BODY COMPOSITION INDICES AND TISSUE LOSS IN PATIENTS WITH RESECTABLE GASTRIC ADENOCARCINOMA

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ABSTRACT

Background:

Body composition analyses from computed tomography (CT) scans have been used to assess cachexia in cancer patients. We investigated body composition indices, tissue change and treatment outcome in patients with resectable gastric adenocarcinoma.

Methods:

A cohort analysis of all patients treated with curative intent for gastric adenocarcinoma in two Scandinavian university hospitals from 2008-2011 was performed (n=137). Body composition analyses were performed on CT images taken for routine diagnostics and staging. Both preoperative single scans and series of repeat CT examinations were analyzed.

Results:

Perioperative chemotherapy was given to 58 (42.3%) patients. Forty patients (29.2%) suffered severe postoperative complications and 70 (51.1%) patients died within three years. There was a significant reduction in patients' lean tissue during neoadjuvant chemotherapy (p=0.001). Poorer survival was observed in patients with preoperative skeletal muscle tissue index within the lowermost quartile, independent of disease stage (HR=1.91, 95% CI 1.11-3.28, p=0.019).

Conclusions:

Patients lost lean tissue during neoadjuvant treatment for gastric adenocarcinoma. Low preoperative skeletal muscle index was associated with poorer survival independent of disease stage.

Keywords: Stomach neoplasms, sarcopenia, cachexia, body composition, gastrectomy

INTRODUCTION

Patients diagnosed with gastric cancer may suffer from cachexia involving muscle loss, which may progress during the course of treatment [1;2]. Resection for gastric cancer is associated with high morbidity and poor long-term prognosis [3]. While perioperative chemotherapy has been shown to increase survival [4], a high degree of toxicity has been reported [5].

Body composition indices based on computed tomography (CT) images have been used to evaluate muscle mass in cancer patients [6-8]. Many studies have reported an association between the relative amount of muscle tissue and morbidity or survival, while others again have failed to show this connection [8-12]. Low muscle mass, assessed from CT images, has also been linked to chemotherapy toxicity and postoperative morbidity [2;13;14]. While most studies on body composition indices have used only single CT examinations (performed at a single point-in-time) [8;10;12], changes over time in the amount of lean and fat tissue during neoadjuvant treatment have been described in patients with gastroesophageal and pancreatic cancer [1;2;15]. These changes have yet to be consistently linked to clinical outcome [1;2;15].

Cancer cachexia has been defined as a multifactorial syndrome with ongoing loss of skeletal muscle mass [16]. To what extent cancer cachexia can be evaluated through preoperative body composition indices from a single CT examination remains uncertain. Furthermore, it is uncertain how these indices relate to disease stage. Information on these issues together with validated disease-specific cut-offs are of key importance for body composition indices to used in an everyday assessment of treatment, risk and prognosis in cancer surgery.

Only a few studies on body composition indices have been performed on patients with resectable gastric adenocarcinoma [8;12]. This is noteworthy as low muscle mass is highly prevalent [12] and series of CT examinations are available due to routine administration of perioperative chemotherapy [5;9].

We aimed to investigate tissue change during neoadjuvant chemotherapy. Furthermore, we aimed to investigate preoperative body composition indices and association with disease stage and treatment outcome.

PATIENTS AND METHODS

Cohort

A complete cohort of all patients who underwent gastric resection with curative intent for adenocarcinoma in the four-year period 2008-2011 in two Scandinavian referral centers (University hospital of Northern Norway, Tromsø, Norway and Karolinska University Hospital at Huddinge, Stockholm, Sweden) was retrospectively analyzed (n=137). Information on general characteristics, co morbidity, histopathological stage, chemotherapy treatment and -toxicity, postoperative complications and overall survival was retrieved from patient files.

Body composition analysis depended on the availability of computed tomography (CT) images of sufficient quality. Hence, all patients with available preoperative CT images were included (n=116). A subgroup analysis was performed on those patients who received neoadjuvant chemotherapy with available CT images from oncological staging (pre-chemotherapy) and response evaluation (preoperatively) (n=45).

Body composition analyses

CT examinations were originally performed for routine diagnostics and staging. CT images were analyzed using Slice-O-Matic software V4.2 (Tomovision, Montreal-Canada) which permitted specific tissue demarcation using Hounsfield unit threshold of -29 to +150 for skeletal muscles [17], -150 to -50 for visceral adipose tissue [18], and -190 to -30 for subcutaneous adipose tissue [17]. Cross-sectional areas (cm^2) were calculated for each tissue by summing tissue pixels and multiplying by the pixel surface area. A transverse CT image from the third lumbar vertebrae (L3) was assessed for each scan and tissue areas estimated

[19]. All CT images were sent to Edinburgh, United Kingdom, and analyzed by a trained observer who was blinded to all clinical data (N.J.)

Cross-sectional area was normalized for stature (cm^2/m^2) [6] and indices were calculated for skeletal muscle tissue (SMT), visceral adipose tissue (VAT), and subcutaneous adipose tissue (SAT). Total whole-body amount of lean tissue (FFM=fat-free mass) and fat tissue (FM=fat mass) were estimated from the following formulas [6]:

FFM (kg) = 0.3 x L3 Skeletal muscle area (cm^2) + 6.06

FM (kg) = 0.042 x L3 Visceral and subcutaneous adipose tissue area (cm^2) + 11.2

Definition of variables

Resections were classified into subtotal gastrectomy, total gastrectomy and distal gastric resection with pancreaticoduodenectomy (performed in four patients with distal gastric adenocarcinoma involving duodenum). Almost all procedures were performed as open surgery with D2 lymphadenectomy. Body mass index (BMI) was calculated from the following formula [20]: BMI (kg/m^2) = Weight (kg)/(Height*Height (m^2)). Obesity was defined as BMI above 30 kg/m^2 [7]. Co morbidity was assessed according to the American Society of Anesthesiologists (ASA) classification. Diabetes mellitus was defined as medically treated disease (insulin or oral medication). Abnormal serum – c-reactive protein (s-CRP) was defined as s-CRP above 5 mg/L. Post-resection histopathological stage was classified according to the TNM classification, 7^{th} edition. The default definition of low muscle mass was according to the cut-off suggested by Mourtzakis et al [6], and supported by an international consensus panel [16]. This cut-off represents a skeletal muscle tissue index

more than two standard deviations from that of healthy young adults (<39 cm^2/m^2 for women and <55 cm^2/m^2 for men) [6]. We also performed analyses with the cut-off suggested by Martin et al [21], which defines low muscle mass relative to BMI: Skeletal muscle tissue index <41 cm^2/m^2 for all women and <43 cm^2/m^2 for men with BMI <25 kg/m^2 and <53 cm^2/m^2 for men with BMI ≥25kg/m^2. Furthermore, survival was analyzed for patients with skeletal muscle tissue in the lowermost quartile in our cohort (<35.4 cm^2/m^2 for women and <43.3 cm^2/m^2 for men). Sarcopenic obesity was defined as Skeletal muscle tissue index within the lowermost quartile in our cohort combined with BMI >30 kg/m^2. Visceral obesity was defined as L3 visceral adipose tissue area above 130 cm^2 [10].

Patients received perioperative chemotherapy according to the indications and standards described by Cunningham et al [4], with a somewhat modified chemotherapeutic regimen [3] i.e. a combination of Epirubicin, Oxaliplatin or Cisplatin, and Capecitabin (EOX or ECX regimen) with three cycles administered both neoadjuvant and adjuvant. Complications (within 90 days after surgery) were classified by the Accordion classification [22;23]. Severe postoperative complications were defined as one or more complication graded Accordion III or higher [22;23]. Overall survival was calculated from date of index surgery and all patients were followed for three years or more.

Statistics

Statistical analyses were performed with SPSS v22 statistics software (IBM, NYC - USA). Normally distributed data were described with mean value and 95% confidence interval (95% CI). Non-normally distributed data were described with median value and interquartile range (IQR). Differences between groups and categories were analyzed with Student's t-test,

analysis of variance (ANOVA) and Pearson chi square test. One-way t-test was used for analysis of two repeated measures. Non-normally distributed data were analyzed with Mann-Whitney U-test and Kruskall-Wallis test. Linear regression analysis was used to analyze the association between patient characteristics, disease stage and body composition indices. Overall survival was analyzed using Cox proportional hazard regression analyses; the assumption of proportional hazards was visually inspected by log-log survival curves. P-values <0.05 were considered statistically significant.

RESULTS

Our cohort consisted of 137 patients with a median age of 70 years and of whom 77 (56%) were male. Perioperative chemotherapy was administered to 58 (42%) patients, 32 (55%) of these patients completed both neoadjuvant and adjuvant treatment. The number of patients who died within three years was 70 (51%). Forty (29%) patients suffered severe postoperative complications. Details on postoperative complications are listed in Table 1.

Preoperative Computed Tomography (CT) images of sufficient quality were available in 116 patients and 49 (42%) of them received neoadjuvant chemotherapy. Of the 116 patients, 30 (26%) suffered severe postoperative complications and 58 (50%) died within three years.

Tissue loss during neoadjuvant chemotherapy

In patients treated with neoadjuvant chemotherapy (NAC) a median of ninety days (IQR: 77-103) passed between the initial diagnostic/staging CT and the preoperative CT examination. There was a significant loss of lean tissue during this period (p=0.001), with a median loss of 1.1 kg (IQR=0.2-3.1 kg) or 3% of the estimated lean tissue at the beginning of NAC. The proportion of sarcopenic patients increased from 58% prior to NAC and to 67% at the end of NAC. No significant loss of fat tissue (p=0.16) was observed.

Preoperative body composition indices

A median of 23 days (IQR=9-43) passed between the preoperative CT examination and surgery. There was a strong correlation between the estimated amount of tissue (lean and fat

tissue combined) from the CT images and total body weight reported in the patient file (r=0.89, p<0.001). Low muscle mass was present in 78 (67%) of the patients. Diabetes mellitus was associated with a higher visceral adipose tissue (VAT) index. The estimated difference in VAT index between patients with (n=11) and without diabetes mellitus was 20.1 cm^2/m^2 (95% CI=1.1-39.2, p=0.039, adjusted for age and gender). Older age was associated with lower SMT index and higher VAT index (Table 2). Male gender was associated both with a higher SMT and VAT index (Table 2). There was no association between co morbidity or disease stage (histopathological stage in resected specimen) and SMT or VAT index (adjusted for age, gender and whether patients received NAC or not) (Table 2). No association between disease stage and SMT index (Table 3), or VAT index was observed when analyzes were stratified on the administration of neoadjuvant chemotherapy.

The only factor associated with increased rate of severe postoperative complications was abnormal s-CRP preoperatively (OR=2.77, 95% CI=1.12-6.89, p=0.025). There was no association between BMI and postoperative complications (p=0.33). Neither SMT nor VAT index were associated with postoperative complications (both p-values >0.4, adjusted for age and gender).

More advanced tumor-stage and regional lymph node metastasis were both associated with poorer survival (Table 4). Increased preoperative SMT index was associated with improved survival (Table 4). Patients with SMT index within the lowermost quartile had poorer survival (HR=2.08, 95% CI=1.21-3.57, p=0.008, adjusted for age and gender), 21 (72%) of these patients died within three years. This association remained relatively unchanged when adjusted for age, gender, disease stage and whether NAC was given or not (HR=1.91, 95% CI

1.11-3.28, p=0.019). There was no association between low muscle mass and survival when using any other cut-offs (Table 4). No significant interaction between the administration of neoadjuvant chemotherapy and muscle mass was observed in the survival analysis, i.e. the administration of neoadjuvant chemotherapy did not affect the association between preoperative muscle mass and survival. The association between increased preoperative SMT index and improved survival (adjusted for age and gender) was similar in both patients who received neoadjuvant chemotherapy (HR=0.95, 95% CI 0.89-1.02, p=0.17) compared to patients who did not (HR=0.98, 95% CI 0.89-1.02, p=0.41).

DISCUSSION

We have demonstrated that patients suffer significant tissue loss during neoadjuvant chemotherapy treatment for gastric adenocarcinoma. Low muscle mass was highly prevalent in our patients compared to what has been reported in patients with other resectable gastrointestinal and hepatobiliary malignancies [8].

Body composition indices from preoperative CT examinations were not associated with disease stage and lower preoperative skeletal muscle tissue index was independently associated with poorer survival. The findings might indicate that low muscle mass is an independent indicator of poor prognosis in patients with resectable gastric adenocarcinoma.

We observed significant tissue loss during neoadjuvant chemotherapy. This might show that estimated tissue loss is quantifiable in patients receiving multiple CT scans for diagnostic and staging purposes and therefore may serve as a feasible continuous outcome in future studies on e.g. nutrition, prehabilitation and rehabilitation.

Lower preoperative SMT index was not associated with complications after gastric resections which is in concordance with another recent study [12]. The pioneer studies of Windsor and Hill in the eighties demonstrated that preoperative protein depletion only constitutes a high risk of adverse outcome when such protein depletion is combined with functional impairment [24]. A more recent study has shown a remarkable association between the combination of sarcopenia, frailty and malnutrition, and complications after colorectal cancer surgery [14].

Preoperative body composition indices might be even more useful if combined with evaluation of functional impairment to assess risk of morbidity after gastric resections.

Neither of the established cut-offs for low muscle mass [6;21], both frequently used in the recent years [11;12;15], were associated with survival in our study. This illustrates the importance of also using continuous variables wherever possible when assessing potential dose-response relationships [25]. The clinical impact of lower skeletal muscle tissue mass seems to depend on both cancer type and stage [8], and appropriate cut-offs have to be developed and validated accordingly.

Increasing BMI was almost statistically significantly associated with *increased* survival and obesity was not associated with either postoperative complications or survival. This is consistent with the findings in several other recent studies and suggests that obesity is not associated with poor outcome after cancer treatment [12;26;27]. Visceral adiposity from CT images in our series was not associated with postoperative complications or survival. While visceral adiposity has been associated with diabetes (also confirmed in our study) and diabetes again has been associated with adverse postoperative outcome, evaluations of a direct association between adipose tissue indices and adverse outcome have shown conflicting results [10;12].

While the total number of patients in our study was limited, they represent a complete cohort of patients with resectable adenocarcinoma of the stomach during a four-year period at two

major Scandinavian university hospitals. As an unselected cohort, our data provide an insight into clinical aspects regarding body composition analyses in gastric cancer surgery.

CONCLUSIONS

Patients with resectable gastric cancer lost lean tissue during neoadjuvant chemotherapy. Lower preoperative skeletal muscle index was associated with worse survival, independent of disease stage.

ETHICAL CONSIDERATIONS

Data retrieval, publication and dispensation from informed consent requirement, was approved by the Regional Committee on Research Ethics, Northern Chapter (REK V).

CONFLICT OF INTERESTS

The authors declare that they have no conflicts of interest

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Table 1. Distribution of postoperative complications

Severity of complication according to the Accordion classification	**Number and percentage of patients[1]**
Minor (Accordion 1 and 2) or no postoperative complications	97 (71%)
Accordion 3: Endoscopic intervention or reoperation without general anesthesia	14 (10%)
Accordion 4: Reoperation in general anesthesia or single organ failure	17 (12%)
Accordion 5: Multi-organ failure (or both criteria from Accordion 4)	3 (2%)
Accordion 6: Postoperative death (within 90 days from index surgery	6 (4%)

1) Only the most severe complication level is noted in patients with multiple complications.

Table 2. The estimated impact of patient characteristics and disease stage on preoperative body composition indices. Linear regression analysis, adjusted for age, gender and whether patients received neoadjuvant chemotherapy (NAC) or not.

		Skeletal muscle tissue index		**Visceral adipose tissue index**	
	N (%)	**Difference (95% CI)**	***p*-value**	**Difference (95% CI)**	***p*-value**
Older age (>70y)	55 (47%)	-6.3 (-9.4/-3.2)	<0.001	8.1 (-5.9/22.1)	0.26
Male gender	67 (58%)	7.8 (5.2/10.3)	<0.001	26.6 (15.2/38.0)	<0.001
ASA 3-4	27 (23%)	-1.9 (-5.0/1.2)	0.23	1.1 (-13.2/15.4)	0.88
T3/T4 stage	64 (55%)	-1.5 (-4.0/1.0)	0.25	-2.6 (-14.2/9.1)	0.66
N+	61 (53%)	-0.2 (-2.4/2.7)	0.90	-5.6 (-17.1/5.9)	0.33

Estimated difference (95% confidence interval) in skeletal muscle and visceral adipose tissue index (cm^2/m^2) compared with:

- Patients with age <70 years (adjusted for gender and NAC only)
- Women (adjusted for age and NAC only),
- Patients with ASA1-2 (American Society of Anesthesiologists classification of co morbidity)
- Patients with T1/T2 tumor stage (TNM, data from histopathological examination)
- Patients with no lymph node metastasis (TNM, data from histopathological examination).

Table 3. The estimated impact of patient characteristics and disease stage on skeletal muscle tissue index. Linear regression analysis, adjusted for age and gender. Stratified on the administration of neoadjuvant chemotherapy.

	Neoadjuvant chemotherapy (n=49)		**No neoadjuvant chemotherapy (n=67)**	
	Difference (95% CI)	***p*-value**	**Difference (95% CI)**	***p*-value**
Older age (>70y)	-4.7 (-10.8/1.4)	0.13	7.3 (-11.0/-3.7)	<0.001
Male gender	9.7 (5.6/13.7)	<0.001	6.0 (2.7/9.4)	0.001
ASA 3-4	-0.3 (-8.1/7.4)	0.93	-1.5 (-5.2/2.1)	0.40
T3/T4 stage	-2.2 (-6.4/2.0)	0.30	0.1 (-3.4/3.5)	0.98
N+	-2.6 (-6.7/1.5)	0.20	-2.1 (-1.2/5.4)	0.21

Estimated difference (95% confidence interval) in skeletal muscle tissue index (cm^2/m^2) compared with:

- Patients with age <70 years (adjusted for gender only)
- Women (adjusted for age only),
- Patients with ASA1-2 (American Society of Anesthesiologists classification of co morbidity)
- Patients with T1/T2 tumor stage (TNM, data from histopathological examination)
- Patients with no lymph node metastasis (TNM, data from histopathological examination).

Table 4. The impact of selected risk factors, preoperative body composition indices and disease stage (histopathological stage in resection specimen) on overall survival. Cox proportional hazard regression analysis, adjusted for age and gender.

Variable	**N (%)**	**HR (95% CI)[1]**	***p*-value**
ASA 1	18 (16%)	Ref	Ref
ASA 2	71 (61%)	1.71 (0.61-4.78)	0.31
ASA 3/4	27 (23%)	2.40 (0.78-7.34)	0.13
Diabetes mellitus	11 (9%)	0.53 (0.19-1.46)	0.23
s-CRP >5mg/L	30 (26%)	1.74 (1.00-3.05)	0.052
BMI (continuous)	-	0.95 (0.89-1.01)	0.086
Obese (BMI >30 kg/m^2)	19 (16%)	0.60 (0.28-1.25)	0.17
SMT index (continuous)	-	**0.95 (0.92-0.99)**	**0.024**
Sarcopenia, Mourtzakis[2]	78 (67%)	1.43 (0.79-2.61)	0.24
Sarcopenia, Martin[3]	52 (45%)	1.12 (0.68-1.86)	0.66
Sarcopenia, 1. Quartile[4]	29 (25%)	**2.08 (1.21-3.57)**	**0.008**
VAT index	-	0.99 (0.99-1.00)	0.11
Visceral obese[5]	57 (49%)	0.66 (0.38-1.16)	0.15
T3/T4 stage[6]	71 (61%)	**2.94 (1.65-5.26)**	**<0.001**
Lymph node metastasis (N+)	61 (53%)	**5.83 (3.24-10.48)**	**<0.001**

Statistically significant values ($p<0.05$) in bold writing

1) Hazard ratio (95% confidence interval) for mortality within the follow-up period.
2) Cut-off for sarcopenia suggested by Mourtzakis et al: Skeletal muscle tissue index <39 cm^2/m^2 for women and <55 cm^2/m^2 for men.
3) Cut-off for sarcopenia suggested by Martin et al: Skeletal muscle tissue index <41 cm^2/m^2 for all women, <43 cm^2/m^2 for men with BMI <25 kg/m^2 and <53 cm^2/m^2 for men with BMI ≥25kg/m^2.
4) Patients with skeletal muscle tissue index within the lowermost quartile: <35.4 cm^2/m^2 for women and <43.3 cm^2/m^2 for men.

5) Visceral adipose tissue area >130 kg/m^2
6) Tumor-stage according to TNM classification. Compared to patients with T1 and T2 tumors

s-CRP = serum – c-reactive protein

BMI = Body Mass Index

SMT = Skeletal Muscle Tissue

VAT = Visceral Adipose Tissue