



Review article

Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: A systematic review



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ABSTRACT

Background/objectives: Cachexia affects ~80% of pancreatic cancer patients. An international consensus defines cachexia as an ongoing loss of skeletal muscle mass (sarcopenia) with or without loss of fat, which impairs body functioning and cannot be reversed by conventional nutritional measures. Weight loss percentage and elevated inflammation markers have been employed to define this condition earlier. This review aimed to assess the prevalence and consequences of cachexia and sarcopenia on survival in patients with pancreatic ductal adenocarcinoma.

Methods: The systematic review was performed by searching the articles with preset terms published in PubMed and Cochrane Database until December 2013. After identifying relevant titles, abstracts were read and eligible articles data retrieved on preformatted sheets. The prevalence and impact of sarcopenia/cachexia on survival was evaluated.

Results: In total 1145 articles were retrieved, only 10 were eligible. Definitions of cachexia and sarcopenia were heterogeneous. In patients with normal weight (BMI 18.5–24.9 kg/m²) the prevalence of sarcopenia ranged from 29.7 to 65%. In overweight or obese patients (BMI >25 kg/m²) were 16.2%–67%. Sarcopenia alone was not demonstrated to be an independent factor of decreased survival, although obese sarcopenic patients were shown to have significantly worse survival in two studies.

Conclusions: Impact of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma is currently understudied in the available literature. Definitive association between cachexia and survival cannot be drawn from available studies, although weight loss and sarcopenic obesity might be considered as poor prognostic factors. Further prospective trials utilizing the consensus definition of cachexia and including other confounding factors are needed to investigate the impact of cachexia and sarcopenia on survival in pancreatic adenocarcinoma.

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Introduction

Cachexia is a multifactorial syndrome with ongoing loss of skeletal muscle mass with or without fat mass [1]. It is a frequent finding in patients with cancer, which causes disability and leads to progressive functional impairment. It also increases patient's morbidity and mortality and is associated with decreased quality of life [2,3].

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Sarcopenia or involuntary loss of skeletal muscle mass and/or strength has recently been acknowledged as the major component of cancer cachexia [4]. Sarcopenia is found to be an independent prognostic factor of reduced survival in various cancers including biliary tract [5,6], lung, colon [7] and adrenocortical carcinoma [8].

Cachexia is highly prevalent in pancreatic adenocarcinoma, and up to 80% of patients with pancreatic cancer suffer from severe cachexia at the time of death [9–11], although most of the authors define cachexia simply as a reduction in the body weight. Pancreatic adenocarcinoma remains associated with a poor overall survival despite continuous advances in therapy, and improvement in overall survival or quality of life could also come from a better management of cachexia/sarcopenia.

However, the impact of cachexia, including weight reduction, and/or sarcopenia on survival in pancreatic cancer patients has been poorly studied. This systematic review aimed to assess the prevalence and consequences of cachexia and sarcopenia on survival in patients with pancreatic ductal adenocarcinoma.

Methods

A systematic review of literature published in PubMed and Cochrane Database till December 2013 was performed. The following search strategy for the MESH and non-MESH heading was used: (pancreatic neoplasm OR pancreatic cancer) AND (sarcopenia OR cachexia OR body mass composition OR denutrition OR tumor wasting OR malnutrition OR weight loss OR emaciation OR muscular atrophy OR body mass index OR lean tissue loss OR fat free mass). The following Pubmed filter was used: Abstract available; Species: Humans; Article type: clinical trials, clinical trials phase III, clinical trials phase IV, comparative studies, controlled clinical trials, journal articles, meta-analysis, multicenter studies, randomized controlled trials, reviews, systematic reviews, validation studies; Age: adults 19+.

After identifying relevant titles, abstracts were read and eligible articles were retrieved. A manual cross-reference search of the bibliography of all publications retrieved was performed, and the «related article» function in PubMed was also used to identify studies that may have been missed in the database search.

Original clinical studies of any level of evidence relevant in English language were included. Unpublished data, abstract or duplicate publications were excluded.

Measured outcomes and data extraction

Data were registered on preformatted sheets. The following information were extracted from each article: authors, year of publication, study type, characteristics of population, sarcopenia or cachexia prevalence, survival, survival in cachexia/sarcopenia group, body composition measurement type, body mass index (BMI), other factors affecting survival.

Prevalence and impact of cachexia and sarcopenia on survival in pancreatic adenocarcinoma patients regardless of stage and received treatment was evaluated.

This article is reported in accordance with the guidelines set out by the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) statement. The search was carried out by 2 authors independently according to the pre-specified protocol, in case of disagreement the third author participated in the discussion.

Results

The search flowchart is presented in Fig. 1. A total of 1145 articles were revealed after electronic search. After a more detailed reading, articles without data about pancreatic adenocarcinoma or

reporting no data about cachexia and survival were excluded. After cross-reference search, 10 articles on cachexia and/or sarcopenia and survival in pancreatic adenocarcinoma patients were included and their data were retrieved according to the specified data for preformatted sheets. One article appeared to be a duplicate publication and was excluded while one other article was added after “related search” in pubmed. Overall these 10 articles include 1685 patients. There were no randomized controlled studies and all included articles were cohort studies. Table 1 shows the characteristics of the included studies.

Prevalence of sarcopenia and cachexia in patients with pancreatic adenocarcinoma

Sarcopenia was defined by means of CT-based skeletal muscle area assessment in all the studies. Sarcopenia was defined as skeletal muscle surface less than 38.9 cm²/m² for females and less than 55.4 cm²/m² for males (Table 1) [12–14]. All underweight stage III and IV patients (BMI ≤18.5 kg/m²) had sarcopenia [13]. In patients with normal weight (BMI 18.5–24.9 kg/m²), prevalence of sarcopenia ranged from 30 to 65% including both resectable and unresectable tumors (Table 1) [12–14]. In obese and/or overweight patients (BMI >25 kg/m²), prevalence of sarcopenia (sarcopenic obesity) ranged from 17% to 67% including mainly patients with stage III/IV pancreatic adenocarcinoma undergoing palliative therapy [13,14].

On the opposite to sarcopenia, definitions and methods used to assess cachexia were non-standardized. Cachexia was mainly defined as weight loss over 10% within 6 months before diagnosis, and its prevalence ranged from 20% to 74% [15,17]. In Bachmann et al. study cachexia defined as weight loss over 10% and was found in 41% of patients, this study included 67% of patients undergoing tumor resection [16]. In Pausch et al. work weight loss >10% within 6 months was present in 74% of patients while BMI below 18.5 kg/m² was found only in 4% of patients. This study included mainly patients undergoing surgery [17]. Fearon et al. used a 3-factor cachexia definition (weight loss >10%, food intake <1500 kcal/d, C-reactive protein >10 mg/L). In their series including patients with stage II to IV tumors, 22% of patients present with all the 3 criteria, although 60% met at least two of the above mentioned criteria [15].

Cachexia and survival

Fearon et al. in patients receiving palliative treatment with a median survival of 130 days, observed that patients who met either all three (22%) or any two criteria (60%) of cachexia *i.e.* significant weight loss, reduced calorific intake (lower 1500 kcal/d) and C-reactive protein (CRP) level higher than 10 in localized disease (stage II–III) group had worse survival (hazard ratio of death 4.9 and 2.4, respectively, with $p < 0.001$). If analyzed individually, low caloric intake and high CRP were also prognostic factors (hazard ratio 2.0 and 3.7, respectively), but not weight loss. In metastatic disease no correlation of those 3 criteria with survival could be found [15].

Bachmann et al. analyzed the results of 227 surgical procedures (150 – resection, 77 – palliative procedure) in patients with pancreatic adenocarcinoma, of whom 41% had weight loss more than 10% in the preceding 6 months. Median survival did not differ between resected patients with and without cachexia (426 vs 483 days, $p = 0.24$). However, when taking into account weight loss even less than 10%, a significant survival difference was found when patients without weight loss were compared to those with weight loss (654 days vs 451 days after resection, $p = 0.001$). In the multivariate analysis, weight loss emerged as an independent prognostic factor for resected patients. On the opposite, in patients

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