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Original article

Impact of presence and degree of pretreatment weight loss in locally-advanced pancreatic cancer patients treated with definitive concurrent chemoradiotherapy

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ABSTRACT

Background: To assess the impact of the presence and degree of pretreatment weight loss (WL) on the survival of locally-advanced pancreas cancer (LAPC) patients treated with concurrent chemoradiotherapy (C-CRT).

Methods: Seventy-three patients who received 50.4 Gy C-CRT were analyzed. All patients underwent laparoscopy (n = 18) or laparotomy (n = 55), and biopsies were obtained for histologic examination of the primary tumor and enlarged/metabolically active regional lymph nodes. Pretreatment WL and percentage WL (PWL) were calculated by utilizing data obtained 6 months prior to and during hospital admission. The primary objective was to assess the influence WL status on overall survival (OS), and the secondary objective was the identification of a PWL cut-off value, if available.

Results: Forty-five (61.6%) patients had WL. Median OS was 14.4 months for the entire study population which was significantly longer in the non-WL than the WL cohort (21.4 vs. 11.3 months; $p < 0.003$). On further analysis a cut-off value of 3.1% was identified for WL. Accordingly, patients with WL < 3.1% had significantly longer OS than those with WL ≥ 3.1% (25.8 vs. 10.1 months; $p < 0.001$). In multivariate analysis, both the WL status ($p < 0.001$) and PWL ($p = 0.002$) retained their independent significance.

Conclusion: Both the presence and degree of WL prior to C-CRT had strong adverse effects on the survival of LAPC patients, even if they presented with a BMI > 20 kg/m^2. Additionally, a WL of ≥3.1% in the last 6 months appeared to be a strong cut-off for the stratification of such patients into distinctive survival groups.

Introduction

Definitive concurrent chemoradiotherapy (C-CRT) or induction chemotherapy followed by C-CRT is the preferred treatment options for patients with locally-advanced pancreatic cancer (LAPC), which accounts for 30–40% of all pancreatic cancers (PC) [1]. However, despite the advances in diagnostic, staging, and treatment methodologies, the prognosis of such patients remains poor, with an estimated median survival of 8–12 months. For LAPC, the conventional prognosticators include gender, age, performance status, presence/absence of pain, pancreatic location of the tumor, tumor size, extension of the primary tumor to neighboring organs/vasculature, tumor grade, lymph node involvement status, serum CA19-9 and CEA levels, weight loss (WL) status before C-CRT, and previous experience of the hospital team [2,3].

Involuntary WL, one of the cardinal signs of anorexia-cachexia syndrome, is present in up to 85% of LAPC patients at the time of diagnosis. The fundamental drivers for involuntary WL in LAPC are complex and are triggered by tumor products and pro-inflammatory cytokines. Regardless of the exact cause, WL does not only lead to decreased personal physical function and increased psychological distress in patients and their care takers, but also leads to increased rates of severe toxicity and reduces the tolerance to any oncologic treatment [4]. Obligatory reductions in chemotherapy and/or RT doses, treatment delays, or total

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abandonment of treatment due to intolerance issues have been shown to lead to reduced tumor control and worse survival outcomes [5,6].

To the best of our knowledge, no study has concentrated specifically on the extent of WL and searched for an objective cut-off value in patients in the era of definitive C-CRT. Moreover, in past studies the research populations were exceedingly heterogeneous in terms of basal weight and body mass index (BMI) measures; namely, both underweight (BMI < 20 kg/m^2), ordinarily weighted (BMI > 20–25 kg/m^2), and overweight (BMI > 25 kg/m^2) individuals were included, which raises problems in interpretation of their outcomes. Therefore, in this retrospective cohort study, we investigated the influence of both the presence and degree of pretreatment WL on survival outcomes of LAPC patients with BMI > 20 kg/m^2 who were treated with definitive CRT, and sought to ascertain a cut-off value for WL that may be utilized as a clinical indicator of survival in conjunction with promptly used traditional factors.

Methods

Patient population

A retrospective database search was performed to identify surgically unresectable LAPC patients that underwent definitive C-CRT between February 2008 and December 2013. In accordance with the AJCC staging system (6th ed.), our institutional definition for technically unresectable PC included patients with celiac axis and/or superior mesenteric artery involvement, namely stage III (T4N0-1M0) disease. In all patients, the disease extent was determined by radiological studies and laparotomy or laparoscopic examination. Standard radiological work-up included contrast-enhanced abdominal tomography (CT), magnetic resonance imaging (MRI), and/or MR-cholangiopancreaticography (MRCP). Additionally, all patients were re-staged via fusion of previous CT images (obtained ≤ 1 week before position-emission tomography/computerized tomography (FDG-PET–CT) scan) with FDG-PET–CT images obtained for radiation therapy planning (RTP). In accordance with the current standard institutional staging procedure for PC, all patients underwent laparoscopic (n = 18) or laparotomic (n = 55) examination and biopsies were obtained for histologic diagnosis of the primary tumor. Biopsies of enlarged/metabolically active regional lymph nodes and isolated single organ metastasis were also obtained if suspected radiologically or if identified during laparotomy/laparoscopy. Patients with a previous history of chemotherapy or abdominal irradiation were considered ineligible. Further eligibility criteria included the following requirements: an age of 18–70 years, a diagnosis of histologically proven adenocarcinoma, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, presence of a measurable or evaluable lesion, no contraindications for FDG-PET-CT imaging, an adequate bone marrow reserve (hemoglobin value of ≥10 g/dL, leukocyte count of ≥4000 cells/μL, and thrombocyte count of ≥100,000 cells/μL), hepatic (aspartate aminotransferase or alanine aminotransferase of <5 times the upper limit) and renal function (serum creatinine < 2 mg/dL), BMI > 20, and available pretreatment weight and height measures just prior to C-CRT and at 6 months prior to referral. The latter information was readily obtained, as it is common at any oncologic examination to question first degree relatives about the relative weight change status of the patient during the last six months. The study design was approved by the Institutional Ethical Committee before any data collection. The study was performed in accordance with the Helsinki Declaration and Rules of Good Clinical Practice.

Treatment planning and chemoradiotherapy

The tumor volumes included the primary tumor and involved LNs and were delineated on the FDG-PET/CT fusion. For each patient, the gross tumor volume (GTV) included the primary tumor (GTV-P) and involved lymph nodes (GTV-N) apparent on contrast-enhanced CT (short axis ≥ 1.0 cm) and/or PET images. Nodes < 1.0 cm were only included in the GTV if they were judged to be metabolically active (SUV_{max} > 2.5) on PET scan. Based on literature [7] depicting nearly 1.5 cm of pancreas movement with respiration and considering the lack of a motion tracking system and image guidance at our department, planning target volume (PTV) was defined by adding 2 cm to GTV in all directions, except for intersecting organs at risk (OAR) restrictions or natural barriers with minimal movement risk (e.g. vertebral bodies), to allow for microscopic extension, organ motion, and set-up errors. Elective nodal irradiation was prohibited in the study. All OAR volumes were contoured from the CT because of the inherent difficulties in edge detection with PET-based contouring.

All patients received 50.4 Gy (1.8 Gy/fx) RT, which was prescribed to encompass the defined PTV with isodose lines between 95% and 107%. Target volume coverage and OAR doses were assessed by utilizing the dose-volume histograms generated for each patient. The maximum dose limits for normal tissues were 45 Gy for spinal cord; 50 Gy for small bowel and stomach; 50 Gy for ≤one-third, 35 Gy for two-thirds, and 30 Gy for three-thirds of the liver; and 20 Gy for at least two-thirds of one functioning kidney. All patients received 1–2 courses of cisplatin (n = 24), continuously infused 5-fluorouracil (n = 24), gemcitabine (n = 11), and cisplatin-based doublet chemotherapy (n = 14) concurrent with radiotherapy. Additionally, 57 patients received 4–6 courses of maintenance gemcitabine or 2–4 courses of adjuvant cisplatin-based doublet chemotherapy following C-CRT.

Weight measures

Body weight and height measures just prior to and 6 months before (baseline) the C-CRT were used to calculate the relative weight change (WC) and body mass index (BMI) changes during this time period. However, WC, which by definition independently reflects the absolute difference during the last 6 months, has the potential to underestimate the value of baseline body mass. For this reason, in addition to absolute change (kg), we also calculated the change in percentage relative to baseline, namely the percentage weight change (PWC). For the purposes of this study, patients with no WL or with any degree of weight gain during the last 6 months were assigned to the no weight loss (NWL) group, while patients with any degree of WL were assigned to the WL group.

Toxicity and response assessments

Toxicity during the course of C-CRT was evaluated by reviewing the treatment charts of all patients, who were examined at weekly intervals, or more frequently if necessary. After completion of the C-CRT, patients were examined bimonthly for the first year, every 3 months for the second year, and at 6 month intervals, or more frequently if needed, thereafter. Both the acute and late toxicity were graded by a radiation oncologist according to the Common Terminology Criteria for Adverse Events scale (version 3.0). The recorded grade reflected the worst grade observed.

Response evaluation and follow-up

Response to treatment was assessed by restaging PET/CT scans 12 weeks after the end of CRT in accordance with the Positron

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