Impact of muscle loss and sarcopenia on dose limiting toxicities in metastatic colorectal cancer patients receiving palliative systemic treatment

Abstract #2-42

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Introduction

- Evidence on the link between skeletal muscle (SM) depletion and poor outcome in metastatic cancer patients is increasing.
- We recently found, using data of the randomized phase 3 CAIRO3 study [1], that SM loss was significantly related to shorter overall survival (OS) (*Table 2*).

Aim

As a potential risk factor for reduced survival we explored whether muscle loss was associated with dose limiting toxicities (DLT) during palliative systemic treatment.

Methods

- Secondary analysis of the randomized phase 3 CAIRO3 study[1] *(Figure 1).*
- DLT = dose delay, reduction, or discontinuation of systemic treatment because of reported CTCAE (v3.0) toxicities.
- The association between DLT, sarcopenia and muscle loss was studied within time periods with available data on DLT (*Figure 1*).

Skeletal muscle analysis

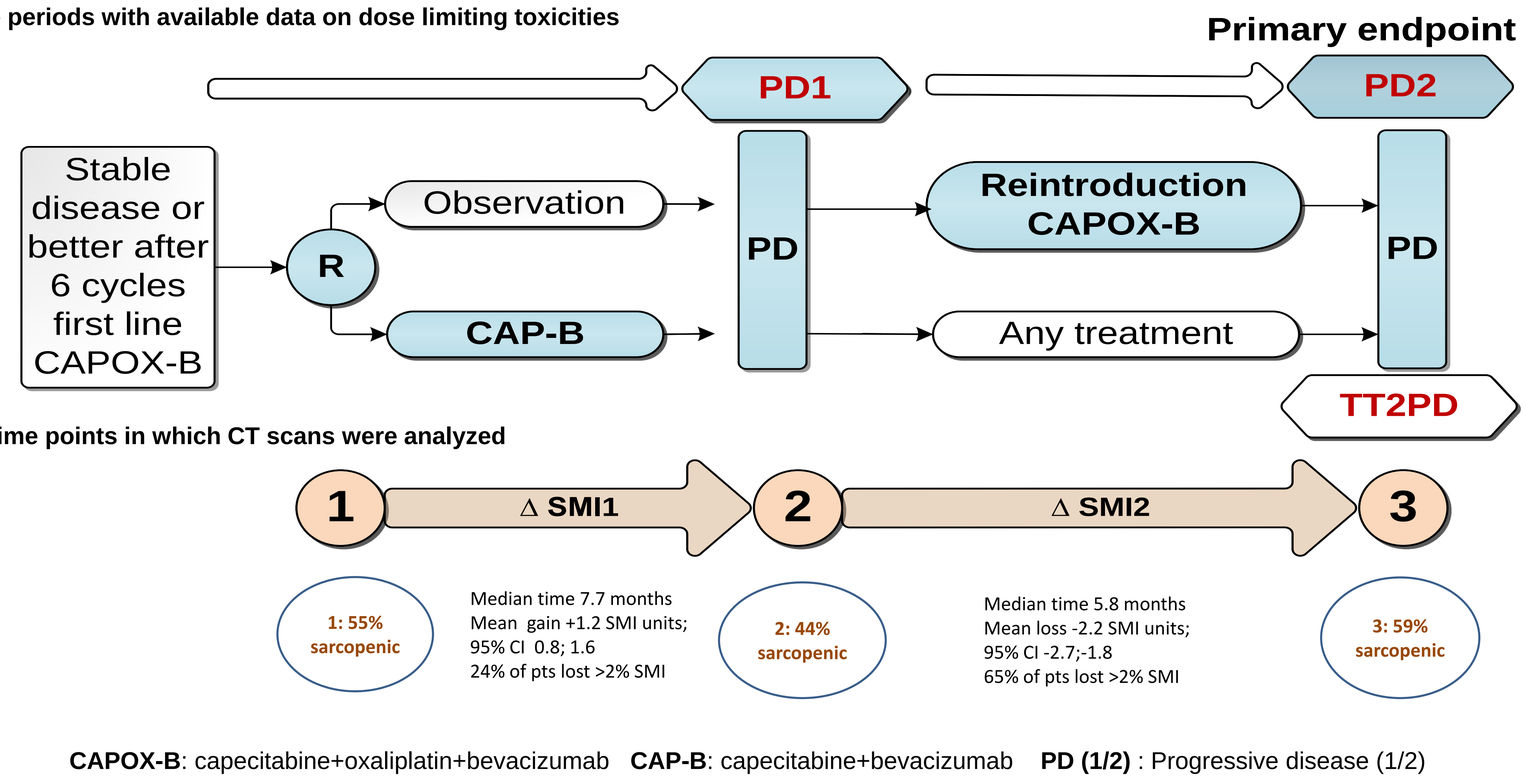
- 1355 CT scans of 450 pts were analyzed for skeletal muscle by Slice-o-matic (Tomovision, version 5.0) at the L3 level using thresholds in Hounsfield Units (-150; -29).
- Per patient, repeated CT-scans were rotated and fused with a rigid fusion method (MeVisLab, version 2.7.1) and L3 as a boney landmark to reduce measurement errors due to variation in the positioning of patients over time.
- **Skeletal muscle index (SMI) =** skeletal muscle area (cm^2) adjusted for height (m^2).
- **Sarcopenia** was determined by applying published cut off points[2] (Table 2).

Patient characteristics total group (Table 1)

	Sarcopenia at randomization	Non sarcopenic at randomization
Age, mean in years (±SD)	64.2 ±9	63.1 ±8
Male, %	59	68
BMI, mean (±SD)	25.0 ±3.9	26.6 ±4.1
WHO performance score, % 0 / 1	60 / 40	62 / 38
Treatment arm after randomization, % CAP-B / observation	49 / 51	51 / 49
Reintroduction treatment, % CAPOX-B / other	57 / 43	58 / 42

Study design CAIRO3 study (Figure 1)

In blue: time periods with available data on dose limiting toxicities



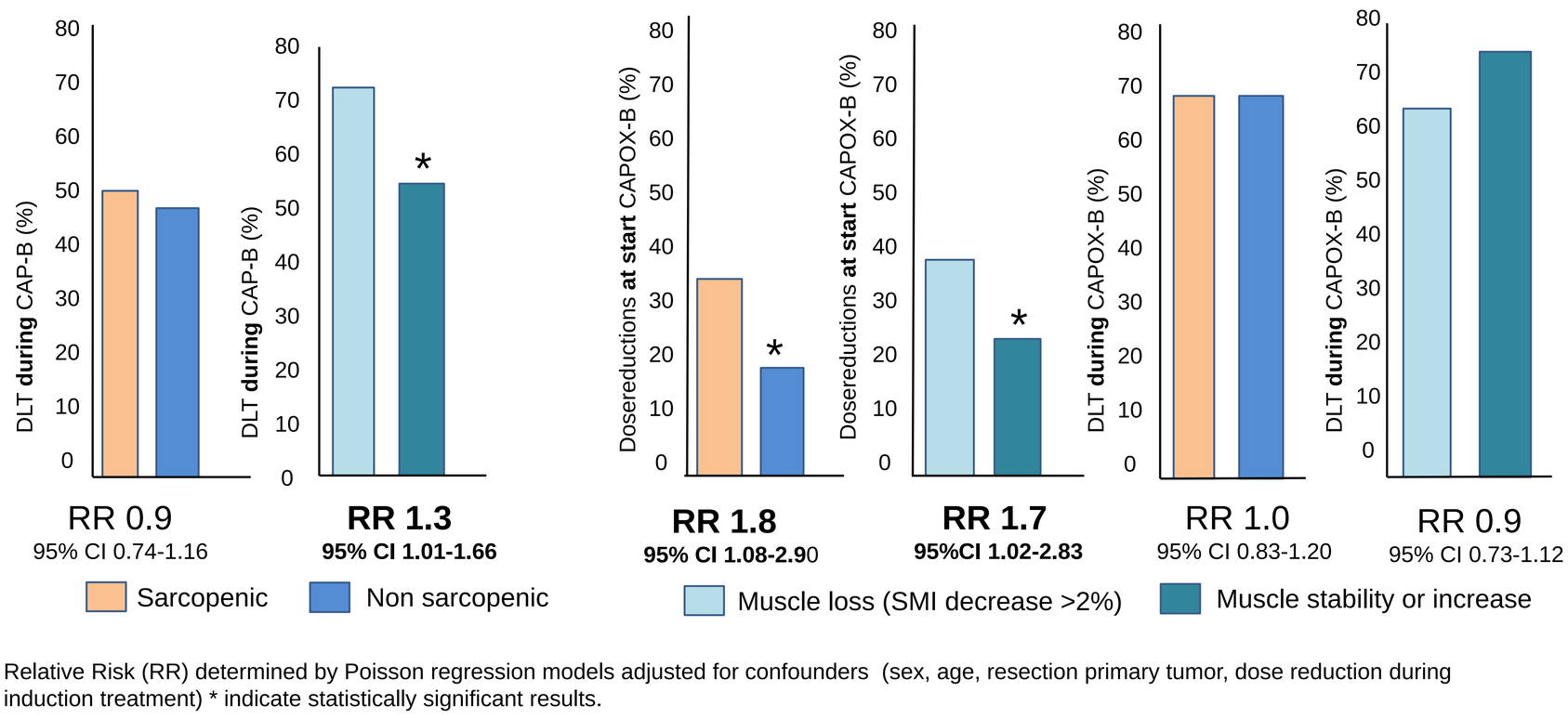
CAPOX-B: capecitabine+oxaliplatin+bevacizumab **CAP-B**: capecitabine+bevacizumab **PD (1/2)** : Progressive disease (1/2)

Muscle (change) and time to progression and survival total group (Table 2)

	Time to PD1	Time to PD2	Time to death
Sarcopenia at randomization	HR 1.02 (0.82-1.27)	HR 1.06 (0.85-1.32)	HR 1.01 (0.87-1.36)
Sarcopenia at PD1	NA	**HR 1.40 (1.10-1.70)**	HR 1.20 (0.96-1.54)
SMI loss during Δ SMI1 per 2 units	NA	HR 1.05 (0.97-1.14)	**HR 1.11 (1.02-1.20)**
SMI loss during Δ SMI2 per 2 units	NA	NA	**HR 1.33 (1.19-1.44)**

Hazard ratio's (HR) determined by Cox models adjusted for *age, sex, WHO PS, stage, primary tumor site, resection primary tumor, response to induction treatment, LDH at randomization, synchronous vs metachronous mCRC, dose reduction during induction treatment.* **Sarcopenia males** SMI <43 if BMI <25 or SMI <53 if BMI ≥25 , **females** SMI <41 any BMI. **NA** = not applicable**. In bold**: statistically significant HR.

Dose limiting toxicities during systemic treatment (Figure 2)



Relative Risk (RR) determined by Poisson regression models adjusted for confounders (sex, age, resection primary tumor, dose reduction during induction treatment) * indicate statistically significant results.

Drug dosing by body surface area (BSA) might contribute to differences in DLT's since BSA does not account for variation in SM mass. In patients with and without DLT we explored the variation in BSA dosed CAP(OX)-B per kg SM mass, and did not observe statistically significant differences.

Conclusions

- **In metastatic colorectal cancer patients during palliative systemic treatment, sarcopenia and/or muscle loss is associated with an increased risk of experiencing dose limiting toxicities, which may contribute to the worse survival in this group of patients.**
- **These data suggest that skeletal muscle preservation may be a therapeutic goal.**

References

[1] Simkens LHJ, Van Tinteren H, May AM, et al. Maintenance treatment with capecitabine and bevacizumab in metastatic colorectal cancer (CAIRO3): a phase 3 randomised controlled trial of the Dutch Colorectal Cancer Group. Lancet 2015; 385(9980):1843-52.

[2] Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31(12):1539-1547. doi:10.1200/JCO.2012.45.2722.

Acknowledgements

We thank all participating patients and staff at each of the study centers. This study was funded by the Dutch Colorectal Cancer Group (DCCG) and the province of Utrecht, The Netherlands.

Poster presented at the SCWD annual meeting 2017, 7-10 December. Correspondence: s.a.kurk@umcutrecht.nl