Fat density is a novel prognostic marker in patients with esophageal cancer

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SUMMARY

Background & aims: While long-term obesity is a well-known risk factor for esophageal adenocarcinoma (ADC), recent weight loss represents a significant concern in esophageal cancer (EC), in relation with dysphagia and disease aggressiveness. These phenomena may diversely impact the adipose tissue density, suggested in other cancer settings as an important prognostic biomarker. The analysis of body mass composition (BMC) parameters, including adipose tissue attenuation is studied here in a population of EC operated with curative intent.

Methods: BMC was retrospectively evaluated on Computed-Tomography (CT)-scan images from fluoro-deoxyglucose (FDG)-positron-emitting (PET)/CT scans performed as a diagnostic procedure in a cohort of 145 EC patients operated with curative intent. The mean subcutaneous (SFD) and visceral fat (VFD) density along with the index (area/height²) (SF index (SFI), VF index (VFI)) were assessed on two adjacent slides at the third lumbar vertebra level by two independent investigators. Overall survival (OS) was calculated from the date of the baseline FDG-PET/CT scan.

Results: Inter-observer correlations are excellent for all BMC parameters (r = 0.94-0.99). As expected, weight loss is associated with worse outcome. We show that low SFD (HR 0.5 (95% CI: 0.3-0.7), p < 0.001) and low VFD (HR 0.6 (95% CI: 0.4-0.9), p = 0.04) at diagnosis are associated with better OS. In contrast, body mass index (BMI) fails to show any relevance in predicting survival.

Conclusions: Adipose tissue density is an important prognostic factor in EC.

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1. Introduction

Esophageal cancer (EC) accounts for 450,000 new cancer cases per year worldwide and is considered one of the most aggressive solid tumors. It consists mostly of two histological subtypes, adenocarcinoma (ADC) and squamous cell carcinoma (SCC) which are characterized by epidemiological and etiopathogenetic differences. ADC accounts for approximately two-thirds of EC cases and its incidence is globally on the rise largely due to its causative association with overweight and gastro-esophageal reflux disease (GERD) [1]. In contrast, SCC incidence has slowly decreased over time, this histotype being associated with other risk factors such as smoking and alcohol consumption.

Most EC patients initially present with weight loss [2] and sarcopenia [3]. These are at least partly secondary to tumor-induced dysphagia and resulting inadequate food intake. Further worsening of the nutritional status of these patients may be caused by the side effects of the anticancer treatments they receive including chemotherapy, radiotherapy and surgery [4]. Body composition

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parameters have therefore been increasingly studied in this disease setting as prognostic indicators as well as targets for supportive therapeutic interventions. For instance, several studies have found an association between sarcopenia and increased treatment-related toxicities [5,6], resistance to chemoradiotherapy (CRT) [7] and poor outcome [3,8].

Body mass index (BMI) is a commonly used parameter that quickly provides a general assessment of the body weight. Nevertheless, it falls short of the information that is needed to accurately evaluate an individual nutritional status. Patients with the same BMI value may differ substantially in terms of nutritional status and body fat or muscle composition. Moreover, aging is associated with sarcopenia and changes in the different fat compartments at rates varying with sex, ethnicity and other unknown individual factors [9], and this is not taken into account as a potential confounding variable in the assessment of BMI. Analysis of the body mass composition (BMC), especially with regard to the actual distribution of muscle and adipose tissues, can overcome the limitations of BMI, providing a much more reliable assessment of the patient nutritional status and possibly acting as a better prognostic parameter. A number of techniques for BMC assessment have been developed so far, such as bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DEXA) and computed tomography (CT), the latter being the most commonly used as a result of its wide availability [10,11].

Although BMC research in cancer patients has primarily focused on muscle tissue, the interest of researchers has gradually shifted towards the evaluation of quantitative and qualitative changes of the adipose tissue during cancer involuntary weight loss [12].

Adipose tissue CT density is thought to represent a radiological surrogate of the biological/metabolic state of the adipose compartment with density variations possibly reflecting alterations of the status quo occurring in pathological conditions. It has been hypothesized that these alterations, largely consisting of increased secretion of adipocyte-derived factors may in turn impact tumor growth, aggressiveness and response to treatment [13,14]. Over the last few years, high visceral fat density has been shown to be a poor prognostic factor in metastatic colorectal [15], head and neck, pancreas and gastric cancers [14,16–18]. Fewer data are available for EC where some studies have reported an association between a high volume of visceral fat or a high ratio of visceral fat volume to subcutaneous fat volume and lymph node metastases, treatment resistance and poor survival [19–21].

The aim of this study was to assess the prognostic value of a number of BMC parameters including adipose tissue volume and density in a cohort of EC patients who were treated with curative intent.

2. Material & methods

2.1. Patient population

Study inclusion was restricted to patients who had been operated with curative intent for an invasive EC in two university hospitals (Institut Jules Bordet and Hopital Erasme, Brussels, Belgium) between 2005 and 2017, had undergone a baseline FDG-PET-CT scan as part of the staging work-up and had follow-up data available. No substantial delay between baseline scan and onset of treatment was observed (either neoadjuvant CT/CRT or surgery for neo-adjuvant treatment-naive patients). Patients were included regardless of tumor histology.

2.2. Body mass composition analysis

BMC parameters were assessed using the non-contrast CT scan images from the baseline FDG-PET scan and the PLANET Onco software (DOSIsoft, Cachan, France). Subcutaneous fat (SF), visceral fat (VF) and skeletal muscle (SM) (psosas, paraspinal and abdominal wall muscles) were defined by density ranges of –190 to –30 Hounsfield units (HU), –150 to –50 HU, and –29 to 150 HU, respectively. The mean density of each area, corresponding to the tissue mean attenuation on the CT scan, was recorded at the level of the third lumbar vertebra. To obtain quantitative information on the tissue, the cross-sectional area (cm²) of SF, VF and SM were delineated and normalized for the square of height (m²) and reported as indexes (cm²/m²). Densities and indexes were calculated on two adjacent CT scan slices by two independent investigators and mean values were used for the analysis. Gender-specific median values were used to define low and high groups in relation to each BMC parameter. The ratio of VFI to SFI was also calculated for each patient.

A random subgroup of N = 25 patients was analyzed also with other softwares (Aquarius® – TeraRecon, Foster City, Canada and SliceOmatic® – Tomovision, Montréal, Canada) to assess the reproducibility of the measurements obtained with the PLANET Onco software.

2.3. Weight loss, BMI and sarcopenia

High weight loss was defined as an unintentional weight loss of >5% in <6 months or >10% in >6 months as compared to baseline [22]. BMI was calculated as weight in kilograms divided by the square of height in meters, with low and high BMI defined according to the World Health Organization (WHO) (Table S1). Sarcopenia was evaluated as defined by Prado et al. [23], as depicted in Table S2.

2.4. Biological and tumor-related parameters

Baseline C-reactive protein (CRP) values were collected from blood samples taken within 15 days before the date of the FDG-PET scan used for the assessment of the BMC parameters. The median value was used to define low- and high-CRP groups. As far as the tumor stage is concerned, patients were divided into early stage (i.e., (y)pTNM T1–T2 N0) and locally-advanced (i.e., (y)pTNM T4 and/or N+) [24].

2.5. Statistical analysis

The primary objective of the study was to assess the association between BMC parameters and OS. This was defined as the time from baseline FDG-PET/CT to the date of death from any cause.

Mann–Whitney tests were used to compare the distribution of the BMC parameters in the study population. For univariate analysis, Kaplan–Meier curves were used, while hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox's proportional hazards model and logrank tests were used to compare survival curves. We performed a multivariate analysis through manual stepwise regression, using forward selection, adding the parameters one by one in order of most significant p-value as shown in univariate analyses. The model with the lowest Akaike Information Criterion (AIC) was selected for Cox analysis.

Results were considered statistically significant at the bilateral p < 0.05 level. Correlations were assessed with Spearman correlation. R version 3.5.1, Graphpad Prism version 7 and SAS version 9.4 were used for statistical analyses.

2.6. Approvals and consent

The study was approved by the Institutional Review Boards and Ethics Committees at the Institut Jules Bordet (CE2986) and Erasme...
3. Results

3.1. Patient characteristics

A hundred and forty-five patients were found to be eligible and were included in the study. Patient’s characteristics and curative intent treatments received are shown in Tables 1 and 2, respectively. There was a predominance of males (75.2%), adenocarcinomas (53.8%) and tumors of the lower third of the esophagus (62.1%). Approximately half of the patients had a history of smoking or alcohol consumption. The majority of patients received a multimodal treatment including neoadjuvant radiotherapy followed by surgery (40%) or neoadjuvant chemotherapy followed by surgery (32%), while surgery alone was carried out in 28% of cases.

At the time of analysis, 52 of the 145 patients (36%) had died. Median OS (mOS) was 2.9 years.

3.2. Body composition parameters

For all BMC parameters a strong correlation ($r$: 0.92 to 0.99, $p < 0.001$) was found between the PLANET ONCO® software and the Aquarius and SliceOmatic softwares (Figs. S1S and S2).

Interobserver agreement was excellent for all BMC parameters with $r$ ranging from 0.94 to 0.99. Correlations between BMC parameters and BMI can be found in Fig. 1.

Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>109 (75.2)</td>
</tr>
<tr>
<td>Female</td>
<td>36 (24.8)</td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>78 (53.8)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>67 (46.2)</td>
</tr>
<tr>
<td>Histological grade</td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>26 (17.9)</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>72 (49.6)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>32 (22.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (10.4)</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>19 (13.1)</td>
</tr>
<tr>
<td>Middle</td>
<td>36 (24.8)</td>
</tr>
<tr>
<td>Lower</td>
<td>90 (62.1)</td>
</tr>
<tr>
<td>( yp )TNM stage</td>
<td></td>
</tr>
<tr>
<td>T1–T2–T3 N0</td>
<td>63 (43.4)</td>
</tr>
<tr>
<td>T4 and/or N+</td>
<td>50 (34.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>32 (22.1)</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>77 (53.1)</td>
</tr>
<tr>
<td>Non smoker</td>
<td>58 (40.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (6.9)</td>
</tr>
<tr>
<td>Drinker</td>
<td></td>
</tr>
<tr>
<td>Drinker</td>
<td>73 (50.4)</td>
</tr>
<tr>
<td>Non drinker</td>
<td>65 (44.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>Sarcopenic</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>74 (51)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>60.3 (54.2–67.5)</td>
</tr>
<tr>
<td>CRP (N = 101)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>24.25 (21.6–27.3)</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery only</td>
<td>ESCC</td>
</tr>
<tr>
<td>Neoadjuvant CT and surgery</td>
<td>ADC</td>
</tr>
<tr>
<td>Neoadjuvant CRT and surgery</td>
<td>ADC</td>
</tr>
</tbody>
</table>

Abbreviations: SCC: squamous cell carcinoma; ADC: adenocarcinoma; CT: chemoradiotherapy; CRT: chemoradiotherapy.

The distribution of BMC parameters across histologies and sex are reported in Tables 3 and 4, respectively.

- **Association analyses**

  No correlation was observed between SFD or VFD and CRP values ($r = 0.1; p = 0.3$).

  Less advanced disease stages appear associated with lower SFD (median density: –98.02 HU vs –95.96 HU; $p = 0.04$) but not with VFD (median density: –94.91 HU vs –90.91 HU; $p = 0.36$).

- **Survival analyses**

  High SF density (SFD) (Fig. 2), high VF density (VFD), high CRP values (Fig. 3), advanced disease stages, high weight loss and sarcopenia were associated with poorer OS.

  The survival analysis by histology showed that high VFD was significantly correlated to a poorer OS in ESCC patients (HR 0.44 (95% CI 0.24–0.80); $p = 0.007$) while it is high SFD that carries a poor prognostic value in the ADC population (HR 0.31 (95% CI 0.16–0.57); $p < 0.001$).

  In contrast, SMD, SMI, VFI, SFI, the ratio of VFI to SFI and BMI did not show any association with survival. The results of the univariate analyses are detailed in Table 5.

- **Multivariate analyses**

  In the manual stepwise selection procedure, the following variables were considered for association with OS: sarcopenia, weight loss, CRP value, disease stage and fat density (SFD for ADC population and VFD for SCC population).

  - In the SCC population, weight loss, VFD and CRP were selected in the multivariate model. In this cohort, only 26 patients (for 18 events) presented complete data for these three parameters. None of these variables was identified as an independent predictor of OS (high weight loss: HR 2.36 (95% CI 0.86–6.46); low VFD: HR 0.44 (95% CI 0.16–1.16); high CRP: HR 1.94 (95% CI 0.64–5.88).

  - In the ADC population, only SFD was retained in the multivariate model (78 patients/47 events) and was identified as a significant independent predictor of OS (HR 0.31 (95% CI 0.16–0.57); $p < 0.001$).

4. Discussion

In the present study, adipose tissue CT attenuation showed significant positive association with mortality risk in EC patients. These patients present commonly a poor nutritional status, partly because abnormal alimentary intake is one of the causative factors underlying the disease (overweight in esophageal ADC, and underweight in SCC histology) and partly because the upper digestive tract localization of the disease prevents a proper nutrition when...
the tumor size is important [25]. Weight loss has long been considered as an important prognostic factor in this disease. Anti-cancer treatments (surgery, preoperative radio(chemo)therapy) may significantly worsen this situation, all of which making nutritional support a huge challenge in EC management.

Despite the existence of an abundant literature on this subject [3,7,8,26], our data did not identify classical nutritional parameters such as BMI as a prognostic factor, despite using classical WHO thresholds or the thresholds established by the Global Leadership Initiative on Malnutrition (GLIM) threshold [22] (data not shown).

Sarcopenia, defined according to Prado was found in 51% of the patients, who displayed a significant poorer OS. Interestingly, Martin’s thresholds, which include BMI as discriminating factor [27], did not show any association with survival (data not shown). This variation questions again the pertinence of BMI and the importance of validated and cohort-specific thresholds for sarcopenia. Hence, our data suggest that BMI is not associated with the patients’ outcome and therefore, despite its availability, cannot be trusted as a relevant factor in EC management.

Remarkably, as recently shown in other tumor types and clinical settings, our data point to adipose tissue attenuation, strongly associated with the patients’ OS in locally advanced non-metastatic non-pretreated EC [28].

The molecular mechanisms underlying fat tissue density remain unclear. Previous projects in the field of cardiovascular diseases [29] have studied the role of adipose tissue in adverse metabolic risk factors. Hence, lower HU is considered as a marker of lipidic dense fat tissue, composed of large, mature adipocytes filled almost entirely by large lipid droplets. Hence, Dahlman and others propose that adipose tissues of higher density would be composed of shrunken adipocytes, increased fibrosis and decreased fat cell volume, resulting from changes in extracellular matrix pathway regulations. These events would occur following adipose tissue remodeling associated with aging, which presents overlapping features with cancer-associated wasting [30,31], or pathological conditions such as obesity or cancer [16].

Beyond their depletion in lipids, high density patients with dysfunctional adipocytes present lower serum levels of leptin and higher level of adiponectin. These alterations of adipose tissue have been shown in non-human primates, where high CT attenuation of adipose tissue has been associated with lower lipid content and fibrotic transition [32]. Eventually, these adipose qualitative alterations would favor cancer aggressiveness and progression [14,17]. The observation that low disease stage patients present lower SFD values than high disease stage patients in the present study supports this scheme.

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Several previous studies associated high CT attenuation of adipose tissues with worse prognosis in various cancer settings. Hence, our team has demonstrated the improved outcome associated to a decreased fat density (SFD and VFD) in chemorefractory advanced CRC [15].

Similar results were obtained in extremity sarcoma, prostate cancer, pancreatic adenocarcinoma and head and neck cancer [14,17,33,34]. Notably, the prognostic impact of fat tissue attenuation was also assessed in a retrospective study of gastric cancer [16]. In this study, high VAT density patients showed worse OS and relapse-free survival compared to patients with low values. Furthermore, this study showed a positive correlation between VAT density and VAT FDG uptake (SUV) on a PET exam, with a subsequent correlation between VAT SUV and tumoral SUV max. According to the authors, this suggests that the qualitative alterations reflected by CT attenuation changes might be more important in aggressive tumors. Nevertheless, SFD was not evaluated in this study.

Hence, colorectal cancer prognosis seems mainly associated to VAT attenuation [15], while some studies in prostate cancer [34] and extremity sarcoma cancer [33] seem to point a more pronounced association between outcome and SAT attenuation. In the present study, VAT or SAT attenuations were significantly associated with OS in SCC or ADC, respectively.

It is possible that depending on the organ involved or on the tumor histology, SAT and VAT may be differently related to the tumor. The prognostic value attributed to VAT and SAT would then involve diverse mechanisms of tissue quality alterations depending on the cancer setting, although these mechanisms remain largely unknown [14]. The multivariate analysis performed in the ADC population showed that SAT attenuation remains an independent prognostic parameter. In the SCC population, weight loss, VFD and CRP values were included in the model but none of these parameters was identified as independent predictor of OS. The reason for this discrepancy between the two EC histologies remains unclear; it might be that the low number of events in the SCC population blurred the results. If high adipose tissue density patients would be associated with more advanced, potentially cachectic stage diseases, it would be plausible to find in these patients higher circulating inflammation markers. In this framework, we tested the potential correlation between dysfunctional, high density adipocyte tissue attenuation and CRP values, but no correlation was observed. This is in line with results in pancreatic and gastric cancers, in which no correlation was found either. Nevertheless, another inflammatory marker, the Platelet-to-Lymphocyte Ratio (PLR) showed significant positive yet weak correlation with VAT density in gastric cancer, suggesting that CRP may not be a reliable predictor of adipose tissue quality [16]. Other inflammatory markers such as TNF-α and IL-6 were also associated with adipose tissue density. Further research is warranted concerning the association of adipose tissue density and inflammation, as these markers are known to promote cancer cell growth [34].

Nonetheless, key questions remain, notably if adipose tissue alteration should be considered as an inherent patient’s frailty or would be a consequence of metabolic changes induced by the tumor. Furthermore, the fundamental molecular mechanism of SAT and VAT tissue density variation, the role of each of these fat compartments, whether this is linked to lipid content and/or inflammation and especially whether this process can be targeted...
in the clinics remains unknown. A prospective study, gathering nutritional support data and collecting plasma and adipose tissue samples might give insights into these intriguing questions.

Overall, our findings suggest the need for deeper characterization of adipose tissue composition and its physiopathological role in EC, as well as for transposition in clinic routine. BMI scales clearly do not reflect accurately the lipid content and the molecular alterations occurring in the fat tissue despite the fact that these events seem to be linked with the patients’ outcome.

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Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2020.07.007.

References


Table 5

Univariate analyses of BMC parameters and clinical parameters on OS. Hazard ratios for BMC parameters were calculated as binary variables (i.e. high SMI vs low SMI, using the cutoff). BMI and sarcopenia thresholds are detailed in Tables S1 and S2, respectively.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Median (years)</th>
<th>95% CI</th>
<th>p value</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarcopenia</td>
<td>2 (2–5)</td>
<td>0.02</td>
<td>1.6 (1.1–2.4)</td>
<td></td>
</tr>
<tr>
<td>High weight loss</td>
<td>2 (1–4)</td>
<td>0.01</td>
<td>2.2 (1.02–4)</td>
<td></td>
</tr>
<tr>
<td>High CRP value</td>
<td>2.5 (2–5)</td>
<td>0.003</td>
<td>2.2 (1.3–3.8)</td>
<td></td>
</tr>
<tr>
<td>Advanced disease stage</td>
<td>4 (2–8)</td>
<td>0.03</td>
<td>1.7 (1.1–2.9)</td>
<td></td>
</tr>
<tr>
<td>High SMI</td>
<td>4 (3–8)</td>
<td>0.08</td>
<td>0.8 (0.5–1.2)</td>
<td></td>
</tr>
<tr>
<td>High VFI</td>
<td>4 (3–NA)</td>
<td>0.15</td>
<td>0.75 (0.5–1.1)</td>
<td></td>
</tr>
<tr>
<td>High SFI</td>
<td>5 (3–NA)</td>
<td>0.06</td>
<td>0.7 (0.45–1.02)</td>
<td></td>
</tr>
<tr>
<td>High VFI/SFI ratio</td>
<td>4 (3–NA)</td>
<td>0.4</td>
<td>0.8 (0.55–1.2)</td>
<td></td>
</tr>
<tr>
<td>High SMD</td>
<td>4 (3–7)</td>
<td>0.9</td>
<td>0.96 (0.6–1.5)</td>
<td></td>
</tr>
<tr>
<td>High SFD</td>
<td>4 (2–4)</td>
<td>&lt;0.001</td>
<td>2.1 (1.4–3.2)</td>
<td></td>
</tr>
<tr>
<td>High VFD</td>
<td>2 (2–5)</td>
<td>0.04</td>
<td>1.6 (1–2.3)</td>
<td></td>
</tr>
<tr>
<td>High BMI</td>
<td>5 (3–NA)</td>
<td>0.09</td>
<td>0.7 (0.5–1.1)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CRP: C-reactive protein; SMI: skeletal muscle index; VFI: visceral fat index; SFI: subcutaneous fat index; SMD: skeletal muscle density; SFD: subcutaneous fat density; VFD: visceral fat density; BMI: body-mass index; CI: confidence interval.

Fig. 3. Kaplan–Meier overall survival of the 101 EC patients for CRP at diagnosis stratified in two groups according to the cut-off level of 2.80: Low level of CRP is an indicator of improved survival. Figure was drawn using the survminer R package.
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