (1980),[63] level 3	Case series	Varied	8	Le Veen	8	2	4	1	4	1	–	–	–
Raaf (1980),[64] level 3	Case series	Varied	5	Le Veen	5	1	–	1 (suspected)	1	0	0	–	–
Cheung (1982),[65] level 3	Case series	Varied	22	19 Le Veen 3 Denver	–	–	3	2	6	0	4	1/6	Pts with neg. cytology = median 120 days, pos. cytology = median 26 days
Gough (1982),[66] level 3	Case series	Varied	10	Le Veen	8	3	–	–	–	0	1	–	1–64 weeks, mean 16 weeks
Qazi (1982),[67] level 3	Case series	Varied	40	Le Veen	28	–	4	–	6/10	0	1	0/8	–
Souter (1983),[28] level 3	Case series	Varied	26	17 Le Veen 9 Dencer	23	8	3	–	0/6	0	2	–	–
Gough (1984),[27] level 3	Case series	Varied	17	13 Le Veen 4 Denver	13	4	3	–	2	0	2	–	1–104 weeks, mean 24 weeks
Timon (1987),[68] level 3	Case series	Varied	7	1 Le Veen 6 Denver	6	2	–	1	2	0	0	–	5–14 weeks, mean 9 weeks
Millard (1988),[69] level 3	Case series	Varied	11	Denver	10	1	0	0	–	0	0	–	Mean 11 weeks
Li (1988)[70,] level 3	Case series		7	Denver	6	0	0	0	–	0	0	0	Mean 10 weeks
Smith (1989),[71] level 3	Case series	Varied	50	12 Le Veen 38 Denver	–	6 Le Veen 10 Denver	6	–	–	3	2	–	Mean 10 weeks for Le Veen
Edney (1989),[72] level 3	Case series	Varied	45	29 Le Veen 26 Denver	34	7	6	–	“Virtually all patients”	1	0	–	–
Gough (1993),[59] level 2–	Not randomized open controlled trial	Varied	42	16 Le Veen, 26 Denver	27	–	–	–	32/32	0	–	–	–
Schumacher (1994),[73] level 3	Case series	Varied	89	Not specified	57	26	12	1	“Nearly every patient”	2?	6	–	Mean 12 weeks
Faught (1995),[74] level 3	Case series	Varied, 21 with ovary	25	Le Veen or Denver	22	4	–	1	5	1	0	–	–
Wickremesekera (1997),[29] level 3	Case series	Varied	19	Denver	16	2	4	–	10	1	0	–	–

Tueche (2000),[75] level 3	Case series	Varied	22	7 Le Veen 15 Denver	22	5	–	–	–	2	2	–	4–382 days, mean 9 weeks
Bielgk (2001),[76] level 3	Case series	Varied	51	11 Le Veen 39 Denver 1 unknown	–	4	1	–	–	3	8	–	–
Zanon (2002),[77] level 3	Case series	Varied	42	Denver	37	3	2	–	–	0	1	–	–
Clara (2004),[78] level 3	Case series	Varied	53	Denver	–	7	1	4	–	0	–	–	10–84 days, mean 35 days
Mean			Total 634	Le Veen 340/520 Denver 298/520	357/458 77.95%	101/530 19.06%	50/523 9.56%	13/270 4.81%	207/295 70.17%	16/592 2.70%	31/531 5.84%	1/31 3.23%	Mean 10 weeks

DIC, disseminated intravascular coagulation

liver disease there are several studies about this topic,[2] but in the context of malignant ascites there is only limited evidence available. Fischer reported about 300 cases of abdominal paracentesis for malignant ascites where 5% dextrose was infused intravenously simultaneously and no episodes of severe hypotension were recorded.[13] Studies in patients with benign ascites showed that in paracentesis of large volume albumin is superior to other plasma expanders in preventing circulatory dysfunction.[14] But randomized studies showed no significant difference in survival between patients treated with albumin and those treated with other plasma expanders.[14] In patients with malignant ascites no trials of concurrent albumin infusions have been performed.

Studies in the context of liver disease showed that up to 5 L can be removed quickly without risk of significantly affecting plasma volume or renal function.[15–17] Stephenson and colleagues retrospectively analysed 30 paracenteses in 12 patients with malignant ascites after implementing a guideline allowing up to 5 L fluid to drain without clamping and giving intravenous fluids only when specifically indicated. In the analysed 30 paracenteses, intravenous fluids or blood products were given only in 6 procedures and there was no case of symptomatic hypotension.[18] McNamara did a prospective study in the context of malignant ascites observing 48 paracenteses in 44 patients in order to evaluate how much fluid needs to be drained for symptom relief. The results suggest that a significant improvement of the symptoms of abdominal pressure occurs with the removal of few litres (range 0.8–15 L, mean 5.3 L, median 4.9 L). Severe adverse effects were not reported and apparently patients did not get intravenous fluids, plasma expanders or blood products, but this was not explicitly specified.[19] There are no randomized trials comparing paracentesis with the use of diuretics in the management of malignant ascites.

3.2. *Symptomatic management by diuretics*

Diuretic use in managing malignant ascites is inconsistent among physicians. A survey by Lee and colleagues showed that diuretics were used by 61% of physicians treating malignant ascites (27/44) but by only 45% (20/44) felt to be effective.[8] There are no randomized controlled trials assessing the efficacy of diuretic therapy in malignant ascites.

Neither efficacy nor effectiveness of diuretics in malignant ascites is sufficiently studied and therefore the evidence for the use of diuretics in malignant ascites is weak. Overall, in patients with different tumours, diuretics seem to be successful in approximately 43% of cases reported in the literature (Table 3). Phase II data suggest that the efficacy of diuretics in malignant ascites depends on plasma renin/aldosterone concentration.[20] In a study from Greenway and colleagues[21] 13 of 15 patients responded to spironolactone (doses varying from 150 to 450 mg) and plasma renin activity was raised in all of 5 patients in whom it was measured. In the prospective study by Pockros and colleagues[20] a response to diuretics was seen in patients with ascites due to massive hepatic metastases who had a serum-ascites albumin gradient >1.1 g/dl (congruent to the serum-ascites albumin gradient of patients with benign ascites due to liver cirrhosis), whereas patients with ascites caused by peritoneal carcinomatosis or chylous malignant ascites who

had no portal hypertension and a serum-ascites albumin gradient <1.1 g/dl did not respond to diuretics. These data suggest that serum-ascites albumin gradient may provide a useful guide to predict response to diuretics. Up to now, there is no approved reliable method for predicting those patients with malignant ascites who will respond to diuretics. The renin–angiotensin–aldosterone system can be involved because of a reduction of the circulating blood volume due to decreased removal of fluid as a consequence of obstructed lymphatics. But this is not the case in all tumour patients.[20] This could explain why the data about diuretics in the context of malignant ascites are controversial and why there is no consensus about their effectiveness.[8] Further work is needed to identify clearly which patients will benefit from diuretic therapy.

3.3. *Symptomatic management by peritoneovenous shunts*

Initially the peritoneovenous shunt was developed for use in patients with intractable ascites as a result of cirrhosis of the liver,[7] but it subsequently became a popular procedure in managing malignant ascites.[8] There are two main types of shunt systems, the Le Veen shunt[22] and the Denver shunt.[23] The Le Veen shunt drains ascitic fluid into the superior vena cava by a one-way valve opening at a pressure of 3 cm H_2O. The Denver shunt works by the same principle. Here the valves open at a positive pressure gradient of about 1 cm H_2O and prevent detectable reflux. There have been no prospective randomized studies comparing the patency rates of the two systems in malignant ascites. One randomized trial has been performed in patients with cirrhotic ascites comparing 12 patients randomized to receive Le Veen shunt and 10 to receive Denver shunt. Data showed a superior patency of the Le Veen shunt.[24] Souter and colleagues evaluated 43 patients with malignant ascites, 16 receiving a Denver Shunt, 27 receiving a Le Veen shunt. They observed that shunt occlusion was more common with the Denver Shunt but the two groups of patients were not selected at random and therefore may not be comparable.[25] The objective of using shunts is to achieve symptom relief and prevent the need for distressing paracentesis and the resulting protein and fluid depletion. Hemorrhagic ascites and ascitic fluid protein content greater than 4.5 g/l are considered as contraindications for shunting because of the higher risk of shunt occlusion.[7,4] Loculated ascites, portal hypertension, coagulation disorders and advanced cardiac or renal failure are also contraindications.[7] Although the shunt drains fluid with malignant cells from the peritoneal space to venous system, clinical observations and findings at necropsy indicate that peritoneovenous shunting does not result in the establishment of clinically important haematogenous metastases.[7,26] However, as postmortem examinations are not performed routinely, this complication may be under-reported.[4] Reported median survival of patients with malignant ascites varies between 52 and 266 days, reflecting patient selection.[7] In all reported studies, patients with ovarian and breast cancer who undergo peritoneovenous shunting have the best response rate ($\geqslant$50%) whereas the response rate in patients with gastrointestinal cancers is far worse (10–15%).[7] Because of poor prognosis, it is agreed by most authors that shunt insertion is contraindicated in patients with malignant ascites due to gastrointestinal cancer.[7,12] An insertion of a shunt is associated with potentially fatal side-effects and costs in terms of time and money, considering that patients need to be monitored closely for at least 24 h after operation with a central venous pressure line to monitor fluid balance. Therefore a shunt should only be used when other treatment options like diuretics have failed and when the life expectancy of the patient is long enough to derive benefit. About the time span there is no consensus, some authors advocate more than one month[7,27] other authors suggest an expected survival of more than 3 months.[12,28,29] The use of shunts has to be balanced by the potential risks of this procedure (Table 4).

4. Discussion

Although abdominal paracentesis, diuretics and peritoneovenous shunting are commonly used procedures in management of malignant ascites, the evidence for these treatment options is weak. There are no randomized controlled trials evaluating efficacy and safety of these procedures in malignant ascites. Practice of managing malignant ascites seems to be influenced by the evidence obtained in the context of non-malignant ascites due to liver disease, because approximately 80% of all cases of ascites are caused by chronic liver disease.[2] Available data show good, although temporary effect of abdominal paracentesis on symptom relief in patients with malignant ascites. There is no consensus on fluid withdrawal speed and concurrent intravenous hydration is not sufficiently studied. Data show that peritoneovenous shunts can control malignant ascites, but have to be balanced by the potential risks of this procedure. The available data about the use of diuretics in malignant ascites are controversial. Therefore the use of diuretics should be considered in all patients, but has to be evaluated individually. A recommendation for further research is a randomized controlled trial comparing the use of diuretics with paracentesis in the management of malignant ascites.

There are also novel approaches in management of malignant ascites. But all these treatment options must be considered as highly experimental, partially investigated in Phase I trials or applied in a limited number of cases.

Some improvement in ascites has been noted in response to immunotherapy with intraperitoneal α or β interferon,[30] tumour necrosis factor TNF[31] or with administration of infectious agents in non-pathogenic form like *corynebacterium parvum*[32] or OK-432, a penicillin- and heat-treated powder of Su-strain *streptococcus pyogenes* A3,in the peritoneal cavity.[33,34] Monoclonal antibody therapy has also been used in treating malignant ascites with some success,[35,36] also intraperitoneal radioisotopes like 198Au[37]or 32CrP.[38] Octreotide, a somatostatin analogue known to decrease the secretion of fluid by the intestinal mucosa and to increase water and electrolyte reabsorption[39] was used successfully in reducing ascites in two of three treated patients with malignant ascites.[40] In tumours associated with increased activity of vascular endothelial growth factor (VEGF) a new concept is to reduce the production of ascites by inhibition of neovascularization of the tumour via inhibition of VEGF[41–43] or inhibition of matrix metalloproteinases.[44–47] Matrix

metalloproteinases are a family of structurally related enzymes present within the normal healthy individual but overexpressed in a variety of cancers.[43,45,46] These enzymes have been shown to facilitate tumour invasion and metastasis by breakdown of the extracellular matrix, and this process is reversed by metalloproteinase inhibitors.[48,49] Metalloproteinase inhibitors are cytostatic but not cytotoxic, so in clinical practice they are used in conjunction with chemotherapeutic agents. Interest in matrix metalloproteinase inhibitors for the treatment of malignant ascites resulted from animal studies showing that intraperitoneal administration of the matrix metalloproteinase inhibitor batimastat resulted in reduced tumour growth, metastatic spread and resolution of ascites.[50–54] Therefore batimastat was investigated in clinical trials on patients with malignant ascites.[44,55,56] Results are inconclusive. Batimastat was evaluated during a phase I/II trial in nine patients with malignant ascites from various primary tumours, receiving a single dose (600–1050 mg/m^2) of batimastat intraperitoneally. A positive response, defined as a reduction in weight and abdominal girth or reduction in frequency of paracentesis was observed in five patients.[56] In a further phase I study of intraperitoneal batimastat, 16/23 patients with malignant ascites did not require drainage within 28 days of initial treatment.[44] There is improved bioavailability reported for marimastat, a second generation matrix metalloproteinase inhibitor. But to date, no studies have addressed the issue of managing malignant ascites by marimastat. Overall, the novel approaches in management of malignant ascites must be considered as highly experimental, partially investigated in Phase I trials or applied only in a limited number of cases.

The evidence on the use of paracentesis, diuretics and peritoneovenous shunting as most commonly used procedures in the management of malignant ascites is weak. Literature is slim and study quality is poor. Further studies are needed, e.g., a randomised controlled trial comparing the use of diuretics with paracentesis. Studies on malignant ascites have to face a couple of difficulties. Malignant ascites occur in association with a variety of neoplasms and therefore, studies will often have to include heterogenous groups of patients. Some patients may possibly be still receiving systemic chemotherapy, which is a potentially confounding variable. Outcome measurement and comparison of different approaches in managing malignant ascites is also difficult, because there is currently no standard definition of response (complete and partial) recognised in the literature[4] and only consensus would allow true comparison of different approaches. Reduction in weight or abdominal girth are dubiously outcome parameters because underlying cancer often also induces loss in weight. Therefore reduced number of paracentesis required is often used clinically to assess response. This can be combined with subjective parameters like feeling of abdominal pressure as secondary outcome measure. Although this is difficult to obtain in patients with malignant ascites, intervention and control group should be as homogenous as possible and outcome measures should be valid and reliable. A potential option is crossover trials, where the random difference between subjects can be eliminated by using a design in which treatment comparisons are largely or entirely within the same patient. Because of this reduction in variance, and because each patient is used several times, crossover studies usually have greater statistical power for a given sample size than parallel group designs. But this design should only be used in patients who are in a comparatively stable condition, because changes in patients' condition over time may introduce great variability into patients' responses and thereby undermine the major potential advantage of crossover design.

5. Guideline on the management of symptomatic malignant ascites in advanced cancer

1. Paracentesis is indicated for those patients who have symptoms of increasing intraabdominal pressure. Available data show good, although temporary relief of symptoms in most patients. Symptoms like discomfort, dyspnoea, nausea and vomiting seem to be significantly relieved by drainage of up to 5 L of fluid. (Grade of Recommendation: D)
2. When removing up to 5 L of fluid, intravenous fluids seem to be not routinely required. (Grade of Recommendation: D)
3. If patient is hypotensive or dehydrated or known to have severe renal impairment and paracentesis is still indicated, intravenous hydration should be considered. Infusion therapy is not sufficiently studied. The only investigated therapy in malignant ascites is infusion of dextrose 5%. There is no evidence of concurrent albumin infusions in patients with malignant ascites. (Grade of Recommendation: D)
4. To avoid repeated paracenteses a peritoneovenous shunting may be considered. Major complications (pulmonary oedema, pulmonary emboli, clinically relevant disseminated intravascular coagulation, and infection) have to be expected in about 6% of patients. (Grade of Recommendation: D)
5. There are no randomized controlled trials assessing the efficacy of diuretic therapy in malignant ascites. The available data are controversial and there are no clear predictors to identify which patients would benefit from diuretics. The use of diuretics therefore should be considered in all patients, but has to be evaluated individually. Patients with malignant ascites due to massive hepatic metastasis seem to respond more likely to diuretics than patients with malignant ascites caused by peritoneal carcinomatosis or chylous ascites. (Grade of Recommendation: D)
6. Choice of diuretics is not evaluated. As available data suggest that the efficacy of diuretics in malignant ascites depends on plasma renin/aldosterone concentration, aldosterone antagonists like spironolactone should be used, either alone or in combination with a loop diuretic. (Grade of Recommendation: D)
7. Dose regimens of diuretics are not evaluated in patients with malignant ascites. There is no evidence to diverge from standard clinical practice. Therefore dosage should be performed according to manufacturer's instructions and package inserts. (Grade of Recommendation: D)

Conflict of interest statement

None declared.

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