Could dosing on muscle mass optimize adherence to chemotherapy and improve chemotherapy-induced peripheral neuropathy?

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FORCE

Background

- Most chemotherapy dosing paradigms are based on body surface area (BSA), without consideration of body composition, and carry significant toxicity.
- Toxicities often lead to **chemotherapy dose modification**, which is associated with higher mortality.
- Muscle mass is independently associated with chemotoxicity and survival.

Objective

To evaluate the utility of considering body composition in chemotherapy dosing, we assess associations between **chemotherapy dose normalized to muscle mass** and modifications to chemotherapy and chemotherapy-induced peripheral neuropathy.

Study Population

- N=94 patients with stage II/III colorectal cancer, participating in the 'FORCE' trial of resistance training during chemotherapy (NCT03291951)
- Recently completed curative-intent surgical resection and prescribed FOLFOX (5-FU/leucovorin and oxaliplatin)

Table 1. Patient Characteristics by 5-FU dosage relative to skeletal muscle area (SMA)

Characteristic	5-FU/SMA < 38.5 (N=47)	5-FU/SMA ≥ 38.5 (N=47)
Age, mean (SD), yr	52 (12)	56 (13)
Female	10 (21)	36 (77)
Race/ethnicity		
White	30 (64)	33 (70)
Asian	4 (9)	6 (13)
African American	3 (6)	3 (6)
Hispanic	7 (15)	2 (4)
Other	3 (6)	3 (6)
Stage III	42 (89)	46 (98)
Resistance training	21 (45)	23 (49)
BMI, mean (SD), kg/m^2	28.2 (4.6)	26.1 (5.2)
SMA, mean (SD), cm^2	173.1 (30.3)	114.4 (18.8)

Methods and Materials

MAIN EXPOSURE

- Chemotherapy dosage relative to skeletal muscle area (SMA, cm^2)
  - ❖ 5-FU/SMA (mg/cm^2)
  - ❖ Oxaliplatin/SMA (mg/cm^2)

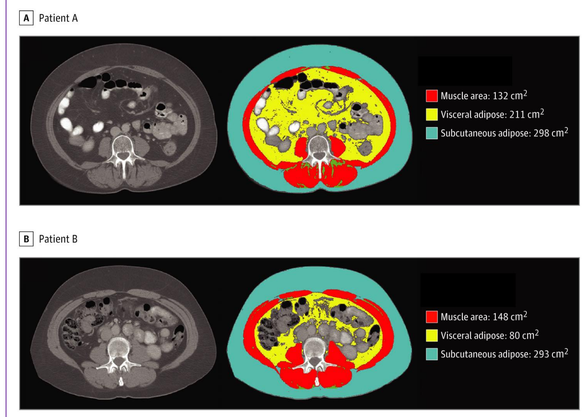

Figure 1. Patients with identical BMI (29kg/m^2) have different muscle and adipose tissue

MAIN OUTCOMES

- Modifications to chemotherapy - RDI
  - ❖ Received dose intensity is a function of chemotherapy dose reduction, delay and early discontinuation
  - ❖ RDI<85% is associated with worse survival

$$Relative\ dose\ intensity\ (RDI) = \frac{Received\ dose\ intensity}{Guideline\ recommended\ dose\ intensity}$$

- Chemotherapy-induced peripheral neuropathy (CIPN)
  - ❖ Evaluated using the CIPN20 questionnaire
  - ❖ Assessed change in score at baseline and follow-up
  - ❖ Higher score indicates worse symptoms

STATISTICAL ANALYSIS

- Receiver operative characteristics (ROC) curve was used to determine optimal cutoff for 5-FU/SMA and oxaliplatin/SMA in predicting RDI≥85%.

Results

- Higher dosage relative to muscle was associated with lower RDI (i.e., more dose modifications)

	Mean (SD)	Range	Beta (SE)*	P value
5-FU/SMA	39.1 (7.4)	26.1 – 58.5	-6.00 (2.37)	0.01
Oxaliplatin/SMA	1.2 (0.2)	0.8 – 1.8	-5.04 (2.11)	0.02

Effect size **per 1 SD increase in relative dosage from multivariable linear regression adjusted for age, gender, stage, baseline BMI, chemotherapy duration, study site and intervention arm*

- Optimal cutoff values for achieving RDI≥85% were 38.5 mg/cm^2 for 5-FU and 1.2 mg/cm^2 for oxaliplatin.

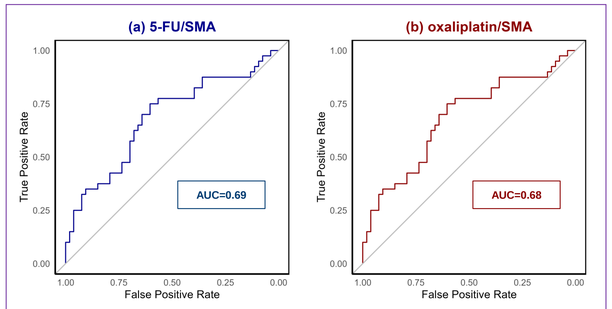

Figure 2. ROC curve for achieving RDI≥85%

- 5-FU: 31% of high relative dose patients achieved RDI≥85% compared to 60% in low relative dose patients.
- Oxaliplatin: 26% of high relative dose patients achieved RDI≥85% compared to 59% in under-dosed patients.

- Patients with higher dose relative to muscle (darker color) reported worse CIPN compared to those with lower dose (lighter color) (P≤0.01).

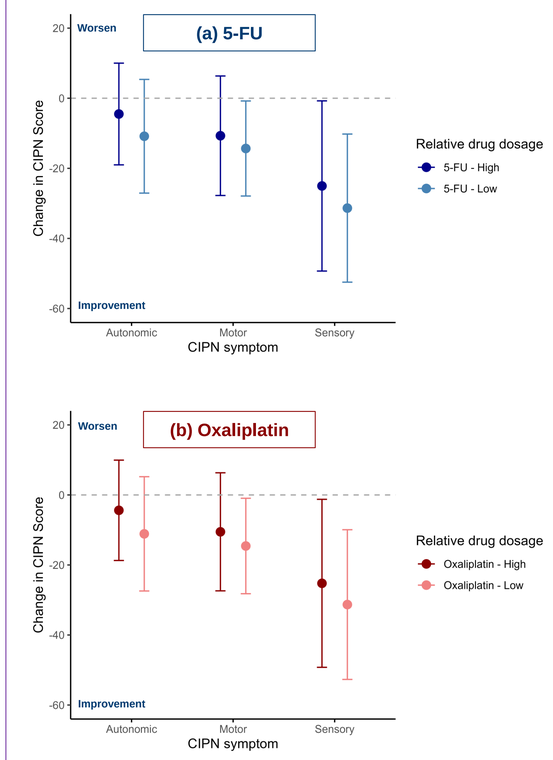

Figure 3. Change in CIPN scores by relative dosage to muscle mass

**Error bars are standard errors from multivariable models*

Conclusions

- Higher doses of 5-FU and oxaliplatin relative to muscle mass are associated with increased dose modification and worse CIPN.
- **Considering muscle in chemotherapy dosing may mitigate toxicities and help patients receive appropriate treatment.**

Next Steps

- Incorporate survival outcome
- Develop a multi-state simulation model to project the long-term outcomes of **muscle mass-based chemotherapy dosing or dosing modification.**

Interested in collaborating or learning more about this study?

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