Combining Sarcopenia and [^{18}F] FDGPET/CT Derived Metabolic Parameters in Patients with Adenocarcinoma Esophageal Cancer Might Improve Outcome Prediction

Reut Anconina (anconinar@gmail.com)
University of Toronto Faculty of Medicine
Claudia Ortega
: University of Toronto Department of Medical Imaging
Ur Metser
: University of Toronto Department of Medical Imaging
Zhihui Amy Liu
Princess Margaret Hospital
Chihiro Suzuki
University of Toronto
Micheal McInnis
University of Toronto Department of Medical Imaging
Gail Elizabeth Darling
Toronto General Hospital
Rebecca Wong
Princess Margaret Hospital: Princess Margaret Hospital Cancer Centre
Kirsty Taylor
Princess Margaret Hospital Department of Medical Oncology and Hematology
Jonathan Yeung
Toronto General Hospital
Eric Xueyu Chen
Princess Margaret Hospital Department of Medical Oncology and Hematology
Carol Jane Swallow
Princess Margaret Hospital: Princess Margaret Hospital Cancer Centre
Jaspreet Bajwa
University of Toronto
Raymond Woo-Jun Jang
Princess Margaret Hospital Department of Medical Oncology and Hematology
Elena Elimova
Princess Margaret Hospital Department of Medical Oncology and Hematology

Patrick Veit-Haibach
University of Toronto Department of Medical Imaging

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Abstract

Purpose

To determine the prognostic value of sarcopenia measurements done on staging [^{18}F] FDG PET/CT together with metabolic activity of the tumor in patients with adenocarcinoma esophagogastric cancer with surgical treatment.

Methods

Patients with early stage, surgically treated esophageal adenocarcinoma and available pre-treatment PET/CT were included. The standard uptake value (SUV) and SUV normalized by lean body mass (SUL) were recorded. Skeletal muscle index (SMI) was measured at the L3 level on the CT component of the PET/CT. Sarcopenia was defined as SMI < 34.4cm^2/m^2 in women and < 45.4cm^2/m^2 in men.

Results

Of the included 145 patients. 30% were sarcopenic at baseline. On the univariable Cox proportional hazards analysis, ECOG, surgical T and N staging, Lymphovascular Invasion (LVI) positive lymph nodes and sarcopenia were significant prognostic factors concerning RFS, and OS. On multivariable Cox regression analysis, surgical N staging ($p = 0.025$) and sarcopenia ($p = 0.022$) remained significant poor prognostic factors for OS and RFS. Combining the clinical parameters with the imaging derived nutritional evaluation of the patient but not metabolic parameters of the tumor showed improved predictive ability for OS and RFS.

Conclusion

Combining the patients' imaging derived sarcopenic status with standard clinical data, but not metabolic parameters offered an overall improved prognostic value concerning OS and RFS.

Introduction

Esophagogastric cancer is one of the leading causes of cancer deaths worldwide [1]. Above 50% of patients are diagnosed with advanced stage at presentation, precluding curative treatment. For patients with early stage disease, surgery, often combined with neoadjuvant chemotherapy or chemoradiotherapy, offers the best curative option [2].

Many of the patients diagnosed with esophagogastric cancer are often malnourished due to disease related symptoms of obstruction, nausea and dysphagia. Sarcopenia, which is defined as the severe depletion of skeletal muscle mass and strength, is a marker of poor nutrition and cachexia [3]. It was

originally described in the geriatric population. However, more recently it is also recognised to be a prognostic factor in various tumor entities and found to be a risk factor for reduced disease-free and overall survival [4-9]. Of the available methods to assess sarcopenia, measurements of skeletal muscle area using computed tomography is found to be one of the most accurate and reproducible methods [10-12]

Positron emission tomography/computed tomography (PET/CT) has gained a central role in the staging pathway of various malignancies including esophagogastric cancers [13], allowing for assessment of the skeletal muscle area and diagnosing sarcopenia at the same as quantification of metabolical properties of the primary tumour. The metabolical information from [^{18}F] FDG PET/CT is also known already for several years to provide important diagnostic as well as prognostic information in patients with esophagogastric cancers [14- 17].

Previous studies had shown sarcopenia to be a risk factor for falls, various diseases and death in the geriatric population [3]. In the oncological population sarcopenia was found to be associated with decreased overall survival and disease-free survival [9], increased perioperative complications [18], and increased chemotherapy toxicity [19-21]. There is conflicting data regarding the relationship between sarcopenia and survival and treatment complications of patient with esophagogastric cancer [22-27]. Also there is a certain body of literature available concerning geriatric populations and in patients with metastasized/palliative situations [28]. However, there is little information available in specific curative surgical cohorts.

The aim of our study was to determine the prognostic value of sarcopenia measured on the staging [^{18}F] FDG PET/CT together with metabolical activity of the primary tumor in patients with esophagogastric adenocarcinoma in patients with early stage disease and initially surgical therapy.

Materials And Methods

Study cohort

The data presented in this study was evaluated retrospectively. Approval by the institutional research ethics board was obtained, which waived the requirement for informed consent (REB# 19-5575).

Patients referred for primary staging for esophageal or gastroesophageal adenocarcinoma and clinically scheduled for curative treatment intent treated at our institution from 2012- 2019 were identified from an institutional registry. Patients with available [^{18}F] FDG PET/CT as part of their disease staging as well as documented measures of height and weight were included.

Clinical and pathology data were obtained from above mentioned institutional database including patiens demographic data and tumor characteristics, treatment and follow up data, such as ECOG status at clinical presentation, history of smoking and alcohol use as well as clinical and pathological staging (according to the 7th edition of the AJCC).

Image analysis and Sarcopenia measurements

PET/CT imaging were preformed according to our institutional protocol as previously published [29]. Iodinated oral contrast material was administered for bowel opacification; no intravenous iodinated contrast was administered. CT was performed from the skull base to the upper thighs. The mean, max and peak standard uptake value (SUV) and SUV normalized by lean body mass (SUL) were recorded for the primary tumour. SUVmax was evaluated with a hand drawn VOI covering the entire tumours volume as defined by PET on multiple cross sectional slices encompassing the entire tumour. The SUVmean was evaluated in a similar way and was derived from the whole-tumour VOI. The SUVpeak was measured as previously defined in a 1 cm^3 spherical VOI centered on the slice with the highest SUVmax (Mirada XD Workstation, Mirada Medical)

Sarcopenia measurements were calculated from the CT component of the PET/CT. The total skeletal muscle area in cm2 was calculated at the lumbar L3 level using Slice-O-Matic software (Version 5.0; TomoVision). Hounsfield units (HU) were used to identify skeletal muscle (threshold -29 to 150 HU) (Figure 1). Skeletal Muscle Index (SMI) was calculated by normalising the muscle area (cm2) for the subject height in meters squared (m2). SMI cut-offs for sarcopenia were 34.4cm2/m2 in females and 45.4cm2/m2 in males based on previously established consensus (Figure 1) [10].

Statistical analysis

Summary statistics were used to describe patient, disease and treatment characteristics. Kaplan Meier (KM) method was used to estimate median overall survival (OS) and relapse free survival (RFS) and their 95% confidence intervals (CI). Univariable Cox proportional hazards models were used to identify potential predictors of death and relapse. Clinical factors with < 5% missing data and a p-value < 0.05 in the univariable analyses (UVA) were selected to build a multivariable Cox model. We also chose to include one PET feature in the multivariable model to represent standard imaging biomarkers. Six PET indices (SUVmax, SUVmean, SUVpeak, SULmax, SULmean, SULpeak) were assessed; since they were highly correlated with each other, only one (SUVmax) was added to the clinical model. Lastly sarcopenia was added to the model with clinical factors and SUVmax. Time-dependent ROC curve analysis was carried out and the resulting area under the ROC curve (AUC) was presented as a function of prediction interval length to assess the prognostic value of sarcopenia over time [30, 31]. The statistics were calculated using leave-one-out cross validation. All analyses were carried out in R (version 4.0.2) and a p-value $\leq$ 0.05 was considered as statistically significant [32].

Results

Baseline characteristics of patients and tumors

Overall 145 patients with adenocarcinoma of the esophagus or esophago-gastric junction were included. All patients underwent surgery as part of the initial treatment either upfront or after neoadjuvant chemotherapy. All patients underwent a baseline [^{18}F] FDG PET/CT for staging. Baseline characteristics

and treatment information are shown in Table 1. There were 117 (81%) men and 28 (19 %) women with a mean age of 64.1 years (range: 28.9-83.8). The majority of patients had ECOG score of 0 or 1 (35 % and 59 % respectively), 6 % of the patients had ECOG score of 2 or above and one case had a missing ECOG score. 70 % of the patients received neoadjuvant therapy. The majority of patients had T3 tumor (58 %). Overall, 43/ 145 (30 %) patients had a low SMI reaching the cut off for sarcopenia indicating lower skeletal muscle mass and poor nutritional state.

Treatment outcomes

Median (95% confidence interval) of recurrence free survival (RFS) and overall survival (OS) for the entire cohort was 21.2 (95% CI 16.9 – 29.1) months and 33.9 (95% CI 29.1 – 45.6) months respectively.

On univariable analysis (UVA) using Cox proportional hazards models, the surgical T and N staging, Lymphovascular Invasion (LVI), number of positive lymph nodes and sarcopenia were significant prognostic factors for worse RFS, and OS. ECOG was also a prognostic factor for worse RFS, for OS it was borderline significant with P-value of 0.053 (Table 2a). The metabolic parameters measured on PET however were not significant prognostic factor on the UVA. Table 2b shows the high correlation between the metabolic parameters.

On multivariable analysis (MVA), surgical N staging (0.025) and sarcopenia (p=0.022) remained significant as poor prognostic factors for both OS and RFS (Table 3). The SUVmax was included as indicated and explained above was again not a significant prognostic factors for OS and RFS on the MVA as well.

We then built a clinical model using the ECOG, surgical T and N staging to predict the OS and the RFS. LVI was not used in the MVA because 8% of the patients had missing values. Number of positive lymph nodes was correlated with N stage, and thus was not included in the MVA. To this clinical model we added the SUVmax as our representative metabolic parameter. Overall, model containing the SUVmax did not perform better compared to the clinical model alone for OS with AUC of 0.71, 0.75 and 0.71 for the clinical model alone compare to 0.72, 0.75 and 0.72 for the clinical model and SUVmax at 12, 24 and 36 months follow up, respectively. Similar findings were found for the RFS with AUC of 0.75, 0.77 and 0.72 for the clinical model alone compare to 0.75, 0.77 and 0.73 for the clinical model and SUVmax at 12, 24 and 36 months follow up, respectively.

Lastly, we added the sarcopenic status of the patient determent by the SMI score. The fully combined model (clinical parameters, metabolic parameters and sarcopenic status) was able to better predicate the OS and RFS especially in the first year of follow up for follow-up. OS AUC of 0.69, 0.77 and 0.78 for the full model compare to 0.58, 0.71 and 0.75 for the clinical model alone at 6, 12 and 33 months follow up, respectively (Figure 2). RFS AUC of AUC of 0.81, 0.78 and 0.79 for the full model compare to 0.67, 0.71 and 0.74 for the clinical model alone at 6, 12 and 33 months follow up, respectively (Figure 3).

Discussion

In the current study we evaluated the prognostic significance of sarcopenia, a marker for poor nutrition, together with standard metabolic activity parameters in patients with esophagogastric adenocarcinoma with early stage disease and undergoing initially surgical therapy. We found that low SMI, calculated from CT component of a baseline PET/CT, was significant prognostic marker for worse OS and RFS. Furthermore, we showed that combining the nutrition status of the patient at time of diagnosis with clinical parameters and pathological parameters but not standard metabolic measurement of the tumor on staging PET/CT might improve prediction of the OS and RFS of the patient.

Recently there has been an increasing interest in assessing additional but readily available quantitative biomarker data from routine, standard of care imaging for i.e. quantifying aortic calcification, fat quantification for liver steatosis, breast density assessment or sarcopenia [11, 33-37].Sarcopenia is a term describing the loss of skeletal muscle mass and strength and it was first described in elderly patient populations [38] and is associated with cardiac and respiratory diseases, increases risk of falls, mobility disorders, cognitive impairment and death[3]. Imaging assessment of sarcopenia using DXA, CT or MRI has been previously investigated in cancer patients. It has been found to correlate with poor prognosis in various types of cancers and including meta-analysis of 38 studies of patients with solid tumors such as pancreatic cancer, pulmonary tumours, HCC, colorectal and esophageal- gastric tumors [9]. In another recent meta- analysis sarcopenia was associated with increased risk for postsurgical complication in patients with gastrointestinal oncology including pancreatic, liver, colorectal, gastric and esophageal tumors [39]. This lead to the notion that improving the sarcopenic status of the patient before treatment may lead to improved outcome.

PET/CT is performed routinely for the staging of many malignancies including esophagogastric cancer. The main role of PET/CT of staging of esophagogastric cancer is to define the tumour stage, the evaluation of the metabolic activity of the primary tumour, evaluation of lymph nodes involvement and detection of distant metastases and consequently allowing for patients to be directed to the correct therapeutic pathway. It is therefore the standard of care imaging test in many jurisdictions for this disease and is embedded in several international oncological guidelines for staging and follow up. Overall, the assessment of disease stage was shown to be performed with high accuracy [14]. In our study we used the routine and clinically standard PET/CT scans for staging purposes as well as for simultaneous measurement of the SMI for each patient, allowing for staging, assessment of the metabolic properties of the primary tumour in conjunction with an additional nutritional biomarker in one step. Such combination of different imaging derived parameters can provide additional insight on the patient prognosis with no additional clinical appointment, cost or radiation exposure.

The impact of sarcopenia in esophagogastric cancer was the subject of few previous studies with conflicting results in different patient populations. In a cohort of 120 patients with advanced esophageal cancer who were treated with esophagectomy after neoadjuvant chemoradiotherapy, Grotenhuis et al. reported that presence of sarcopenia evaluated on pre-treatment CT was not related to negative short- and long-term outcome [26]. Similar findings were found by Siegal et al. in a cohort of 173 cases undergoing esophagectomy, and by Saeki et al. in patients with locally advanced esophageal cancer [27,

40]. All three studies used similar method to ours for calculation of the muscle mass using the cross-sectional CT at the level of the third lumbar spine, however they used different cut-offs of SMI than ours to determine sarcopenia. The topic of different threshold used for the definition of sarcopenia is actually an on going discussion within the literature. Some publications in the beginning have even used self-developed software for these measurements. Recent publications however usually used validated commercial software which is at least partly mitigating the problem of having different evaluation approaches. Also, the cut-off which was used in our study is one of the most used cut-offs within the literature.

Another difference between those studies and ours was the included cohort – the first two studies included all types of esophageal cancer and the third study included only patient with SCC, while our cohort looked at patient with esophagogastric adenocarcinoma with early stage disease and having curatively intended surgical treatment upfront or after neoadjuvant chemotherapy.

There are however several studies which found that sarcopenia is actually a poor prognostic factor in patients with early esophagogastric cancer receiving definitive treatment. Tamandl et al as well as Kudou at el both found that sarcopenia on CT at the time of diagnosis correlated with poorer survival in esophageal cancer patients treated with esophagectomy [22, 23]. The latter study looked only on patients with esophagogastric adenocarcinoma, well comparable to our study. Pairedere at al found similar finding in a cohort of patients treated with esophageal resection following neoadjuvant chemoradation [24]. In a different clinical setting, Sato et al evaluated a cohort of patients with unresectable locally advanced esophageal cancer receiving chemoradiotherapy. Sarcopenia was found again to be a poor prognostic factor in this group, contradictory to some of the above mentioned studies [25]. Harada et al found that sarcopenia significantly reduced the overall survival of patients with esophageal squamous cell carcinoma without lymph node involvement treated by surgical resection or definitive chemoradiation [41]. Our study had similar results to the latter publications which reinforces the trend that the nutritional status, manifested as the patient SMI, can have a degrading influence on the patient prognosis and clinical performance.

There are only very few studies using staging PET/CT for measuring sarcopenia. Zhou et al, found that low attenuation and SUV of the psoas muscle on staging PET/CT represent sarcopenia in patients with esophageal cancer and were correlated with worse prognosis [42]. However, based on the currently available literature, it is discussable if such measurement truly represents sarcopenia. Another study used the staging PET/CT for assessment of sarcopenia and found it to be a prognostic factor for worse survival in patients with locally advanced esophageal cancer treated with chemoradiation [43]. The concept of having several, imaging derived prognostic factors simultaneously available in one exam is obviously appealing from a logistical point of view for the patient as well as the treating physician. However, we showed that combining the sarcopenic status of the patient, but not the metabolic activity of the tumor to the clinical and pathological information better predict the patient OS and RFS than any of those parameters alone. To our knowledge this was never addressed or published before and is partly not reflected by the available literature. The improved outcome prediction is predominantly evident in the first

6-12 month after treatment. There are several publications over the years and even recently demonstrated the value of PET/CT and the value of different metabolical parameter concerning staging and prognosis in patient with esophageal cancer. It has been shown that the measurement of SUV-derived parameters may be reflective of the immune status of the primary esophageal tumors, that PET/CT can partly predict pathological response (and thereby prognosis) prior to neoadjuvant chemoradiation and that metabolic PET/CT can predict short-term curative effects in esophageal cancer. Furthermore, an association of SUV with survival after surgery in very early stage esophageal cancer was demonstrated. Thus, since the value of PET/CT and SUV-parameters for staging and prognosis is known from the literature and since sarcopenia measurements were shown to be predictive of several outcome parameters (and all of those parameters are available in one exam), a further improvement in prognostication by combining these complementary parameters was the goal of this study. However, while PET/CT is still obviously the mainstay in staging these patients, when combining the SUV's, the clinical data and sarcopenia, only two latter proved to be predictive for the given endpoints. For future evaluations, further in-depth imaging evaluation of minable imaging parameters (radiomics) combined with sarcopenia information might even further improve the predictive value of those methods.

The limitations of our study include the retrospective design and a relatively small patient population. However, we evaluated a very specific group of patients with early disease which had local disease eligible for surgery. No larger group of patients with distant metastatic disease were evaluated. We did not assess SMI on post treatment images, nor did we combine the clinical parameters, the SUV's and SMI from the post-treatment imaging. One of the reasons for that is that in our current environment it is only funded for staging and post-neoadjuvant therapy. The evaluated metabolic parameters were not statistically significant on the univariate and multivariate analysis. Since there are partly conflicting results on this available in the literature, this might be due to statistical underpower. However, since the main focus of the study was to show a possible advantage of evaluating sarcopenia alongside metabolic measurements, both were used in the multivariate analysis. Furthermore, due to its retrospective design of the study there was no attempt to intervene and modify the sarcopenia status of the patient before or during treatment.

Conclusion

This study demonstrates that sarcopenia is a poor prognostic factor in a cohort of esophageal adenocarcinoma patients treated with surgery. Combining the patient sarcopenic status measured on clinical PET/CT with standard clinical data, but not with metabolic activity measurements from the primary tumor offered an overall improved prognostic value concerning OS and RFS especially early on after treatment.

Declarations

Funding – We had no external funding for this work**.**

Conflicts of interest/Competing interests- We have nothing to disclose**.**

Ethics approval - This study was approved by the institutional research ethics board (REB# 19-5575).

Consent to participate - Informed consent requirement was waived by the institutional research ethics board as this is a retrospective study not influencing patient treatment or outcome.

Consent for publication- Not applicable

Availability of data and material – all the study data and material is stored according to the Storage, Transport & Destruction of Confidential Information policy of the institutional research ethics board

Code availability - Not applicable

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Tables

Table 1. Baseline clinicopathologic characteristics. $^{+}$BMI- Body Mass Index ^Surgical staging *LVI- Lymphovascular Invasion

Characteristic	N = 145 (%)
Age, median (range), years	64.1 (28.9-83.8)
Male	117 (81%)
Asian	6 (4%)
BMI[+], mean (range)	27.7 (15.5-52.5)
ECOG performance status	
0	51 (35%)
1	85 (59%)
≥2	8 (6%)
Unknown	1
T stage^	
T0	6 (4 %)
T1	19 (13 %)
T2	18 (12 %)
T3	84 (58 %)
T4	5 (3 %)
Tx	13 (9 %)
N stage^	
N0	62 (43%)
N1	31 (21%)
N2	30 (21%)
N3	19 (13%)
Nx	3 (2%)
LVI*	
Yes	72 (54 %)
No	61 (46 %)
Missing	12
Treatment	
Upfront surgery	44 (30%)

Received neoadjuvant therapy	101 (70%)
Number of positive LNs, mean (range)	3.5 (0-38)
Sarcopenia	
Yes	43 (30%)
No	100 (70 %)
Missing	2

Table 2a. Univariable Cox regression analysis for overall survival and relapse free survival. [+]BMI- Body Mass Index ^Surgical staging *LVI- Lymphovascular Invasion

Covariate	OS		RFS	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1.02 (1,1.04)	0.093	1 (0.98,1.02)	0.74
Sex (male)	1.22 (0.68,2.18)	0.5	1.15 (0.7,1.91)	0.58
Race (non-Asian)	1.47 (0.46,4.66)	0.52	1.2 (0.44,3.27)	0.72
BMI+	0.99 (0.96,1.03)	0.74	0.98 (0.95,1.02)	0.3
ECOG		0.053		**0.018**
0	Reference		Reference	
1-3	1.61 (0.99,2.61)		1.69 (1.09,2.62)	
T staging^		**0.0073**		**0.0064**
T0	Reference		Reference	
T1	0.66 (0.17,2.57)	0.55	0.63 (0.16,2.45)	0.51
T2	0.61 (0.16,2.32)	0.47	0.88 (0.24,3.21)	0.84
T3	1.17 (0.36,3.76)	0.79	1.76 (0.55,5.62)	0.34
T4	4.45 (1.06,18.79)	**0.042**	4.32 (1.03,18.2)	**0.046**
TX	0.6 (0.15,2.42)	0.47	1.09 (0.29,4.03)	0.9
N staging^		**0.001**		**0.001**
N0	Reference		Reference	
N1	1.5 (0.79,2.85)	0.22	1.6 (0.91,2.79)	0.1
N2	3.37 (1.87,6.06)	**0.001**	2.87 (1.67,4.91)	**0.001**
N3	2.68 (1.39,5.17)	**0.0032**	4.16 (2.32,7.47)	**0.001**
NX	2.21 (0.51,9.52)	0.29	2.19 (0.52,9.21)	0.28
LVI*	2.53 (1.56,4.11)	**0.001**	2.72 (1.76,4.18)	**0.001**
Number of positive LNs	1.08 (1.05,1.12)	**0.001**	1.09 (1.06,1.12)	**0.001**
SUVmax	0.99 (0.96,1.02)	0.51	0.99 (0.96,1.01)	0.33
Sarcopenia	1.93 (1.19,3.11)	**0.0073**	1.86 (1.21,2.85)	**0.0044**

Table 2b. Pairwise Pearson's correlation coefficient of SUV/SUL features.

	SUVmax	SUVmean	SUVpeak	SULmax	SULmean	SULpeak
SUVmax	1.00	0.93	0.96	0.96	0.89	0.95
SUVmean	0.93	1.00	0.91	0.91	0.96	0.91
SUVpeak	0.96	0.91	1.00	0.94	0.88	0.94
SULmax	0.96	0.91	0.94	1.00	0.94	0.98
SULmean	0.89	0.96	0.88	0.94	1.00	0.93
SULpeak	0.95	0.91	0.94	0.98	0.93	1.00

Table 3. Multivariable Cox regression analysis for overall survival and relapse free survival. ^Surgical staging

Covariate		OS		RFS	
		Adjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
ECOG	0	reference		reference	
	1-3	1.26 (0.72,2.21)	0.41	1.22 (0.74,2.01)	0.44
T staging^			0.067		0.11
	T0	reference		reference	
	T1	0.63 (0.16,2.55)	0.52	0.56 (0.14,2.22)	0.41
	T2	0.67 (0.17,2.56)	0.55	0.8 (0.22,2.97)	0.74
	T3	0.7 (0.21,2.38)	0.57	1.05 (0.32,3.47)	0.93
	T4a	3.13 (0.69,14.25)	0.14	3.47 (0.77,15.62)	0.11
	TX	0.44 (0.1,2.06)	0.3	0.88 (0.22,3.53)	0.85
N staging^			**0.025**		**0.0021**
	N0	reference		reference	
	N1	1.58 (0.79,3.18)	0.2	1.59 (0.87,2.91)	0.13
	N2	2.87 (1.43,5.77)	**0.003**	2.17 (1.16,4.04)	**0.015**
	N3	2.31 (1.09,4.92)	**0.03**	3.69 (1.92,7.08)	**0.001**
	NX	3.46 (0.59,20.48)	0.17	2.3 (0.45,11.78)	0.32
SUVmax		1 (0.96,1.03)	0.89	0.99 (0.96,1.02)	0.66
Sarcopenia		1.85 (1.09,3.12)	**0.022**	1.83 (1.15,2.91)	**0.011**

Figures

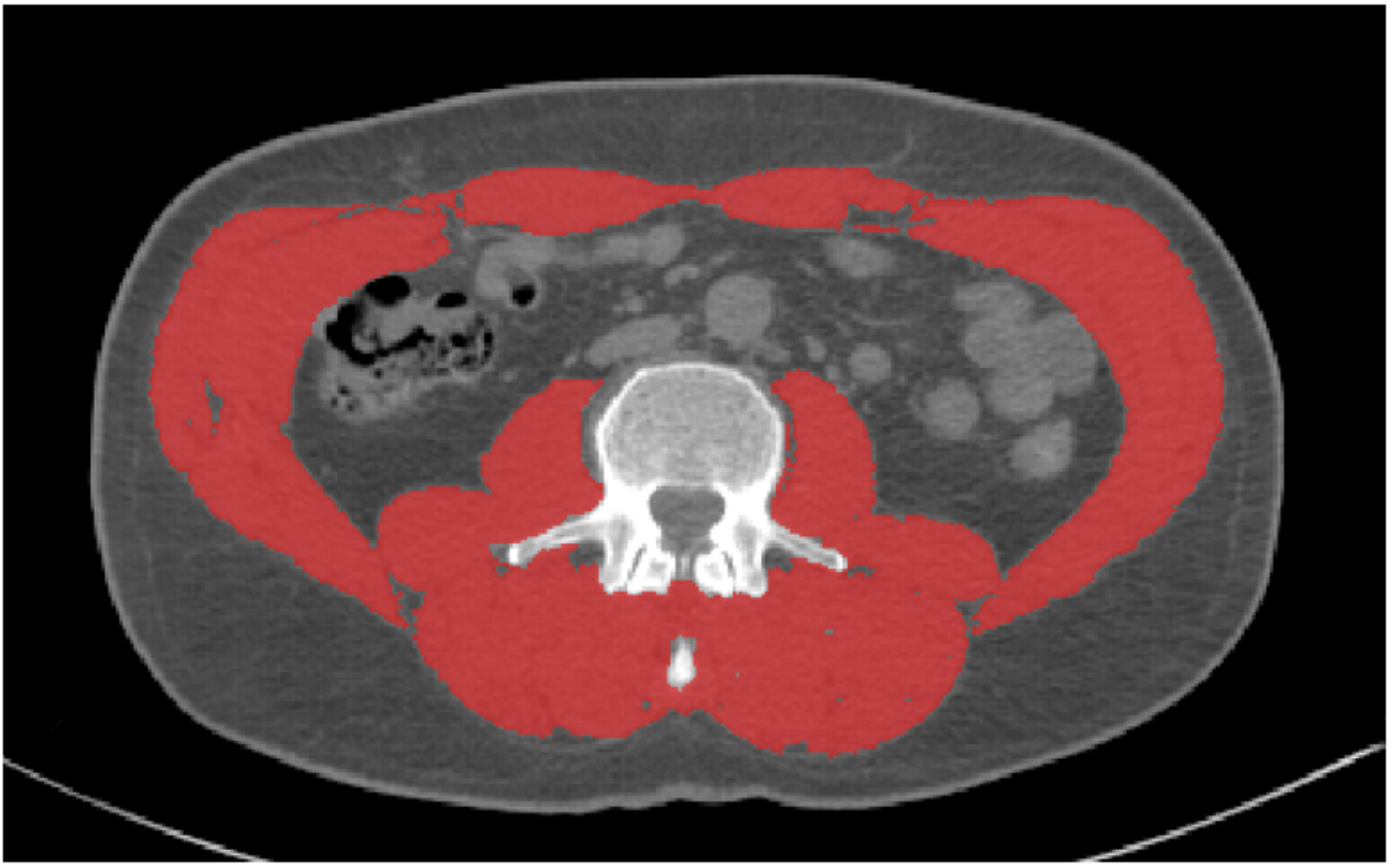

Figure 1

Example of seletal muscle measured (threshold -29 to 150 HU) on a cross sectional image at the level of L3 and outline in red

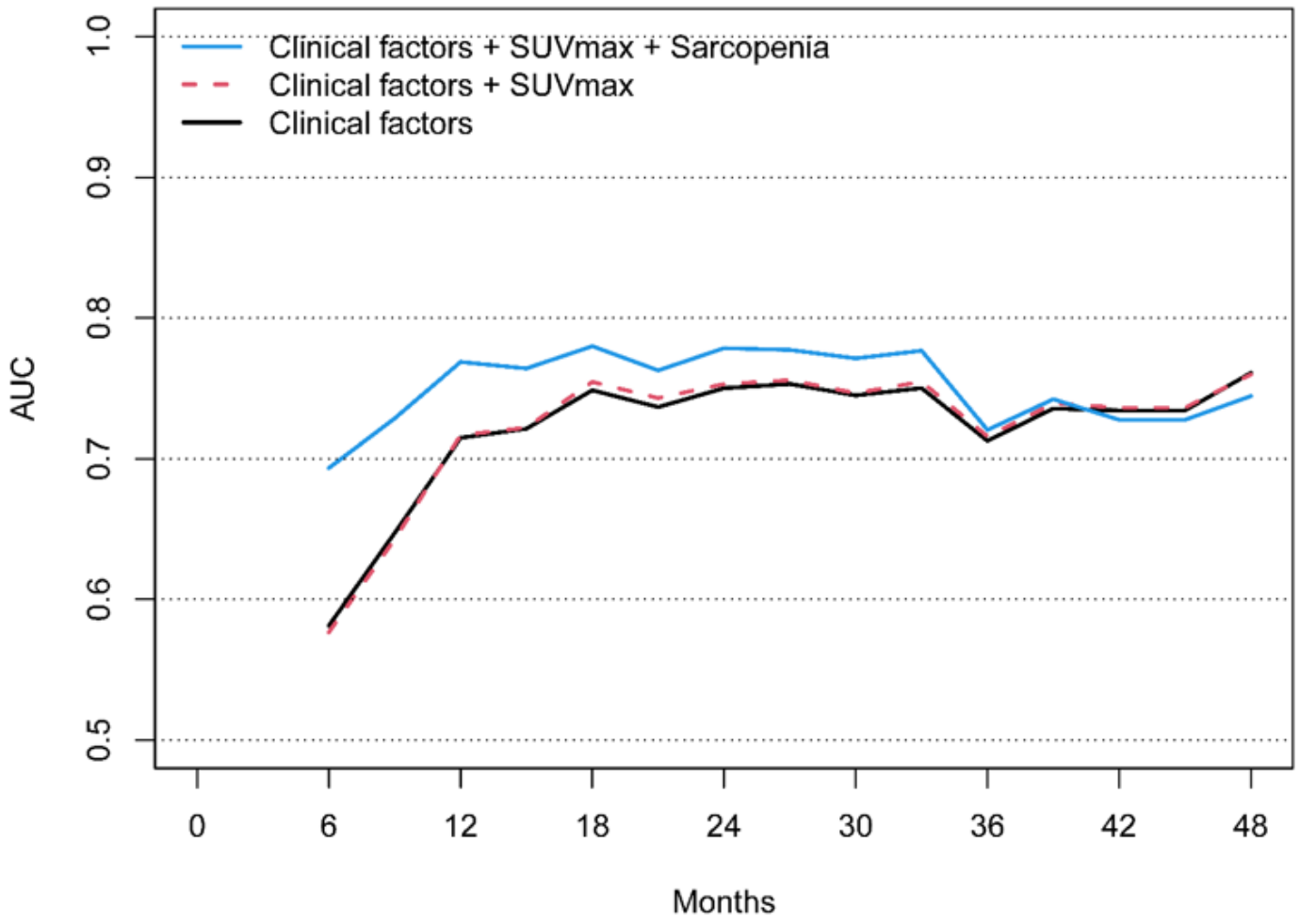

Figure 2

Time-dependent AUC for OS Clinical features - ECOG, surgical T and N staging

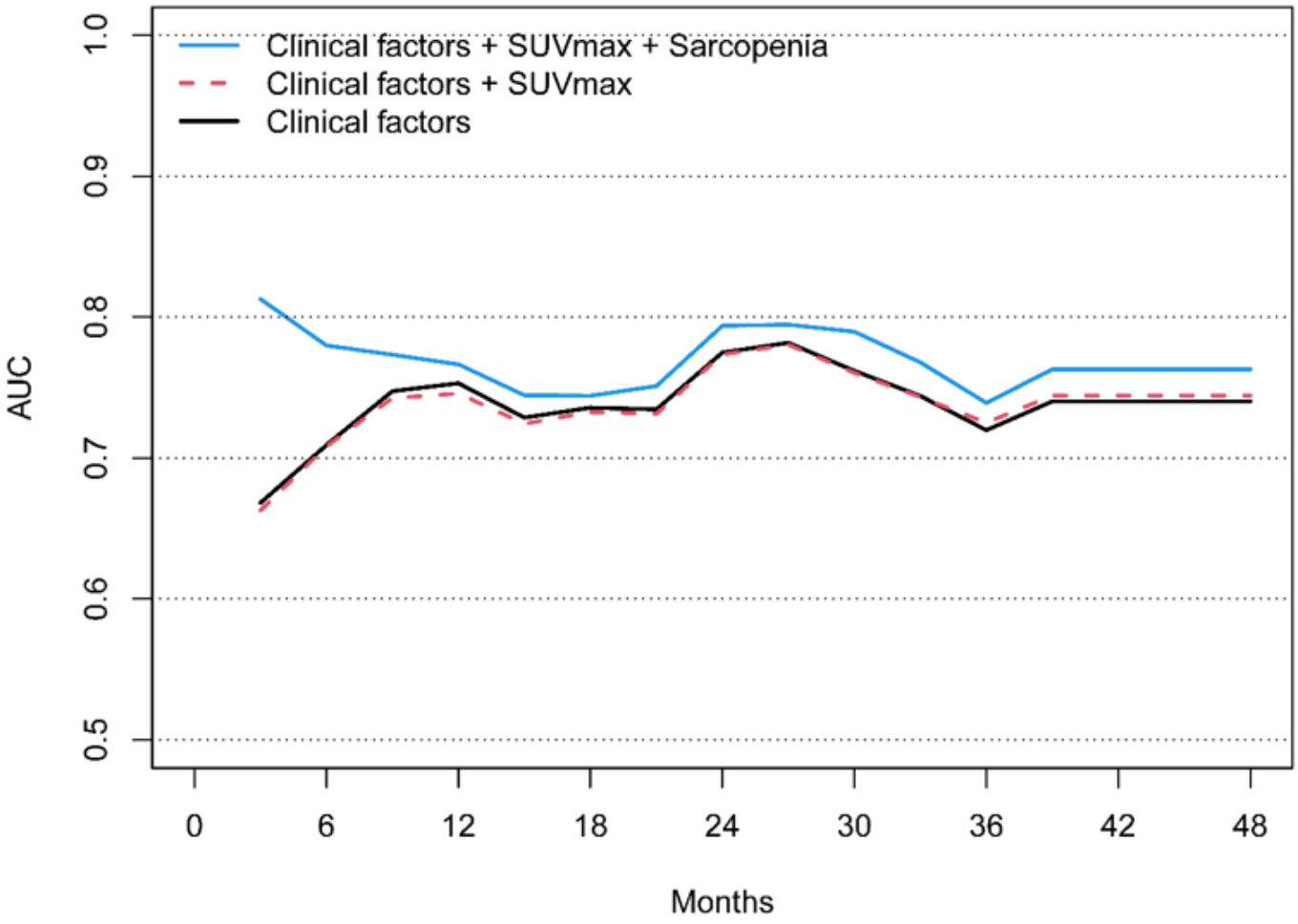

Figure 3

Time-dependent AUC for RFS Clinical features - ECOG, surgical T and N staging