A comparison of CT based measures of skeletal muscle mass and density from the Th4 and L3 levels in patients with advanced non-small-cell lung cancer

Bjørn H. Grønberg,[1,2] Bjørg Sjøblom,[3] Tore Wentzel-Larsen,[4,5,6] Vickie E. Baracos,[7] Marianne J. Hjermstad,[8,9] Nina Aass,[3,8] Roy M. Bremnes,[10,11] Øystein Fløtten,[12] Asta Bye,[9,13] Marit Jordhøy[8,14]

[1]Department of Clinical and Molecular Medicine, Faculty of Medicine, NTNU, Norwegian University of Science and Technology, Trondheim, Norway

[2]The Cancer Clinic, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway

[3]Department of Oncology, Oslo University Hospital, Oslo, Norway

[4]Norwegian Centre for Violence and Traumatic Stress Studies, Oslo, Norway

[5]Centre for Child and Adolescent Mental Health, Eastern and Southern Norway, Oslo, Norway

[6]Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway

[7]Department of Oncology, Division of Palliative Care Medicine, University of Alberta, Edmonton, Canada

[8]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

[9]European Palliative Care Research Centre, Department of Oncology, Oslo University Hospital, Oslo, Norway

[10]Department of Oncology, University Hospital North Norway, Tromsø, Norway

[11] Department of Clinical Medicine, Faculty of Medicine, University in Tromsø, Norway

[12]Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway

[13]Department of Nursing and Health Promotion, Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway

[14]Department of Internal Medicine, Innlandet Hospital Trust, Hamar, Norway

Keywords:

lean body muscle mass; skeletal muscle mass; prognostic factor; body composition

Abstract:

Background

Muscle mass and density assessed from CT-images at the L3 level are prognostic for survival and predict toxicity in cancer patients. However, L3 is not always included on routine CT-scans. We aimed to investigate whether images at the Th4 level may be used instead.

Methods

Patients from three chemotherapy trials in advanced NSCLC were eligible (n=1305). Skeletal muscle area (cm^2), skeletal muscle index (SMI, cm^2/m^2) and skeletal muscle density (SMD) at Th4 and L3 levels were assessed from baseline CT-scans. SMI and SMD at the Th4 and L3 level were transformed into z-scores and the agreement between scores was investigated by Bland-Altman plots and estimated by intra-class correlation analyses. Linear regression was used to test if Th4 SMI and SMD z-scores predicted L3 SMI and SMD z-scores.

Results

CT-images from 401 patients were analyzable at both levels. There was a moderate agreement between Th4 and L3 SMI z-scores with an intra-class correlation of 0.71 (95% CI 0.64–0.77) for men and 0.53 (95% CI 0.41–0.63) for women. Regression models predicting L3 SMI z-scores from Th4 SMI z-scores showed coefficients of 0.71 (95% CI 0.62-0.80) among men and 0.53 (95% CI 0.40-0.66) among women. R-squares were 0.51 and 0.28 respectively, indicating moderate agreement. A similar, moderate agreement between Th4 and L3 SMD z-scores was observed.

Conclusion

There was only moderate agreement between muscle measures from Th4 and L3 levels, indicating that missing data from the L3 level cannot be replaced by analyzing images at the Th4 level.

Introduction

Changes in human body composition related to aging and disease is gaining increasing interest. A particular focus has been rendered to muscle wasting and thereby loss of lean body mass (LBM). In aging, muscular depletion is associated with frailty and several negative health outcomes, including mortality.[1, 2] In cancer populations, an increasing body of evidence links this feature to cachexia,[3] worse survival,[4-7] and increased risk of toxicity from systemic cancer therapy.[8-12] Associations with postoperative infections and delayed recovery after surgery for colorectal cancer have also been reported.[13] Muscle wasting may occur in obese patients (sarcopenic obesity) as well as in those who are normal or underweight. It is, however, frequently undetected since both weight and body mass index (BMI) are poor indicators of LBM.[14]

There are several options for body composition assessment, including bioelectrical impedance analyses (BIA), dual energy X-ray absorptiometry (DXA) and analyses of computed tomography (CT) images.[15] The latter method is particularly convenient in oncology settings due to frequent, routine CT-imaging for diagnosis, staging, treatment evaluation and follow-up. In contrast to BIA and DXA, CT images provide specific details on muscle characteristics, adipose tissues and organs. Furthermore, skeletal muscle area quantified from a single CT slice at the third lumbar level (L3) is closely correlated to the estimated total lean body skeletal muscle mass (LBM).[15, 16] Thus, utilizing CT images at the L3 level to assess body composition has become the gold standard in studies on cancer patients.[3, 17]

CT based assessment makes it possible to measure skeletal muscle radiodensity (SMD) in addition to muscle mass. SMD is expressed as the mean Hounsfield Units (HU) of the measured cross sectional muscle area. Low values reflect increased fat deposits,[18] are associated with older age,[19, 20] and when measured at the lumbar level, they are also linked to worse survival in cancer patients.[7, 21] In non-cancer populations, both SMD- and age-related differences between muscle groups have been found, indicating that the underlying etiological factors for muscle wasting may not affect all muscles similarly.[19]

In non-small cell lung cancer (NSCLC), cachexia and muscle wasting are common and associated with worse prognosis and increased risk of treatment toxicity.[7, 12, 22] However, diagnostic work-up of these patients is usually restricted to a CT-scan of the thorax and upper abdomen which often does not include the L3 level. Thus, CT-images at the fourth thoracic level (Th4) have been used to assess skeletal muscle mass and its relation to survival in lung cancer patients.[23, 24] There is, however, limited knowledge about the agreement between muscle-measures at the L3 and at Th4 level,[25] and none have compared muscular SMD at these levels in cancer patients. Based on data from three Norwegian randomized controlled trials (RCT) comparing first line chemotherapy regimens in advanced non-small cell lung cancer (NSCLC),[26-28] we aimed at investigating whether L3 muscle mass and SMD might be reliably predicted from Th4 measures.

Methods

Study sample

The trials which this study is based upon were conducted from 2003 to 2009, and the main inclusion criteria were: Chemonaïve patients, age ≥18 years, stage IIIB/IV NSCLC and performance status (PS) 0-2. In all trials, the diagnostic work-up included a CT scan of the thorax and upper abdomen obtained within four weeks before chemotherapy commenced. These CT scans were collected retrospectively for assessment of LBM. For the present study, we included patients if the baseline CT-scan included analysable images both at the Th4 and L3 levels.

Body composition assessments

The diagnostic CT scans were analysed using Slice-O-Matic software (v.4.3 Tomovision, Montreal Canada) by three similarly trained observers blinded for other patient data. The first image in the caudal direction where both vertebral transverse processes were visible was used to manually outline the skeletal muscle tissue at the Th4 and L3 level, respectively. Based on pre-established thresholds of Hounsfield Units (HU) in the range of –29 to + 150 HU,[15, 16] the cross-sectional areas (cm^2) of the outlined muscle tissues at the Th4 and L3 levels were automatically calculated by the software, normalised for stature (height squared), and expressed as Th4 and L3 skeletal muscle index (Th4 SMI, cm^2/m^2 and L3 SMI, cm^2/m^2). Optimally the whole circumference of the body should be included in the images at the L3 and Th4 levels to enable an exact quantification of the respective tissue areas. In some patients, parts of the muscular tissue were missing on the CT scans. If less than half of the circumference was missing, the total area was estimated by doubling the area of the opposite half of the body. If more than half of the circumference was missing, no quantification was possible and the patient was excluded from the analyses. SMD was assessed as the mean HU of the entire cross sectional muscle area at levels Th4 and L3.

The patients' BMI (weight (kg)/height (m^2) were calculated based on baseline data from the RCTs. No systematic registration of weight loss at baseline was conducted, hence we used appetite loss registered on the European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) as a supplementary indicator of nutrition status.

Statistics

Data from all RCTs were analysed jointly. Body composition measures were compared between men and women by independent sample t-tests, and all analyses investigating agreement between measures at the Th4 and L3 level were done for each gender separately.

First, we investigated the agreement between the L3 skeletal muscle area, SMI and SMD and the corresponding measures at the Th4 level using scatterplots. Then, the SMI and SMD from both levels were transformed into z-scores, separately for men and women. The agreement between Th4 SMI z-scores and L3 SMI z-scores were investigated by Bland-Altman diagrams with locally fitted smooth (loess) curves, and by intraclass correlation. Whether Th4 SMI and SMD z-scores could predict L3 SMI and SMD z-scores were tested using linear regression. Finally, we tested the precision with which individual missing L3 SMI and SMD values could be estimated by using the patients' z-scores from the corresponding Th4 SMI and SMD values. L3 SMI was recomputed using the mean L3 SMI for the cohort + SD x Th4 SMI z-score. The L3 SMD was recomputed similarly. The agreement between actual and recomputed L3 SMI and SMD were then examined by scatter plots.

All p-values were two-sided and p-values < 0.05 were used to define statistical significance. The statistical analyses were performed using IBM SPSS version 18 (IBM Corporation, Armonk, NY, USA).

Ethics

The study was performed according to the Helsinki declaration and approved by the Regional Committee for Medical and Health Research Ethics in South-East Norway.

Results

Overall, we were able to retrieve CT scans from 1119 of the 1305 study participants (85.7%). Among these, 688 scans did not include images at the levels of interest or enough of the circumference, or the quality was too poor for the analyses (Figure 1). Furthermore, 30 patients were excluded due to missing data on SMD either at the L3 or Th4 level (24 patients) or on relevant baseline characteristics (e.g. height and weight) (6 patients). Thus, 401 patients (30.7%) were included in the present study (Figure 1). The main baseline characteristics of these patients are presented in Table 1. 220 were men 54.9%); mean age was 66 years; 100 (25%) were younger than 60 years, 79 (19.7%) were 75 years or older; 316 patients (78.8%) had stage IV disease; and 89 (22.2%) had PS 2.

Body composition

The mean cross-sectional muscle area (cm^2) and the SMI (cm^2/m^2) of the overall study sample were larger at the Th4 level than at the L3 level: 176.4 cm^2 versus 130.6cm^2, and 60.0 cm^2/m^2 versus 44.5 cm^2/m^2. Th4 SMD was also higher than the L3 SMD in the overall sample (41.5 HU vs 36.9 HU) both among men (42.0 HU vs. 37.2) and women (40.8 vs 36.5) (Table 2). Comparing men to women, muscle area and SMI were

significantly larger in men, whereas no significant difference between genders was found for SMD. The muscle measures were close to normally distributed.

Agreement between thoracic and lumbar muscle measures

Scatterplots of the Th4 and L3 muscle area (cm^2), and Th4 and L3 SMI (cm^2/m^2) showed a substantial spread around the lines of complete agreement, indicating only moderate agreement (Figure 2).

A Bland Altman plot (Figure 3A) investigating the agreement between Th4 and L3 SMI, transformed into corresponding z-scores, showed no substantial systematic deviation between the two levels and no substantial difference by gender. There was, however, a considerable spread in the difference between Th4 and L3 z-scores, and the intraclass correlation (single measures) was 0.71 (95% CI 0.64 – 0.77) for men and 0.53 (95% CI 0.41 – 0.63) for women, i.e. consistent with a medium agreement. Regression models predicting L3 SMI z-scores from Th4 SMI z-scores showed coefficients of 0.71 (95% CI 0.62 - 0.80) in the male population and 0.53 (95% CI 0.40 - 0.66) among females. The R squares for these models were 0.50 and 0.28 respectively, indicating that the Th4 SMI z-scores were only moderately related to the L3 SMI z-scores.

Regarding the agreement between z-scores transformed from Th4 and L3 SMD, the Bland Altman plot (Figure 3B) showed results fairly consistent with those for the SMI, except that the spread of differences was considerably larger. The intraclass correlation (single measures) between Th4 SMD and L3 SMD z-scores was 0.71 (95% CI 0.64 – 0.77) for men, and 0.76 (95% CI 0.70 – 0.82) for women. The regression models predicting L3 SMD z-scores from Th4 SMD z-scores showed closely similar coefficients for men and women, 0.71 (95% CI 0.62 - 0.80) and 0.76 (95% CI 0.67 – 0.86), respectively. The R squares for these models were 0.50 for men and 0.58 for women.

Scatterplots of the actual L3 SMI and SMD plotted against the L3 SMI and SMD recomputed by Th4 SMI by z-scores (Figure 3 B and C) showed a substantial spread of the actual values when compared to the estimated values.

Discussion

In this study comparing muscle measures from CT images at both Th4 and L3 levels, using widely accepted methodology, we found that the muscle area was larger at the thoracic level in both genders. There was also a substantial difference between the Th4 SMD and L3 SMD, with higher SMD in the thoracic muscle. Furthermore, the agreement between SMD and SMI at the two levels was only moderate, and for SMI there was also less agreement between Th4 and L3 among the women than among the men. According to

regression analyses, z-scores at the Th4 level were not strongly related to L3 z-scores. The agreement between actual L3 SMI and SMD and the measures recomputed by means of Th4 z-scores was moderate.

We are aware of only one other study comparing muscle measures at the thoracic- and lumbar levels in cancer patients. Kim et al. analysed 90 patients with both limited and extensive small-cell lung cancer, and found poor agreement between pectoral muscle mass at the level above the aortic arch (which is approximately at the Th4-level) and cross sectional muscle area at the L3 level.[25] Though there are differences in patient populations, software for assessing muscle area, the thoracic level for muscle assessment, and muscle groups measured, their study support our findings.

Body composition analyses were not a pre-planned part of the RCTs we collected data from. CT images of the thorax and upper abdomen were mandatory for trial inclusion, but specific requirements for the CT protocols were not defined in the study protocols. Adequate CT-images at both levels were available for only 38% of the patients. We anticipated that muscle measures at the Th4 level would be available for the majority of patients, whereas images at the L3 level would be missing in more cases. As it turned out, a large number of the Th4 level images were insufficient for muscle analyses. This was mostly due to “cutting of edges”, i.e. the outer circumference of the muscle mass was missing, or the image quality was not satisfactory for quantification of muscle mass. Thus, future studies of LBM in cancer patients should include specific instructions to radiology departments to ensure that body composition can be assessed.

A strength of our study is the large sample size of patients with similar diagnosis and stage of disease, though the cohort was too small to allow for subgroup analyses. None of the patients had received any former systemic cancer treatment, and the study sample included a relatively large proportion of elderly and PS 2 patients. Thus, although muscle measures could be obtained for only a minority of the targeted population, we find it reasonable to believe that our findings are representative for advanced NSCLC patients eligible for first-line palliative chemotherapy. For generalisation of our results, confirmation from other studies and other cancer populations is, however, necessary.

CT images at the L3 level include core muscles, such as the rectus abdominis, external and internal oblique and erector spinae, which are assumed to initiate most full-body functional movement and are fundamental for stabilizing the body in dynamic movements. Although some of these muscles (erector spinae) extend into the Th4 level, the major muscles captured at Th4, such as the pectoralis muscles, have other functions, mainly related to arm and shoulder movements. Their volume and strength may therefore to a larger extent depend on specific manual activities, and activities that more often apply to men than women. These functional differences between the muscle groups might contribute to the only moderate agreement between Th4 SMI/SMD and the L3 SMI/SMD, although the reasons may be more complex. We have not

found any good explanations in the literature, but a substantial difference in SMD between muscle groups has formerly been reported.[19] We are not aware of any studies investigating whether there is a different impact of cancer-related muscular depletion between muscle groups.

The gold standard for measuring LBM is analysing whole body CT or MRI scans. Analyses of single slices may not predict the LBM correctly, especially in longitudinal studies,[29] but is currently the most feasible approach in larger and multicentre studies of cancer patients. Whole body CT scans are seldom available unless it is part of specific studies. Thus, such scans were not available from our patients, and it was not possible for us to investigate whether the Th4 or L3 SMI is in best agreement with the whole body muscle mass. Further studies are needed to investigate the relationship between Th4 muscle measures and whole body skeletal muscle mass, and the clinical role of Th4 muscle measures. Until such studies are conducted, we believe that adequate CT images at the L3 level remains the recommended approach in studies of the clinical role of muscle measures in cancer patients.

In conclusion, there is a large variation between the skeletal muscle areas at the Th4 and L3 levels in patients with advanced non-small-cell lung cancer, and muscle measures at the L3 level cannot be reliably estimated by transformation of measures at the Th4 level using z-scores.

Conflicts of interest and source of funding

The study was funded by the South-Eastern Norway Regional Health Authority. The collection of CT scans was supported by unrestricted grants from Pierre Fabre, Norway. The Canadian participation in the body composition analyses was supported by the Canadian Institute of Health Research and Alberta Cancer Foundation. None of the authors have any conflicts of interests to declare.

Acknowledgements

We want to thank Rachel Murphy (PhD) and Nina Esfandiari (B.Sc) both at Dept of Oncology, University of Alberta, Canada, for their participation in the body composition analyses. Thanks to Nina Helbekkmo and Ingrid Sandstad for handling the collection of CT scans from the RCT1. We also thank the Departments of Radiology at Haukeland University Hospital, Bergen, St Olav University Hospital, Trondheim and Hamar, Gjøvik and Kongsvinger Hospital, Innlandet Hospital HF, as well as the following and their respective Departments of Radiology for their participation in the collection of CT scans:
Bjørn Wembstad, Hammerfest Hospital and Kåre Hansen, Kirkenes Hospital; Helse Finnmark HF. Nina Helbekkmo, University Hospital North Norway Tromsø and Nada Zafran Groh, University Hospital North Norway Harstad; University Hospital North Norway HF.

Heinrich Backmann, Nordland Hospital Bodø and Finn Larsen Aas, Nordland Hospital Vesterålen; Nordland Hospital HF. Kristina Helander, Helgeland Hospital Mo i Rana, Hans Henrik Strøm, Helgeland Hospital Sandnessjøen, Reidar Berntsen Helgeland, Hospital Mosjøen; Helgeland Hospital HF. Randi Sudbø, Namsos Hospital and Thor Naustdal, Levanger Hospital; Nord Trøndelag HF. Bjørn Jakobsen, Molde Hospital, Finn Wammer, Ålesund Hospital, Ivar Blix, Kristiansund Hospital and Inge Eskeland, Volda Hospital; Helse Møre og Romsdal HF.

Anita Spikkeland, Voss Hospital; Helse Bergen HF. Tesfaye Madebo and Oddveig Garpestad, Stavanger University Hospital HF, Sverre Fluge, Haugesund Hospital; Helse Fonna HF.

Frode Ramslien, Telemark Hospital Skien and Oddvar Øygarden, Telemark Hospital Rjukan; Telemark Hospital HF. Heidi Rolke Sørlandet Hospital Kristiansand and Terje Torp, Sørlandet Hospital Arendal; Sørlandet Hospital HF. Karin Semb, Vestfold Hospital Tønsberg; Vestfold Hospital HF. Per Fredrik Ekholdt, Østfold Hospital Fredrikstad; Østfold Hospital HF. Ellinor Heitman, Ringerike Hospital, Leiv Rusten, Drammen Hospital, Martin Cornelius Ruppert, Bærum Hospital, and Peter Gottschalk, Kongsberg Hospital; Vestre Viken HF.

Anders Fjeld, Oslo University Hospital (OUS) Aker, Odd Terje Brustugun and Paal Fr Brunsvig, OUS Radiumhospitalet, Kjersti Hornslien and Frøydis Stornes, OUS Ullevål; OUS HF. Svein Olav Saxrud, Akershus University Hospital HF. Carl Birger Alm, Lovisenberg Hospital Oslo.

References

1. Muhlberg W, Sieber C. Sarcopenia and frailty in geriatric patients: implications for training and prevention. *Z. Gerontol. Geriatr.* 2004; **37**(1)**:** 2-8. e-pub ahead of print 2004/03/03; doi: 10.1007/s00391-004-0203-8

2. Landi F, Cruz-Jentoft AJ, Liperoti R, Russo A, Giovannini S, Tosato M *et al.* Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study. *Age Ageing* 2013; **42**(2)**:** 203-209. e-pub ahead of print 2013/01/17; doi: 10.1093/ageing/afs194

3. Baracos V, Kazemi-Bajestani SM. Clinical outcomes related to muscle mass in humans with cancer and catabolic illnesses. *Int. J. Biochem. Cell Biol.* 2013; **45**(10)**:** 2302-2308. e-pub ahead of print 2013/07/04; doi: 10.1016/j.biocel.2013.06.016

4. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L *et al.* Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol.* 2008; **9**(7)**:** 629-635. e-pub ahead of print 2008/06/10; doi: 10.1016/s1470-2045(08)70153-0

289 5. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese
290 patient is an adverse prognostic factor in pancreatic cancer. *Clin. Cancer Res.* 2009; **15**(22)**:** 6973-6979. e-
291 pub ahead of print 2009/11/06; doi: 10.1158/1078-0432.ccr-09-1525
292 6. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and
293 outcome in patients undergoing resection of colorectal liver metastases. *Br. J. Surg.* 2012; **99**(4)**:** 550-557. e-
294 pub ahead of print 2012/01/17; doi: 10.1002/bjs.7823
295 7. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ *et al.* Cancer cachexia in
296 the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass
297 index. *J. Clin. Oncol.* 2013; **31**(12)**:** 1539-1547. e-pub ahead of print 2013/03/27; doi:
298 10.1200/jco.2012.45.2722
299 8. Prado CM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T *et al.* Body composition
300 as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin. Cancer Res.* 2007;
301 **13**(11)**:** 3264-3268. e-pub ahead of print 2007/06/05; doi: 10.1158/1078-0432.ccr-06-3067
302 9. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K *et al.* Sarcopenia as a
303 determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients
304 receiving capecitabine treatment. *Clin. Cancer Res.* 2009; **15**(8)**:** 2920-2926. e-pub ahead of print
305 2009/04/09; doi: 10.1158/1078-0432.ccr-08-2242
306 10. Barret M, Antoun S, Dalban C, Malka D, Mansourbakht T, Zaanan A *et al.* Sarcopenia is linked to
307 treatment toxicity in patients with metastatic colorectal cancer. *Nutr. Cancer* 2014; **66**(4)**:** 583-589. e-pub
308 ahead of print 2014/04/09; doi: 10.1080/01635581.2014.894103
309 11. Cousin S, Hollebecque A, Koscielny S, Mir O, Varga A, Baracos VE *et al.* Low skeletal muscle is
310 associated with toxicity in patients included in phase I trials. *Invest. New Drugs* 2014; **32**(2)**:** 382-387. e-pub
311 ahead of print 2013/12/18; doi: 10.1007/s10637-013-0053-6
312 12. Sjoblom B, Gronberg BH, Benth JS, Baracos VE, Flotten O, Hjermstad MJ *et al.* Low muscle mass is
313 associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. *Lung*
314 *Cancer* 2015; **90**(1)**:** 85-91. e-pub ahead of print 2015/07/23; doi: 10.1016/j.lungcan.2015.07.001
315 13. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with
316 postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br. J. Cancer* 2012;
317 **107**(6)**:** 931-936. e-pub ahead of print 2012/08/09; doi: 10.1038/bjc.2012.350
318 14. Romero-Corral A, Somers VK, Sierra-Johnson J, Thomas RJ, Collazo-Clavell ML, Korinek J *et al.*
319 Accuracy of body mass index in diagnosing obesity in the adult general population. *Int. J. Obes. (Lond.)*
320 2008; **32**(6)**:** 959-966. e-pub ahead of print 2008/02/20; doi: 10.1038/ijo.2008.11

15. 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. *Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme* 2008; **33**(5)**:** 997-1006. e-pub ahead of print 2008/10/17; doi: 10.1139/h08-075

16. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J *et al.* Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *Journal of applied physiology (Bethesda, Md. : 1985)* 2004; **97**(6)**:** 2333-2338. e-pub ahead of print 2004/08/18; doi: 10.1152/japplphysiol.00744.2004

17. Cesari M, Fielding RA, Pahor M, Goodpaster B, Hellerstein M, van Kan GA *et al.* Biomarkers of sarcopenia in clinical trials-recommendations from the International Working Group on Sarcopenia. *Journal of cachexia, sarcopenia and muscle* 2012; **3**(3)**:** 181-190. e-pub ahead of print 2012/08/07; doi: 10.1007/s13539-012-0078-2

18. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT *et al.* Measurement of skeletal muscle radiation attenuation and basis of its biological variation. *Acta physiologica (Oxford, England)* 2014; **210**(3)**:** 489-497. e-pub ahead of print 2014/01/08; doi: 10.1111/apha.12224

19. Anderson DE, D'Agostino JM, Bruno AG, Demissie S, Kiel DP, Bouxsein ML. Variations of CT-based trunk muscle attenuation by age, sex, and specific muscle. *J. Gerontol. A Biol. Sci. Med. Sci.* 2013; **68**(3)**:** 317-323. e-pub ahead of print 2012/08/21; doi: 10.1093/gerona/gls168

20. Esfandiari N, Ghosh S, Prado CM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. *The Journal of frailty & aging* 2014; **3**(1)**:** 3-8. e-pub ahead of print 2014/01/01; doi: 10.14283/jfa.2014.1

21. Sjoblom B, Gronberg BH, Wentzel-Larsen T, Baracos VE, Hjermstad MJ, Aass N *et al.* Skeletal muscle radiodensity is prognostic for survival in patients with advanced non-small cell lung cancer. *Clin. Nutr.* 2016. e-pub ahead of print 2016/04/23; doi: 10.1016/j.clnu.2016.03.010

22. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am. J. Clin. Nutr.* 2010; **91**(4)**:** 1133s-1137s. e-pub ahead of print 2010/02/19; doi: 10.3945/ajcn.2010.28608C

23. Wieland BM, Stewart GD, Skipworth RJ, Sangster K, Fearon KC, Ross JA *et al.* Is there a human homologue to the murine proteolysis-inducing factor? *Clin. Cancer Res.* 2007; **13**(17)**:** 4984-4992. e-pub ahead of print 2007/09/06; doi: 10.1158/1078-0432.ccr-07-0946

24. Go SI, Park MJ, Song HN, Kang MH, Park HJ, Jeon KN *et al.* Sarcopenia and inflammation are independent predictors of survival in male patients newly diagnosed with small cell lung cancer. *Support. Care Cancer* 2016; **24**(5)**:** 2075-2084. e-pub ahead of print 2015/11/08; doi: 10.1007/s00520-015-2997-x

25. Kim EY, Kim YS, Park I, Ahn HK, Cho EK, Jeong YM *et al.* Evaluation of sarcopenia in small-cell lung cancer patients by routine chest CT. *Support. Care Cancer* 2016; **24**(11)**:** 4721-4726. e-pub ahead of print 2016/07/02; doi: 10.1007/s00520-016-3321-0

26. Helbekkmo N, Sundstrom SH, Aasebo U, Brunsvig PF, von Plessen C, Hjelde HH *et al.* Vinorelbine/carboplatin vs gemcitabine/carboplatin in advanced NSCLC shows similar efficacy, but different impact of toxicity. *Br. J. Cancer* 2007; **97**(3)**:** 283-289. e-pub ahead of print 2007/06/28; doi: 10.1038/sj.bjc.6603869

27. Gronberg BH, Bremnes RM, Flotten O, Amundsen T, Brunsvig PF, Hjelde HH *et al.* Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. *J. Clin. Oncol.* 2009; **27**(19)**:** 3217-3224. e-pub ahead of print 2009/05/13; doi: 10.1200/jco.2008.20.9114

28. Flotten O, Gronberg BH, Bremnes R, Amundsen T, Sundstrom S, Rolke H *et al.* Vinorelbine and gemcitabine vs vinorelbine and carboplatin as first-line treatment of advanced NSCLC. A phase III randomised controlled trial by the Norwegian Lung Cancer Study Group. *Br. J. Cancer* 2012; **107**(3)**:** 442-447. e-pub ahead of print 2012/07/05; doi: 10.1038/bjc.2012.284

29. Shen W, Chen J, Gantz M, Velasquez G, Punyanitya M, Heymsfield SB. A single MRI slice does not accurately predict visceral and subcutaneous adipose tissue changes during weight loss. *Obesity* 2012; **20**:2458-2463

Legends

Figure 1 Patient selection

Figure 2 Scatterplot illustrating the agreement between measures at the Th4 and L3 for muscle area (cm^2), skeletal muscle index (SMI) (cm^2/m^2) and skeletal muscle radiodensity, for men and women separately. A line for perfect agreement has been added to all plots.

Figure 3 A) Bland Altman plot for the agreement between Th4 SMI and L3 SMI z scores (with loess curves for each gender). B) Bland Altman plot for the agreement between Th4 SMD and L3 SMD z scores (with loess curves for each gender). C) Scatter plot showing actual L3 SMI values and L3 SMI values recomputed from Th4 SMI-scores (by z-scores) (linear fit line for overall sample with 95% CI and loess curves for each gender). D) Scatter plot showing actual L3 SMD values and L3 SMD values recomputed from Th4 SMI-scores (by z-scores) (linear fit line for overall sample with 95% CI and loess curves for each gender).

Table 1 Baseline characteristics

Table 2 Body composition measures at the Th4 and L3 levels

Table 1 Baseline characteristics

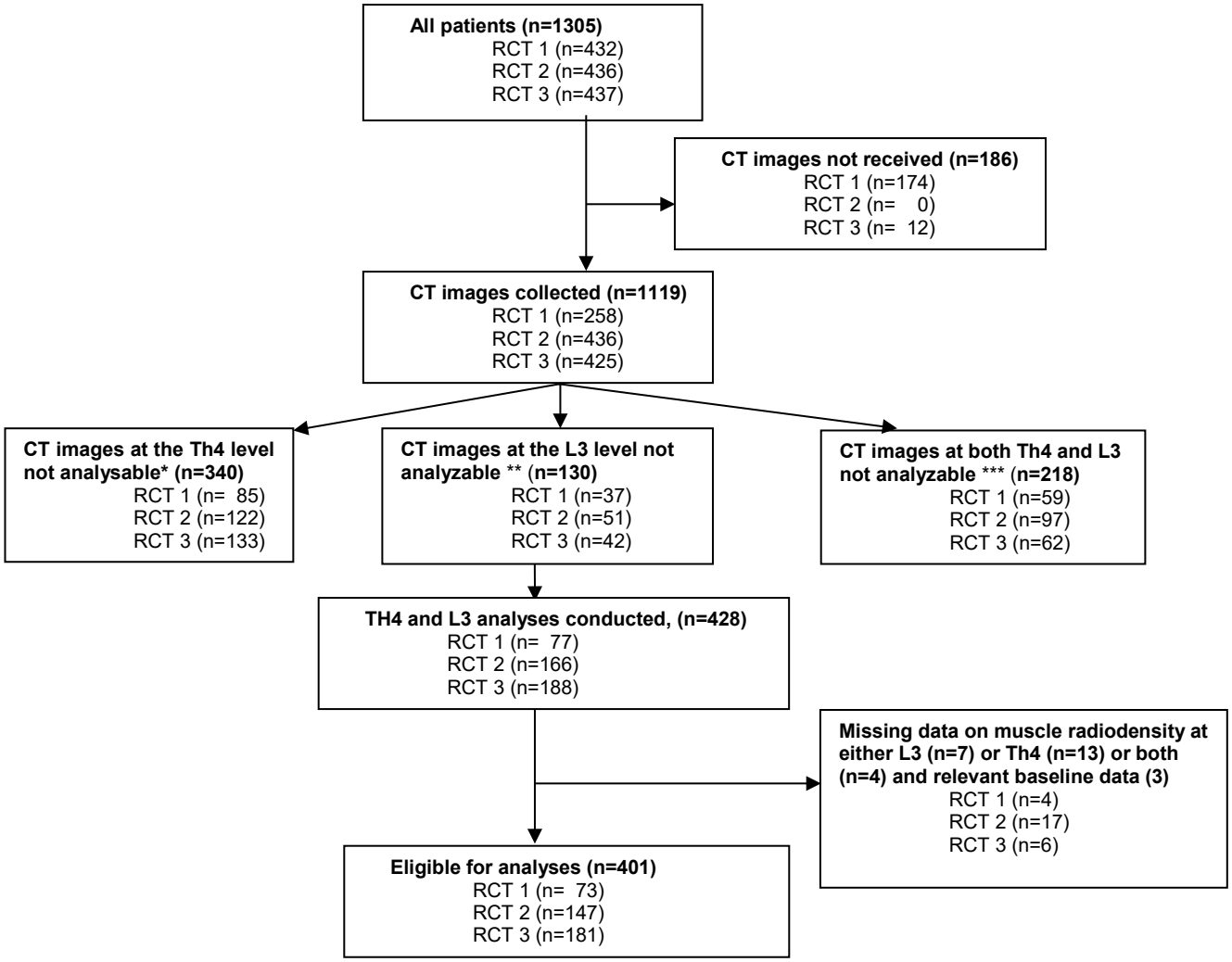
		All patients (n=401)		Men (n=220)		Women (n=181)	
Age	Mean (range)	66 (37-90)		68 (37-90)		64 (37-85)	
	≥ 75 years	79	19.7%	48	21.8%	31	21.0%
Histology	Squamous cell carcinoma	92	22.9%	64	29.1%	28	15.5%
	Adenocarcinoma	217	54.1%	104	47.3%	113	62.4%
	Other	92	21.0%	52	23.7%	40	22.1%
Disease stage	IIIB	85	22.9%	47	21.4%	38	21.0%
	IV	316	78.8%	173	78.6%	143	79.0%
Performance status	0	80	20.0%	46	20.9%	34	18.8%
	1	232	57.9%	122	55.5%	110	60.8%
	2	89	22.2%	52	23.6%	37	20.4%
Body weight, kg, mean (SD)		69.0 (13.8)		73.7 (11.9)		65.1 (13.1)	
Body Mass Index, kg/m^2, mean (SD)		23.9 (3.9)		23.8 (3.4)		23.9 (4.5)	
Appetite loss	Yes	211	52.6%	113	51.4%	98	54.1%
	No	190	47.4%	107	48.6%	83	45.9%

Table 2 Body composition measures at the Th4 and L3 levels

	Measures at the Th4 level							Measures at the L3 level						
	All (n=401)		Men (n=220)		Women (n=181)		p*	All (n=401)		Men (n=220)		Women (n=181)		p*
	Mean	SD	Mean	SD	Mean	SD		Mean	SD	Mean	SD	Mean	SD	
Measured muscle area, cm2	176.4	39.6	200.7	31.7	147.0	25.8	< 0.001	130.6	29.2	149.0	23.4	108.2	17.5	< 0.001
Skeletal muscle index (SMI), cm2/m2	60.1	10.9	65.0	10.1	54.1	8.8	< 0.001	44.5	8.1	48.3	7.7	39.8	6.0	< 0.001
Skeletal muscle radiodensity (SMD), HU	41.5	6.9	42.0	6.8	40.8	6.9	0.107	36.9	8.4	37.2	7.9	36.5	9.0	0.357

**p-value for the comparison between men and women*

Figure 1 Patient selection



*Whole cross sectional area not included; or too poor image quality
**Lack of images at the L3-level; whole cross sectional area not included in the images; or image-quality too poor
*** Either of the above

Figure 2 **Scatterplots illustrating the agreement between measures at the TH4 and L3 for muscle area (cm^2), skeletal muscle index (SMI) (cm^2/m^2) and skeletal muscle radiodensity, for men and women separately. A line for perfect agreement has been added to all plots.**

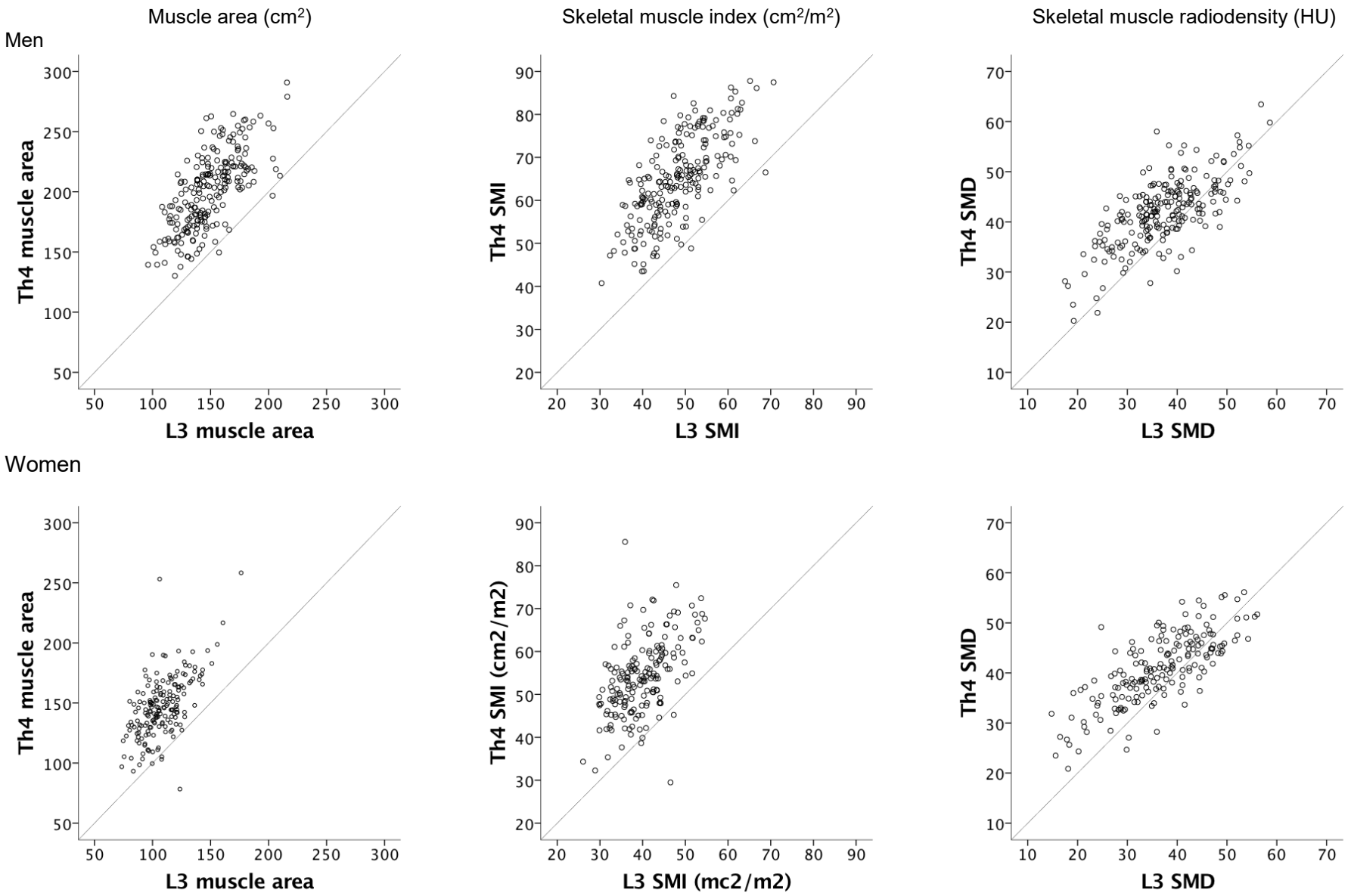


Figure 3 **A) Bland Altman plot for the agreement between Th4 SMI and L3 SMI z-scores (with loess curves for each gender). B) Bland Altman plot for the agreement between Th4 SMD and L3 SMD z-scores (with loess curves for each gender). C) Scatter plot showing actual L3 SMI values and L3 SMI values recomputed from Th4 SMI-scores (by z-scores) (linear fit line for overall sample with 95% CI and loess curves for each gender) D) Scatter plot showing actual L3 SMD values and L3 SMD values recomputed from Th4 SMI-scores (by z-scores) (linear fit line for overall sample with 95% CI and loess curves for each gender).**