Cardiac atrophy is a distinct component of cachexia in metastatic pancreatic adenocarcinoma with implications for therapy

Author: Miles Cameron
University of Florida

Secondary Authors: Patrick Underwood, MD; Andrew Judge, PhD; Thomas George, MD; Jose Trevino, MD
University of Florida

Background: Pancreatic ductal adenocarcinoma (PDAC) is the deadliest common malignancy. Cancer cachexia, a systemic wasting syndrome consequent of tumor burden, is present in roughly 80% of patients with advanced PDAC and precipitates death. Cachexia worsens tolerance to chemotherapy and directly precipitates death. Though skeletal muscle loss is most commonly studied, cardiac changes also occur. We aimed to assess pre-treatment left ventricular (LV) mass in newly diagnosed patients. We hypothesize that LV atrophy is a distinct and central element of cachexia in metastatic PDAC with profound therapeutic implications.

Methods: We included patients with biopsy-proven metastatic PDAC enrolled on a clinical trial of 5-fluorouracil (5-FU), oxaliplatin, and dasatinib (FOLFOX-D; NCT01652976). Body composition analysis was performed from pre-treatment computed tomography (CT). Non-cancer control patients were matched by sex, age, and cardiovascular disease history. Cardiac measurements were obtained from axial plane CT slices at end diastole. LV mass was estimated by the Deveroux-Reichek equation. Quartiles were established based on LV mass. Lumbar skeletal muscle indices (SMI) were measured using sliceOmatic software version 5.0 (Tomovision).

Results: Mean PDAC age was 65.3 (10.4) years. Males and females with PDAC had significantly lower LV mass than controls (M: 31.8 g/m2 g vs. 47.5 g/m2 g, $p < 0.0001$; F: 28.4 g/m2 vs. 46.0 g/m2, $p < 0.005$). LV mass correlated significantly with SMI ($R = 0.6394$, $p < 0.0001$), and myopenic patients (55%) had significantly lower LV mass ($p < 0.001$). ACE inhibitor use attenuated atrophy in PDAC patients (36.9 g/m2 vs. 29.0 g/m2, $p < 0.05$). Quartile 3 (Q3) of LV mass had the highest hemoglobin level (Q1: 12.7 g/dL; Q2: 11.9 g/dL; Q3: 13.6 g/dL; Q4: 12.0 g/dL; $p < 0.05$). Other markers of cachexia were similar across quartiles. Q3 had the longest mean duration on FOLFOX-D (Q1: 163 days; Q2: 139 days; Q3: 400 days; Q4: 191 days; $p < 0.05$), and significantly longer treatment duration than all other quartiles by log-rank test ($p < 0.05$). Q4 had the highest rate of hypertension (73%). 5-FU dose (2800 mg/m2 BSA) per gram LV myocardium was higher in Q1 (90.3 mg/g) and Q2 (67.2 mg/g) than Q3 (56.1 mg/g) and Q4 (46.5 mg/g).

Conclusion: LV mass correlates to skeletal muscle mass. LV mass is significant in determining toxicity and dosing in cardiotoxic agents such as 5-FU, and cancer patients may benefit from echocardiography. Patients with less LV mass change have the longest treatment duration while others with high LV mass may have underlying heart disease. Curiously, ACE inhibitor use may attenuate LV atrophy and improve patient outcomes.