Impact of skeletal muscle index (SMI) loss during palliative systemic treatment (Tx) on time to progression and overall survival (OS) in metastatic colorectal cancer (mCRC) patients

Kurk SA[1], Peeters PHM[2], Stellato RK[2], Dorresteijn B[3], Jourdan M[3], Creemers G-J M[4], Erdkamp FLG[5], de Jongh FE[6], Kint PAM[7], Poppema BJ[8], Radema SA[9], Simkens LHJ[10], Tanis BC[11], Tjin-A-Ton MLR[12], Van Der Velden A[13], Punt CJA[14], Koopman M[1], May AM[2]* (* = equal contribution)*

[1] University Medical Center Utrecht, Utrecht; [2] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht; [3] Nutricia Research, Nutricia Advanced Medical Nutrition, Utrecht; [4] Catharina Hospital, Eindhoven; [5] Orbis Medical Center, Sittard; [6] Ikazia Hospital, Rotterdam; [7] Amphia Hospital, Breda; [8] University Medical Center, Groningen; [9] Nijmegen University, Nijmegen; [10] Máxima Medical Center, Eindhoven; [11] Groene Hart Hospital, Gouda; [12] Hospital Rivierenland, Tiel; [13] Tergooi Hospital, Hilversum; [14] Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Introduction

- Evidence for a strong link between skeletal muscle depletion (sarcopenia) and poor outcomes in mCRC is growing. However, the impact of skeletal muscle index (SMI) changes on survival is not known.
- **Aim: to investigate SMI (changes) in mCRC patients on multiple time points during palliative systemic treatment and its association with time to progression and survival.**

Methods

- Secondary analysis of the randomized phase 3 CAIRO3 study† in which mCRC patients with stable disease (SD) or better after 6 cycles capecitabine+oxaliplatin+bevacizumab (CAPOX-B) were randomized between maintenance treatment with capecitabine+bevacizumab (CAP-B) and observation *(figure 1).*
- Upon first disease progression (PD1) CAPOX-B or other treatment was reintroduced until second disease progression (PD2) .

Skeletal muscle analysis

- 1355 CT scans of 450 pts were analyzed for skeletal muscle by Slice-o-matic (version 5.0; Tomovision) at the L3 level using thresholds in Hounsfield Units (-29 ; – 150).
- **Skeletal muscle index (SMI)** was skeletal muscle area (in cm^2) adjusted for height (in m^2).
- **Sarcopenia** was determined by applying published cut off points ††
  - Males SMI <43 if BMI <25 or SMI <53 if BMI ≥25
  - Females SMI <41 any BMI.

Statistical analysis

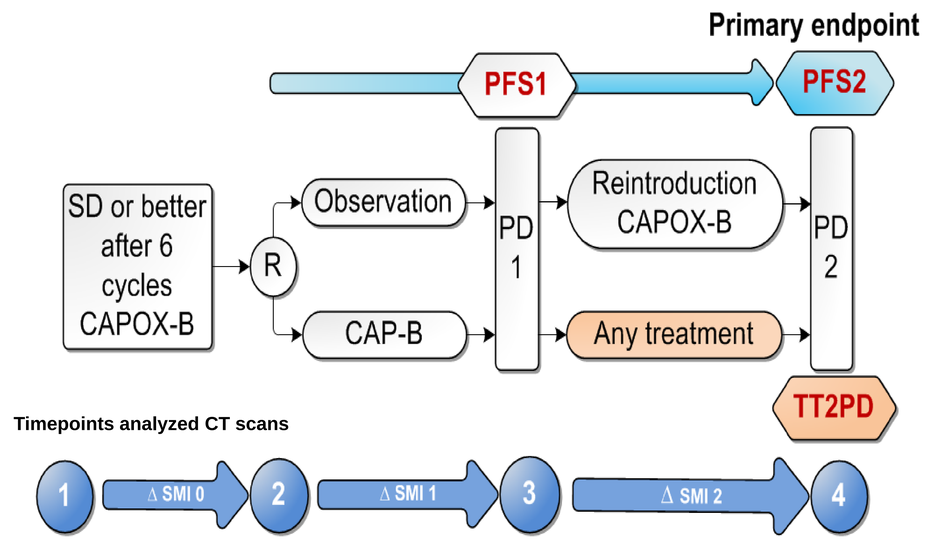
- Linear mixed effect models were used to study SMI changes over time.
- Cox proportional hazard models adjusted for relevant confounders were used to study the association between sarcopenia, SMI changes and time to PD1, PD2 and death.

Patient characteristics total group (table 1)

Age, mean in years (±SD)	64 (±8.8)
Male, %	63
BMI, mean (±SD)	26.0 (±4.3)
WHO performance score, % 0 / 1	65 / 35
Location primary tumor, % Colon / rectum / rectosigmoid	50 / 29 / 21
Multilesion, % 1 / >1	46 / 54
Primary tumor resected, %	60
Sarcopenia at randomization, % No / yes / missing	36 / 45 / 18
Treatment arm after randomization, % CAP-B / observation	50 / 50
Reintroduction treatment, % CAPOX-B / other	44 / 56

Results

Study design CAIRO3 study (figure 1)

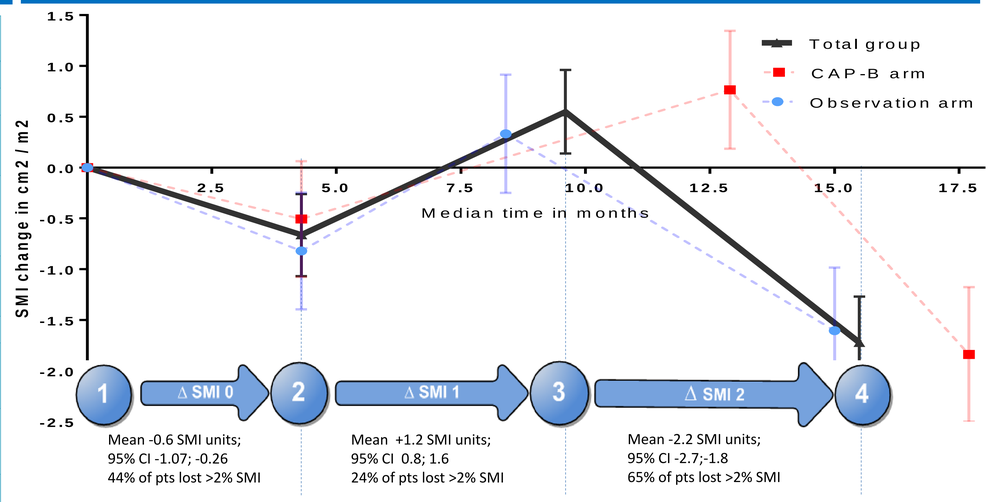


Muscle (change) and time to progression and survival total group (table 2)

	Time to PD1	Time to PD2	Time to death
SMI loss during Δ SMI 0 per 2 units	1.00 0.97-1.04	1.01 0.97-1.04	1.01 0.95-1.09
SMI loss during Δ SMI 1 per 2 units	NA	HR 1.05 0.97-1.14	**HR 1.11 1.02-1.20**
SMI loss during Δ SMI 2 per 2 units	NA	NA	**HR 1.33 1.19-1.44**
Sarcopenia at start 6 cycles CAPOX-B	1.01 0.86-1.37	1.16 0.92-1.45	1.07 0.84-1.35
Sarcopenia at randomization	1.02 0.82-1.27	1.06 0.85-1.32	1.01 0.87-1.36
Sarcopenia at PD1	NA	**HR 1.40 1.1-1.7**	HR 1.20 0.96-1.54
Sarcopenia at PD2	NA	NA	HR 1.10 0.84-1.46

HRs 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. NA = not applicable. **In bold**: statistically significant HRs.

SMI changes during palliative systemic treatment (figure 2)



SMI changes determined by mixed model analysis with age, sex, treatment arm and resection primary tumor as fixed effects
CAP-B / observation arm were combined in the analysis ($p^{interaction} > 0.05$)

Conclusions

- In mCRC patients, loss of SMI during palliative systemic treatment was related to shorter overall survival.
- Sarcopenia at time of first disease progression was related to shorter time to second disease progression.
- This large longitudinal study suggests that SMI preservation may be a therapeutic goal.

References

† 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.

†† 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 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 ASCO annual meeting 2017,2-6 June. Correspondence: s.a.kurk@umcutrecht.nl

Abstract #10087