Sex differences of cytokine profiles and muscle loss in pancreatic cancer patients

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Introduction

Pancreatic adenocarcinoma is one of the most aggressive human malignancies, with survivorship at 5 years less than 10%

The Cancer Anorexia - Cachexia Syndrome (CACS) is a major symptomatic problem in patients with cancer. It is defined as "a wasting syndrome involving loss of muscle and fat directly caused by tumor factors, or indirectly caused by an aberrant host response to tumor presence"[1]

There seem to be sex differences in systemic inflammation and CACS[2]

Objectives

In patients with newly diagnosed pancreatic cancer:

- To explore sex differences in changes of muscle mass over time
- To explore sex differences in C-reactive protein and cytokine profiles measured at diagnosis

Methods

Patients

- Forty (40) patients with newly diagnosed pancreatic cancer from the McGill University Health Centre or the Jewish General Hospital in Montreal, Canada
- All stages
- ECOG performance status: 0-3
- Life expectancy ≥ 3months

Muscle areas delineated using Slice-O-Matic software (Tomovision, Montreal, Canada)
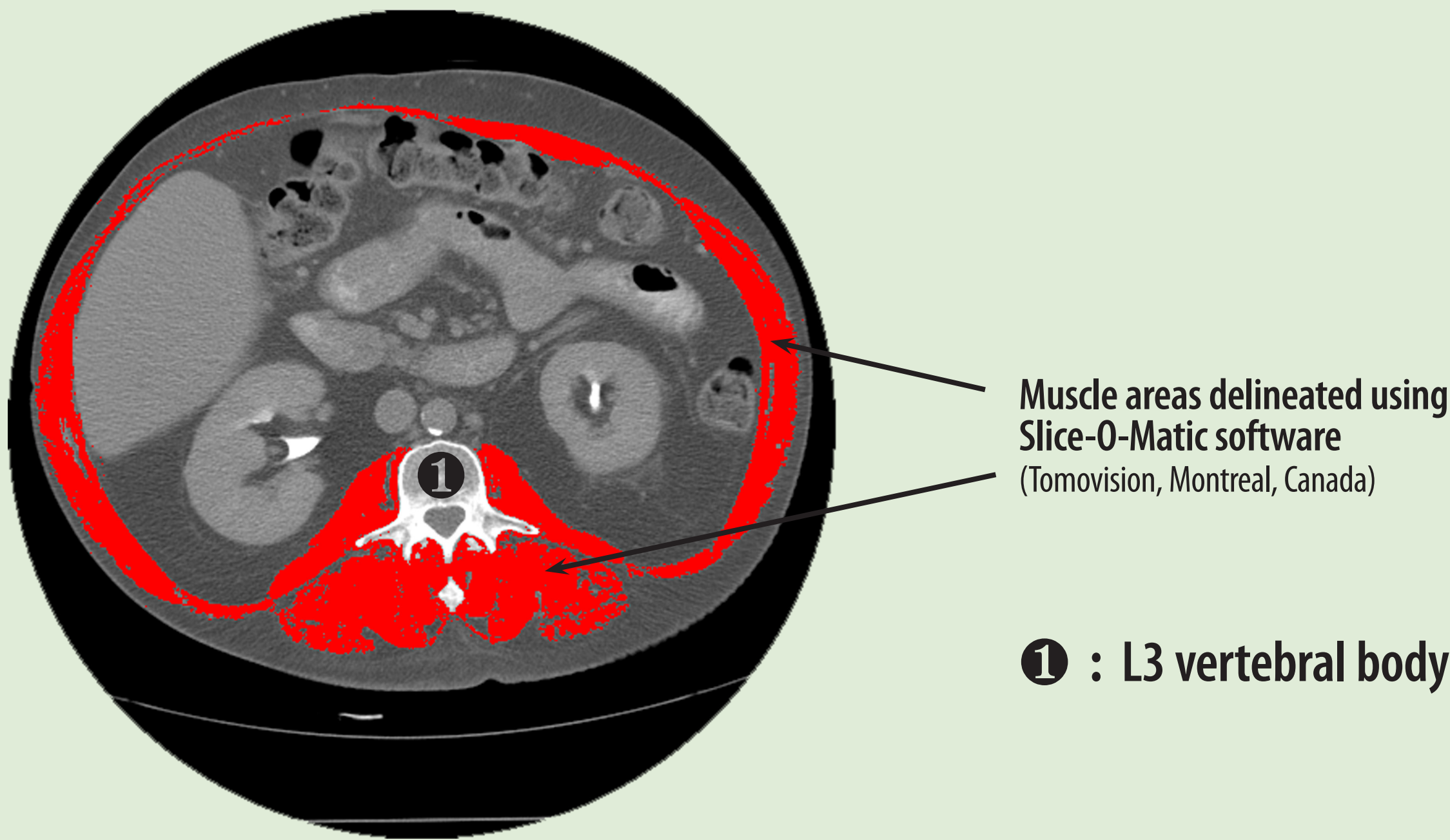
❶ : L3 vertebral body

Figure 1 Description of the Method to Measure Muscle Surface area

- A lumbar vertebral landmark (L3) was extracted from all available computed tomography (CT) images performed for clinical purposes
- Then Slice-O-Matic software was used to assess cross-sectional muscle area (cm²)
- Cross-sectional muscle area, identified by this technique, has been shown to correspond to whole-body skeletal muscle mass in patients with cancer[3]

Cytokine Profiling

- Cytokines were measured, with the Bio-PlexR system, from plasma samples collected at the time of diagnosis and before any oncology treatment
- Data output was analyzed with the Bio-Plex Manager™ software
- Results are presented above normal values, except for Il-8, which had a bimodal distribution, is presented low versus high within normal range[4]

Statistical Analyses

- Patients were grouped according to changes in muscle surface area over time using trajectory modeling
- *Fisher Exact Probability test* and t-tests were used to compare proportions and means, respectively

RESULTS

Figure 2 : Trajectories of Muscle Surface Area in Patients with newly Diagnosed Pancreatic Cancer

- Four trajectories of changes in muscle surface area were identified
  - **Group 1:** patients with decreasing muscle area over time (n = 20)
  - **Groups 2 – 4:** patients with stable muscle area over time (n = 20)
- A significantly higher proportion of women (81%) than men (29%) were losing muscle mass (p= 0.001)
- The group of patients who were losing muscle mass had at diagnosis, on average, a lower muscle mass than the other 3 groups
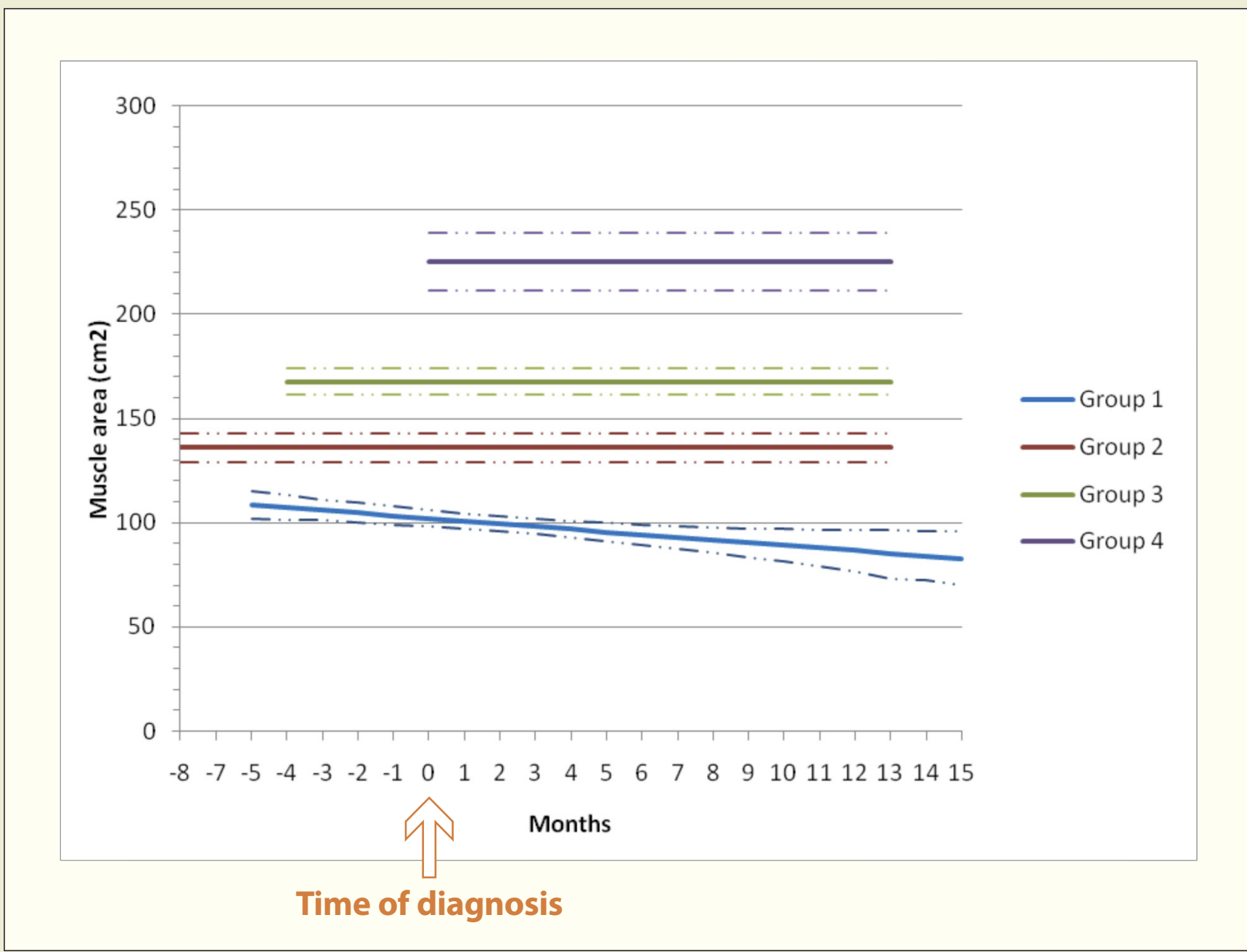

Table 1 Patient Characteristics and Biomarkers at Diagnosis by Loss of Muscle Mass and Sex

	Maintaining Muscle Mass	Losing Muscle Mass		
	Men (n = 17)	Men (n = 7)	Women (n = 13)	p-value*
Age (years): mean (SD)	66.71 (11.67)	75.7 (8.6)	62.8 (11.4)	0.02
Chemotherapy (yes): %	82.4	71.4	92.3	0.02
Surgery: % Curative Palliative/Exploratory	10.0 10.0	14.3 14.3	23.1 15.4	--
CRP > 5.0mg/L †: (%)	68.8	71.4	18.2	0.02
IL-4 > 3.0 pg/ml ‡: (%)	50.0	33.3	63.6	NS
IL-6 > 9.0 pg/ml ‡: (%)	41.7	33.3	45.5	NS
IL-8 > 20.0 pg/ml ‡: (%)	41.7	83.3	27.3	0.01
IL-1β > 0.7 pg/ml ‡: (%)	16.7	33.3	36.4	NS
IL-10 > 2.0 pg/ml ‡: (%)	50.0	50.0	36.4	NS
IL-12(p70) > 6.0 pg/ml ‡: (%)	41.7	33.3	36.4	NS
IFN- g > 124 pg/ml ‡: (%)	16.7	33.3	36.4	NS
TNF- a > 98 pg/ml ‡: (%)	0.0	16.7	0.0	NS
TRAIL > 272.0 pg/ml ‡: (%)	33.3	0.0	18.2	NS

*Comparing difference between men and women losing muscle mass; †n = 35; ‡n = 29

- In patients losing muscle mass, women were younger than men (p=0.02)
- Men losing muscle mass were, on average, older than men not losing muscle mass (p=0.08)
- In patients losing muscle mass , a significantly higher proportion of women were losing muscle mass despite receiving more chemotherapy than men (p=0.02)
- In patients losing muscle mass, a significantly lower percentage of women had a CRP ≤ 5 mg/L measured at diagnosis than men (p=0.02)
- Cytokine levels were not associated with loss of muscle mass, except a significantly lower percentage of women had Il-8 > 20.0 pg/ml than men (p=0.01)

DISCUSSION

- This pilot study on patients with pancreatic cancer suggests that women are more likely to lose muscle mass than men, despite receiving similar anti-cancer treatment. Differences in gonadal status between men and women were suggested as a possible explanation[2]
- Contrary to common knowledge[5], in our sample, the level of CRP does not seem to predict loss of muscle mass
  - The proportion of men with increased CRP was the same between men losing and not lot losing muscle mass
  - Very few of the women losing muscle mass had increased CRP
- In our sample, Il-6, TNF-α, IFN-γ were not predictors of loss of muscle mass as previously suggested[6]

Conclusion

- **In patients with Pancreatic Cancer, women seem to be losing muscle mass faster than men**

References

1. Macdonald N, Easson AM, Mazurak VC, Dunn GP, Baracos V. Understanding and managing cancer cachexia. Journal of the American College of Surgeons 2003;197(1):143-161.
2. Skipworth RJ, Moses AG, Sangster K et al. Interaction of gonadal status with systemic inflammation and opioid use in determining nutritional status and prognosis in advanced pancreatic cancer. Support Care Cancer 2011;19(3):391-401.
3. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008;33(5):997-1006.
4. Chapman P. Normal Physiological Levels of Human Cytokines Using Bio-Plex Pro Cytokine Assays. 2004. Hercules, CA, Bio-Rad Laboratories, Inc.
5. Fearon K, Strasser F, Anker SD et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12(5):489-495.
6. Tisdale MJ. Mechanisms of cancer cachexia. Physiol Rev 2009;89(2):381-410.