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Cachexia-anorexia syndrome in patients with peritoneal metastasis: an observational study

Abstract

Background: Little is known about the nutritional status of patients with peritoneal metastasis (PM), in particular about the evolution of the so-called anorexia-cachexia syndrome in these patients. The objective of the study was to assess nutritional status in PM patients at the end of life, including metabolic aspects.

Methods: Observational study. Prospective nutritional status assessment in 87 PM patients, including Subjective Global Assessment: (SGA), physical examination (body mass index [BMI], bioelectrical impedance analysis [BIA], anthropometry and blood chemistry).

Results: 85 % patients had received previous chemotherapy. Peritoneal carcinomatosis index was 16 ± 11, Karnofsky 81 ± 14 % and ascites volume $1,000 \pm 1,690$ ml. SGA was reduced with 22.0 ± 9.6 points, BMI normal with 25.3 ± 5.8 kg/m^2 and resting metabolism was $1,527 \pm 248$ kcal/day. Serum total protein and albumin were at the inferior normal limit (6.5 ± 0.8 g/dl, respectively 3.7 ± 0.8 g/dl) and C-reactive protein (CRP) was elevated (2.9 ± 4.1 g/dl). Serum levels of protein (p = 0.05), albumin (p = 0.003) and transferrin (p = 0.001) were higher in gastrointestinal than in ovarian PM patients. When patients were grouped according to time from first assessment to death, serum protein and albumin decreased until end of life, whereas ascites volume, resting metabolism and CRP increased.

Conclusion: Both increased resting metabolism and decreased caloric intake contribute to the development of the cachexia-anorexia syndrome in PM patients. End of life is caused by energetic dysbalance and exhaustion.

Keywords: anorexia, cachexia, cancer, nutrition, peritoneal metastasis.

Introduction

Cachexia is a complex metabolic syndrome associated with underlying chronic illness. It is a multifactorial process resulting in progressive weight loss and skeletal muscle atrophy – with or without loss of fat mass. In the case of cancer, cachexia results from adaptation to the disease, creating an environment characterized by inflammation, loss of appetite (anorexia), low levels of anabolic hormones and anemia [1]. Anorexia and decreased food intake result into an energy deficit. In addition, inflammation increases energy demands, cells become insulin resistant, and low levels of anabolic hormones result in muscle wasting (reviewed in [2]). Cachexia and anorexia are forming together the so-called "cachexia-anorexia syndrome". In cancer, the cachexia-anorexia syndrome is associated with poor quality of life, poor physical function, and poor prognosis [3].

Peritoneal metastasis (PM) is a relatively common spreading pattern of malignant tumors originating in the gastrointestinal tract [4], the ovary [5] and other origins [6]. Very few data on the nutritional state of peritoneal metastasis patients have been published. To our knowledge, there are no specific data available on the evolution of nutritional status of patients with advanced peritoneal metastasis at the end of life.

The aim of this study is to assess the nutritional state of patients with advanced peritoneal metastasis and to determine its evolution until end of life.

Patients and methods

Study design

This is a non-interventional study observing the nutritional status on the basis of clinical and laboratory data collected routinely in peritoneal metastasis patients at our institution.

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Patients

Between 4/2014 and 05/2015, 111 patients with advanced peritoneal metastasis were referred to our institution (setting: specialized therapy centre for peritoneal cancer, University hospital, tertiary care center). Before admission, each patient history was discussed in the interdisciplinary tumor board and best therapy was recommended on a case-by-case, individual basis. There were no specific inclusion or exclusion criteria.

Regulatory framework

Nutritional status is recorded routinely in all peritoneal metastasis patients at our institution in order to screen malnutrition and to offer nutritional support and/or drug therapy in these patients. Data are entered into a prospective registry authorized by the Ethics Committee of Ruhr-University Bochum, Germany (Nr. 15–5280). All patients gave their written informed consent for data collection. Beside clinical standard of practice, no additional tests were performed for the present study. Therapy, data collection, and data analysis were performed according to the Declaration of Helsinki (1983), in particular patients were free to refuse collection and/or storage of nutritional data.

Data collection

The day of admission, following data were collected:
- Subjective Global Assessment Score Sheet (SGA) as described elsewhere [7] including medical history (weight and diet changes) and gastrointestinal symptoms.
- Physical examination including body weight and estimation of body composition by bioelectrical impedance analysis (BIA) according to the instructions of the manufacturer.
- Skinfold measurement using Slim Skinfold Caliper Measure Body Fat Tester (0 to 80 mm, eaglefit GmbH, Ulm-Langenau, Germany) measuring skinfolds to determinate the amount of subcutaneous fat. Then, body density and body fat percentage were predicted according to the instructions of the manufacturer [8].
- Blood chemistry including C-reactive protein (CRP), total protein, albumin and transferrin. Normal range was CRP: <0.5 mg/dl, total protein: 6.6–8.7 g/dl, serum albumin: 3.5–5.2 g/dl and transferrin 200–360 mg/dl.

All these methods are non-invasive and are not inducing any extra physical or psychical stress for the patients. Determination of nutritional status was performed by two specialized, registered study nurses.

Statistical analysis

This is an observational, explorative study intended to generate pilot data for later therapeutic studies. No sample size was calculated beforehand. Usual descriptive statistics are provided, including means and standard deviations. A non-parametric test (Mann-Withney U-test) was used to compare means between ovarian and gastrointestinal cancer patients. A $p < 0.05$ was considered significant. Body fat data were derived from skinfold measurement using a dedicated Microsoft-Excel based calculation tool [9]. We used the software SPSS for Windows (SPSS 20.0, SPSS Inc., Chicago, IL, USA) for statistical analysis and graphical design.

Results

Within the period of time under investigation, 111 consecutive patients with peritoneal metastasis were admitted to our hospital. All of these patients were invited to fill out the SGA questionnaire and to undergo physical examination but 24 refused to do so or gave incomplete information, so that 87 datasets remained for further analysis. A complete set of nutritional data, including anamnestic scores (SGA), physical examination (BMI, bioelectrical impedance analysis, anthropometry) and blood chemistry, could be obtained in these patients.

Patients characteristics are summarized in Table 1. The vast majority of patients (85 %) were in the salvage

Table 1: Patient characteristics.

Patients characteristics	All patients (n = 87)	%
	n	
Number of patients	87	
Gender		
Male	30	34.5
Female	57	65.5
Age, years		
Median (min-max)	63 (26–83)	
Peritoneal Carcinomatosis Index		
(mean ± SD)	16 (± 11)	
Karnofksy Index		
(mean ± SD)	81 (± 14)	
Primary tumor		
Ovarian	29	33.3
Gastric	15	17.2
Colorectal	14	16.1
CUP (of unknown origin)	10	11.5
Appendiceal	4	4.6
Gallbladder	4	4.6
Small intestine	2	2.3
Breast	3	3.5
Mesothelioma	1	1.1
Pancreas	2	2.3
Others (neuroendocrine, sarcoma, oesophagus)	3	3.5
Previous chemotherapy	74	85.1

situation: they had already received at least one line of systemic palliative chemotherapy and the mean time from cancer diagnosis was 36 ($\pm$ 35) months. General condition was moderately impaired with a mean Karnofsky Index of 81 $\pm$ 14 %. Peritoneal metastasis was advanced with a mean Peritoneal Carcinomatosis Index (PCI) of 16 $\pm$ 11.

Table 2 describes the nutritional status of these 87 patients with PM. At admission, moderate malnourishment was documented with a mean Subjective Global Assessment Score (SGA) of 22.5 ($\pm$ 4) (stage B). Physical examination showed a normal Body Mass Index (BMI), a normal skeletal muscle percentage, a normal visceral fat level and a normal fat percentage according to the bioelectrical impedance analysis (BIA). Skinfold measurement confirmed a normal skeletal muscle percentage and a normal body fat percentage. Laboratory values showed a 6-fold increase of C-Reactive Protein with 2.8 ($\pm$ 4) g/dl as a sign of major and chronic systemic inflammation as a reaction to peritoneal tumor involvement. Total serum protein (6.4 $\pm$ 0.9 g/dl), serum albumin (3.6 $\pm$ 0.8 g/dl) and transferrin (230 $\pm$ 68 mg/dl) levels were at the lower normal limit.

To determine the natural evolution of nutritional status in PM patients, we stratified the patients according to the time period between first admission and the end of life. C-reactive protein level further deteriorated until death as a sign of massive inflammatory systemic response to peritoneal involvement (Figure 1). As a rule, most nutritional parameters deteriorated until death, as exemplified by albumin and total protein serum levels (Figure 2). Resting metabolism increased in the last months of life (Figure 3), which is explained both by tumor growth and systemic inflammatory response. Ascites volume increased until end of life, contributing to protein loss, hypoproteinemia and skeletal muscle consumption. (Supplementary Material 1). The available protein pool was significantly less in ovarian than in gastrointestinal PM patients (total protein ($p = 0.05$), albumin ($p = 0.003$), as shown in Supplementary Material 2.
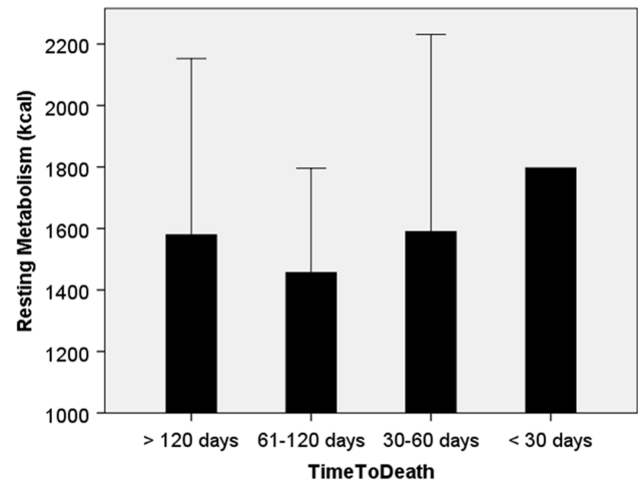
Table 2: Natural evolution of nutritional status in PM patients. Patients are stratified according to the time period between first admission and the end of life.

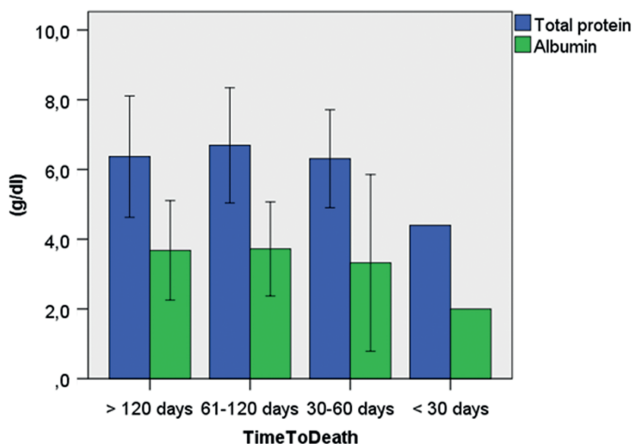| Time to death	>120 Days	61–120 Days	< 60 Days	Normal range
	(n=51)	(n=25)	(n=11)	
Subjective Global Assessment Score Points (SGA) (median±SD)	22.7±3.6	21.2±4.3	22.8±3.2	>24
Ascites (ml; mean±SD)	754±1607	915±1571	1533±1763	0
PCI (min 0; max 39)	11.1±9.2	19.1±9.4	22.8±12.1	0
Karfofsky Index (min 0 %, max 100 %)	83±15.7	80.9±10.2	78.9±11,7	100%
Body mass index, kg/m^2	26.4±7.2	24.3±3.3	25.7±6.9	M: >20 F: >19
Bioelectrical impedance analysis (BIA)				
Resting metabolism, kcal	1566±281	1466±176	1586±340	#
Body fat percentage, %	M: 22.8±8.8	M: 21.4±6.0	M: 23.2±10.7	#
	F: 30.9±11.7	F: 30.9±7.6	F: 31.5± 6.9	#
Skeletal muscle percentage, %	M: 34.6±3.8	M: 34.5±2.8	M: 34.1±5.7	#
	F: 29.1±5.0	F: 29.0±3.6	F: 26.2±6.2	#
Visceral fat level	9.2±5.6	7.9±3.5	9.2±8.3	9-Jan
Skinfold measurement				
Body fat weight, kg	23.9±11.1	20.3±5.6	23.7±11.8	#
Fat free mass, kg	M: 62.4±9.6	M: 59.2±5.9	M: 64.5±14.1	#
	F: 45.9±9.8.	F: 42.4±3.8.	F: 47.4±8.8	#
Body fat percentage, %	M: 26.2±7.0	M: 24.4±5.1	M: 30.3±5.7	#
	F: 32.7±8.7.	F: 32.5±5.2	F: 28.3±7.1	#
Blood chemistry				
CRP, mg/dL	2.6±3.3	2.6±3.2	4.1±6.2	< 0.5
Total protein, g/dL	6.4±0.9	6.6±0.8	6.2±0.7	6.6-8.7
Albumin, g/dL	3,7±0.7	3.6±0.7	3.2±1.3	3.5-5-2
Transferrin, mg/dl	231.3±59.2	237.9±75.3	205±74.5	200-360

normal values are depending on the age and on the sex of patients. M, male; F, female.
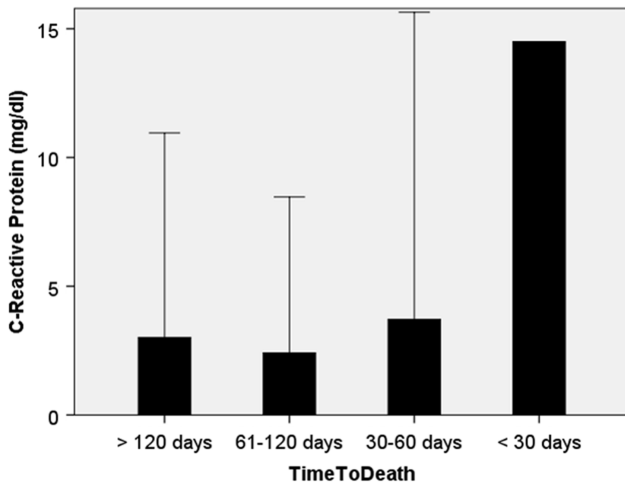
Figure 1: C-reactive protein (CRP) serum levels in 87 peritoneal metastasis patients, grouped according to their survival time. Source: CRP was already elevated (by a factor 6-fold) at first admission and further increased during the last 4 months of life. Cachexia results from adaptation to the disease, creating an environment characterized in particular by inflammation.

Figure 2: Total serum protein and serum albumin in 87 peritoneal metastasis patients, grouped according to their survival time. Source: Both parameters deteriorated until end of life, as a manifestation of natural history of disease.

Discussion

Prior work has documented that patients with advanced cancer are generally affected by the so-called cachexia-anorexia syndrome [10]. However, to our knowledge, there is no clinical data describing quantitatively the nutritional status of patients with peritoneal metastasis. The aim of this study was to assess the nutritional status of patients with PM with simple but effective methods by combining anamnestic scores, physical examination and

Figure 3: Resting metabolism increased over the last 4 months of life in peritoneal metastasis patients (n = 87).

laboratory tests. This assessment included the Subjective Global Assessment Score Sheet (SGA), physical examination including body weight, estimation of body composition by body impendance analysis (BIA), anthropometry (SM) and blood chemistry.

Nutritional screening at admission

The majority of patients with peritoneal metastasis were moderately or severely malnourished at time of first admission (56 % patients with SGA-Index B or C). This finding underscores the crucial role of nutritional assessment in PM patients. A first nutritional screening is indicated at an early point of time, for example just after diagnosis of PM. This first assessment (for example the SGA score) is simple and can be performed by any physician or specialized nurse.

Evolution of nutritional status

When peritoneal metastasis patients were grouped according to the time period between hospital admission and death, we found a progressive deterioration in most subjective, physical and laboratory parameters of nutrition. CRP was already elevated (by a factor 6-fold) at first admission and further increased during the last 4 months of life. Cachexia results from adaptation to the disease, creating an environment characterized in particular by inflammation. This finding is in accordance with previous work showing that, in patients with advanced cancer, the anorexia-cachexia syndrome deteriorates progressively until death [2].

The negative evolution of the nutritional status appears to be significant and rapid in PM patients. Patients reported about a slow but continuous deterioration of the SGA score, confirming quality of life results obtained in a previous study [11]. When gastrointestinal symptoms were determined using the QLQ30 questionnaire of EORTC in PM patients, appetite loss, but also nausea/vomiting, diarrhea and obstipation deteriorated at the end of life. Physical examination and laboratory tests are coherent with the subjective data.

On the basis of the above data, we suggest to repeat nutritional assessment at regular intervals in PM patients, investigating in particular gastrointestinal symptoms and performance status. All patients with SGA score C and probably most patients with SGA score B should be referred to a specialist to determine a nutrition support plan with the hope of delaying and slowing down the development of the cachexia-anorexia syndrome – and prolong life.

Weight loss is a powerful independent variable that predicts mortality in patients with cancer [12]. It is very likely that, in peritoneal metastasis as well as in other cancers, tumor growth increases energy consumption. Cancer cells are programmed to rely on aerobic glycolysis to support their proliferation and anabolic growth [13]. Increased tumor metabolism is harming healthy organs by stealing their energy resources. This process results into modified body metabolism with loss of muscle mass and possibly of fatty tissue [14]. Moreover, peritoneal tumor spreading causes progressive intestinal dysfunction by infiltration of the bowel wall. Patients report about ill-defined abdominal pain, nausea and anorexia which in turn impair an adequate oral nutritional intake [15]. Vomiting is observed when malignant bowel obstruction develops and finally patients have to receive parenteral nutrition [16].

Finally, drug-related side effects: (e. g. caused by chemotherapy, morphine derivatives, antibiotics, etc.) can cause anorexia or interfere with the ingestion of food [17]. Systemic chemotherapy can induce severe gastrointestinal symptoms in a significant proportion of patients. Chemotherapy acts on all rapidly dividing cells including tumor cells but also normal cells lining the gastrointestinal tract, susceptible to damage and growth inhibition. This can result in patients experiencing clusters of gastrointestinal symptoms such as lack of appetite, nausea, vomiting, diarrhea, etc. [18].

It is most likely that in peritoneal metastasis patients, all these three pathways together contribute to the development of the cachexia-anorexia syndrome and finally to death, as represented in Figure 4. Both increased resting metabolism and decreased caloric intake contribute to the development of the cachexia-anorexia syndrome, which is ultimately incompatible with life. Patients with PM die from energetic dysbalance and exhaustion. Therapeutic approaches should tackle systematically each of these pathways.

As the multimodal therapy of PM is increasingly effective, the diagnosis and treatment of cachexia are becoming important goals to improve both life expectancy and quality of life. Providing and ensuring adequate caloric intake to PM patients is indeed necessary
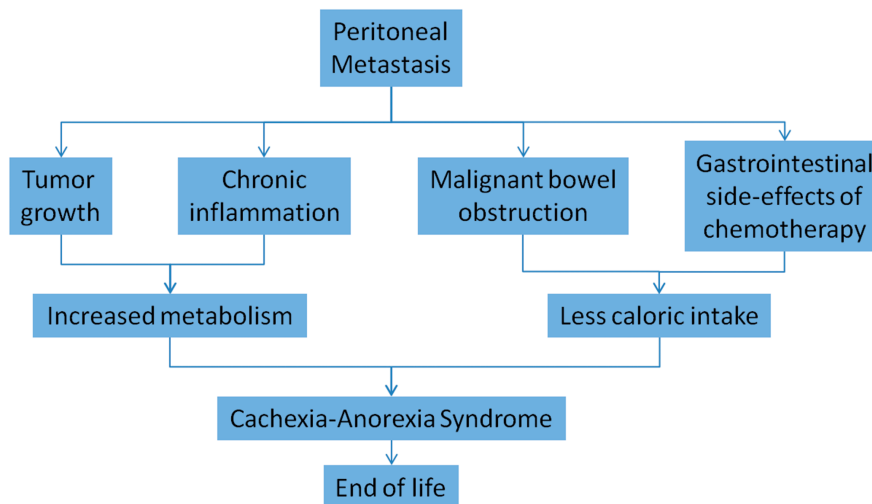
Figure 4: Pathways leading to development of cachexia-anorexia syndrome in peritoneal metastasis patients.
Source: Both increased resting metabolism and decreased caloric intake contribute to the development of the cachexia-anorexia syndrome, which is ultimately incompatible with life.

to maintain body weight. Unfortunately, adequate nutritional supply is not sufficient, since weight stabilization does not prevent the continuing loss of skeletal muscle mass in PM patients, and does not correct the underlying metabolic abnormalities. Potential pharmacological strategies targeting skeletal muscle wasting might be associated with nutritional support and include for example androgens, selective androgen receptor modulators, anti-myostatin drugs, growth hormone and insulin-like growth factor (reviewed in [1]). However data demonstrating effectiveness of these agents is lacking. At the present time, anti-inflammatory trials in cachectic cancer patients have not been successful [19].

To our knowledge, there is no published recommendation for treating the cachexia-anorexia syndrome in PM patients. Since we cannot refer to previous work, we propose to address the problem by tackling systematically the increased tumor metabolism, the progressive intestinal dysfunction and the adverse effects of systemic chemotherapy. Tumor metabolic demands might be best reduced by effective cancer therapy, which has been made possible in some cases by new therapeutic options in PM that appeared in the recent years. These options include potentially curative approaches such as the combination of CytoReductive Surgery (CRS) and Hyperthermic IntraPEritoneal Chemotherapy (HIPEC), and palliative approaches such as personalized palliative systemic chemotherapy [19] or various forms of intraperitoneal chemotherapy [20, 21]. Gastrointestinal side-effects of systemic chemotherapy might be prevented, at least in part, by suspending this therapy early enough in the course of disease and before the development of painful and disabling symptoms. Another alternative might be for example intraperitoneal drug delivery using pressurized aerosols (PIPAC) using low dose chemotherapy since this form of drug delivery has been reported to be effective without causing severe additional gastrointestinal symptoms in the vast majority of patients [11, 22]. There are reasons to be optimistic about the possibility that in the future, cachexia may be treated effectively. A number of drugs have already been developed that target key underlying mechanisms, namely, reduced food intake and altered metabolism and regulation of muscle mass [23]. These potential therapeutic avenues have now to be evaluated in adequate studies in PM from the nutritional perspective.

In summary, this pilot study is providing for the first time baseline and evolution nutritional data in patients with PM and underlines the need for diagnosis and treating the anorexia-cachexia syndrome in these patients. Obviously, the cachexia-anorexia syndrome is deteriorating until end of life in PM patients, with the development of a severe inflammatory syndrome and an increase of resting metabolism. In the next research step, we intend to confirm the value of nutritional status for predicting life expectancy in PM patients in a prospective study. The data presented here will be useful to determine inclusion and exclusion criteria for this study.

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