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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Low Visceral Fat Content is Associated with Poor Prognosis in a Database of 507 Upper Gastrointestinal Cancers

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ABSTRACT

Background. Excess visceral adipose tissue may promote cancer development and progression via an obesity-related metabolic derangements, including adipocytokine-related inflammation, insulin resistance, and hypoxia. The relationship between visceral fat content and patient prognosis has been reported in some types of cancers, but not in the upper gastrointestinal cancer. The purpose of this retrospective study was to investigate the relationship between visceral fat status and clinical outcome in patients with upper gastrointestinal cancers (esophageal cancer and gastric cancer) treated by surgical resection.

Methods. This retrospective study was conducted in a single, academic hospital in Kumamoto, Japan, and involved 507 patients with upper gastrointestinal cancers between April 2005 and December 2010. Preoperative visceral fat content was quantified by radiologic measures using standard computed tomography scans.

Results. Higher visceral fat mount was correlated with male sex, presence of preoperative comorbidity, absence of preoperative therapy, low tumor depth, low tumor stage, and gastric cancer. Compared to high visceral fat cases, low visceral fat cases experienced a higher overall mortality rate [log-rank $p = 0.0050$; univariate hazard ratio (HR) = 1.73, 95 % confidence interval (CI) 1.16–2.54; $p = 0.0075$; multivariate HR 1.57; 95 % CI 1.02–2.37; $p = 0.031$]. Interestingly, the influence of low visceral fat on patient outcome was modified by age at surgery (p for interaction = 0.036); low visceral fat was associated with a poor prognosis, especially in elderly patients (log-rank $p < 0.0001$).

Conclusion. Visceral fat content in the upper gastrointestinal cancers was associated with a poor prognosis, thus suggesting that it has potential for use as a prognostic biomarker.

The number of overweight and obese individuals has increased in recent years, and obesity is a growing global health problem. Excess body weight is associated with diseases, such as diabetes mellitus and cardiovascular anomalies, which contribute to the increased overall mortality rate of obese individuals.[1–3] Importantly, epidemiological studies have shown that increased body mass index (BMI) is a risk factor for several types of cancers, including esophageal adenocarcinoma, but is negatively associated with the risk of esophageal squamous cell carcinoma.[4,5] On the other hand, no significant association has been identified between obesity and gastric cancer incidence.[4,5] These findings suggest that body fat distribution influences the development of upper gastrointestinal cancers, such as esophageal and gastric cancers. Biologically, excess visceral adipose tissue promotes greater obesity-related metabolic disturbances, including insulin resistance, perturbations in adipokines, and chronic inflammation, than subcutaneous adipose tissue.[6] Thus, visceral adipose mass might more accurately measure

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dysfunctional adipose tissue that facilitates cancer development and progression than BMI.

The "gold standard" for measuring visceral fat is quantitative radiologic measurements using standard computed tomography (CT) scans.[7] This precise and reliable measure of abdominal fat compartments permits a possible redefinition of obesity, in terms of visceral fat rather than BMI. The relationship between visceral fat content and patient prognosis has been reported in colon cancer, pancreatic cancer, hepatocellular carcinoma, and others.[8–10] No study has evaluated the clinical, pathological, and prognostic value of visceral fat volume in upper gastrointestinal cancer.

Therefore, in this study we examined whether visceral fat status alters clinical outcome in 507 patients with upper gastrointestinal cancers (i.e., esophageal and gastric cancers) treated by surgical resection within a single institution. Our data suggest a possible role for visceral fat content as a prognostic biomarker.

METHODS

Study Subjects

The study initially recruited 556 patients with upper gastrointestinal cancer (esophageal and gastric cancers) who underwent surgical resection at Kumamoto University Hospital (Kumamoto, Japan) between April 2005 and December 2010. Three esophageal cancer patients and nine gastric cancer patients whose resections were noncurative were excluded. Visceral fat areas in 16 gastric cancer and 20 esophageal cancer patients could not be measured, due to intestinal distention or problems importing CT data into the SYNAPSE VINCENT system (FUJIFILM, Japan). Thus, 507 patients (245 esophageal cancer patients and 262 gastric cancer patients) were ultimately eligible for the study. Patients were observed at 1- to 3-month intervals until death or October 30, 2013, whichever came first. Overall survival was defined as the time between the operation date and the date of death. Disease-free survival was defined as the duration between the operation date and the date of cancer recurrence or death. Tumor staging was assessed by the American Joint Committee on Cancer's Cancer Staging Manual (7th edition).[11] Written, informed consent was obtained from each subject, and the study procedures were approved by the institutional review board. Throughout this article, the term "prognostic marker" is used in the context of the REMARK Guidelines.[12]

Visceral Fat Measurement

The visceral fat areas were measured by the SYNAPSE VINCENT system. Preoperative CT scans were taken within 4 weeks of surgery, and the slices at the umbilicus level were evaluated. The areas covered by visceral fat were calculated from pixels with densities ranging from −190 to −30 HU (Fig. 1a). This density range admits fat tissues, but excludes bone, muscle, and other intra-abdominal organs, such as liver, spleen, or small bowel, which manifest as regions of much higher or lower pixel density.

Statistical Methods

The results were statistically analyzed by JMP software (Version 9, SAS Institute, Cary, NC). All p values were two-sided. The means were compared by t test, assuming unequal variances. The survival time distribution was determined by the Kaplan–Meier method using the log-rank test. The independent effect of visceral fat on mortality was assessed by Cox regression modeling, using the tumor stage (I, II, III) as the matching variable to avoid residual

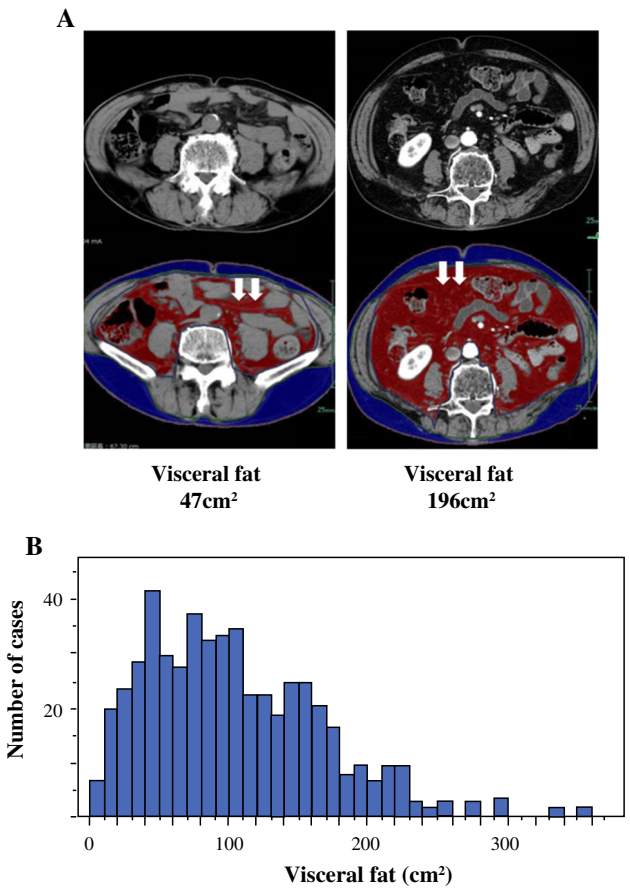


FIG. 1 Measurement and distribution of the visceral fat content in upper gastrointestinal cancer patients. **a** Axial CT slice of the umbilicus level. *Red* and *blue* areas indicate visceral and subcutaneous fat, respectively. **b** Distribution of the visceral fat content in 507 patients with upper gastrointestinal cancer

confounding and overfitting. The hazard ratio (HR) corresponding to visceral fat status was computed from a multivariate model, including sex (male vs. female), age at surgery (continuous variable), preoperative treatment (present vs. absent), preoperative comorbidity (present vs. absent), cancer type (esophageal cancer vs. gastric cancer), postoperative therapy (present vs. absent), postoperative complications (present vs. absent), BMI (continuous variable), preoperative weight loss (present vs. absent), albumin level (≥3.5 vs. <3.5 g/dl), lymphocyte count (≥1200 vs. <1200/μl), and C-reactive protein (CRP) level (≥0.5 vs. <0.5 g/dl). To assess whether any of these variables were associated with the visceral fat variable, they were cross-multiplied with the visceral fat variable and subjected to the Wald test.

RESULTS

Visceral Fat Content in Patients with Upper Gastrointestinal Cancers

The visceral fat in the 507 patients with upper gastrointestinal cancers was distributed as follows (Fig. 1b): mean, 102.5; median, 93.1; standard deviation (SD), 60.9; range 3.1–350.3; interquartile range 53.6–144.5. Higher visceral fat content was correlated with male sex ($p = 0.0012$), presence of preoperative comorbidity ($p = 0.0009$), absence of preoperative therapy ($p < 0.0001$), low tumor stage ($p = 0.029$), and low tumor depth ($p = 0.0032$; Table 1). Importantly, the mean visceral fat content was higher in gastric cancer patients (109.7) than in esophageal cancer patients (94.7, $p = 0.0053$). Visceral fat status was not significantly correlated with age at operation (Table 1). Consistent with previous reports, visceral fat content was significantly associated with BMI ($p < 0.0001$, $R = 0.52$; supplemental Fig. 1).[13] Regarding short-term surgical outcome, high visceral fat content was associated with increased blood loss ($p = 0.0014$, $R = 0.020$) but not with postoperative complications or operation time (Table 1; supplemental Fig. 2).

TABLE 1 Visceral fat status in the upper gastrointestinal cancer, and clinical and tumor features

Clinical or pathologic feature	Total *N*	Visceral fat (cm^2) mean ± SE)	*p* value
All cases	507	102.4 ± 2.7	
Age (years)			
<67	240	100.2 ± 4.1	0.43
≥67	267	104.5 ± 3.5	
Sex			
Male	404	106.9 ± 3.1	0.0012
Female	103	85.2 ± 4.8	
Comorbidity			
Present	311	109.6 ± 3.4	0.0009
Absent	196	91.2 ± 4.3	
Tumor type			
Esophageal cancer	245	94.7 ± 3.4	0.0053
Gastric cancer	262	109.7 ± 4.1	
Preoperative therapy			
Present	120	83.3 ± 4.7	<0.0001
Absent	387	108.4 ± 3.2	
Stage			
I	248	109.8 ± 4.0	0.029
II	118	96.7 ± 5.2	
III	141	94.4 ± 5.0	
Tumor depth			
T0–2	330	108.3 ± 3.3	0.0032
T3–4	177	91.6 ± 4.5	
Postoperative complication			
Present	126	107.5 ± 5.4	0.29
Absent	381	100.8 ± 3.1	

SE standard error

Association between Visceral Fat and Nutrition Status

Next, we examined the association between visceral fat and nutritional status. Among 507 patients, 83 patients had lost weight before the operation, as determined from their medical interview sheets and initial check-ins. The visceral fat content was significantly lower in these patients than in patents without preoperative weight loss ($p < 0.0001$; supplemental Fig. 3). Moreover, low visceral fat content was significantly associated with hypoalbumia (<3.5 g/dl) and low lymphocyte count (<1200/μl; $p < 0.0001$ and $p = 0.0042$ respectively; supplemental Fig. 3) but was unassociated with elevated CRP levels (≥0.5 mg/dl; $p = 0.65$; supplemental Fig. 3). These results suggest that while low visceral fat content reflects a malnutrition state, visceral fat depletion and inflammation status are uncorrelated.

Visceral Fat Content and Patient Survival

Among the 507 evaluated patients, 140 patients died before or during the follow-up period. Among the 140 deceased patients, 86 died of their upper gastrointestinal cancer and 54 died of other diseases. The median follow-up time for censored patients was 3.6 years. We performed Cox regression analysis with visceral fat as a continuous variable. Although higher visceral fat content appeared to increase the overall mortality, the effect was not statistically significant (univariate analysis $p = 0.051$). We then

performed Cox regression analysis using a categorical variable [with visceral fat binned into first quartile cases (Q1; ≥144.6 cm^2), second quartile cases (Q2; 93.2–144.5 cm^2), third quartile cases (Q3; 53.6–93.1 cm^2), and fourth quartile cases (Q4; <53.6 cm^2)]. Clinical and pathological features among each quartile group have been shown in Supplemental Table 1. In univariate Cox regression analysis, the overall mortality rate was significantly higher in Q4 cases than in Q1 cases ($p = 0.031$, HR 1.74; 95 % CI 1.05–2.95), whereas that of Q1, Q2 and Q3 was statistically similar (Table 2). From this analysis, we defined a dichotomous visceral fat variable, defining Q4 as the "low visceral fat group" and combining Q1, Q2, and Q3 into the "high visceral fat group."

In the Kaplan–Meier analysis, the "low visceral fat group" (Q4 cases) experienced significantly shorter overall survival rate (log-rank, $p = 0.0032$) and disease-free survival (log-rank, $p = 0.037$) than the "high visceral fat group" (combining cases Q1–3; Fig. 2). In the univariate Cox regression analysis, the mortality and disease-free survival rates were again significantly reduced in patients with low visceral fat content (statistics of mortality rate: HR 1.73; 95 % CI 1.16–2.54; $p = 0.0075$; statistics of disease-free survival rate: HR 1.43; 95 % CI 1.01–2.00; $p = 0.044$; Table 2). In the multivariate Cox model adjusted for clinical and pathological features, low visceral fat was associated with a significantly higher overall mortality rate (multivariate HR 1.61; 95 % CI 1.01–2.56; $p = 0.047$), although the disease-free survival rates were similar in the "low visceral fat" and "high visceral fat" groups (multivariate HR 0.98; 95 % CI 0.62–1.54; $p = 0.85$).

Interaction between Visceral Fat and other Variables in the Survival Analyses

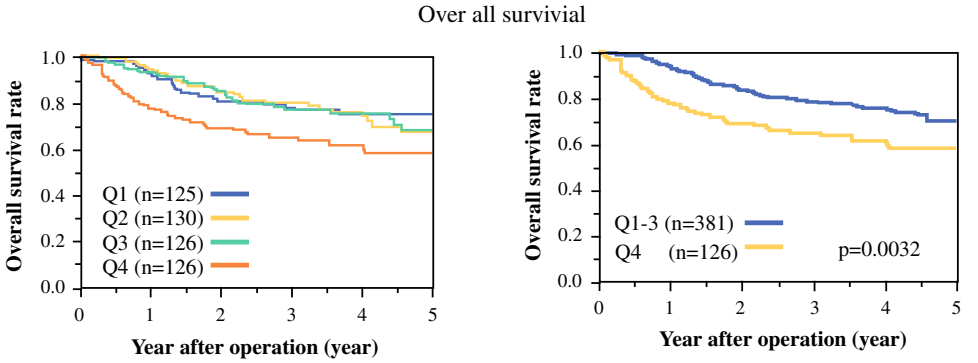
We also examined whether the influence of low visceral fat on overall survival was modified by any of the clinical and pathological variables. The relationship between visceral fat and survival rate was significantly modified by age (p of interaction = 0.036; Fig. 3a), although multiple hypothesis testing does not rule out a chance emergence of this trend. The overall postoperative survival time was significantly reduced in patients older than age 67 years with low visceral fat content (log-rank, $p < 0.0001$; Fig. 3b). In contrast, among patients younger than age 66 years, visceral fat and overall survival were uncorrelated (log-rank, $p = 0.61$; Fig. 3b). Other tested variables did not significantly interact in the relationship between visceral fat and overall survival (p of all interactions > 0.05; Fig. 3a). Regardless of the possible relationship between tumor stage, tumor depth, and

TABLE 2 Visceral fat status in the upper gastrointestinal cancer and patient mortality

Visceral fat (quartile)*	Total *N*	Overall survival		Disease-free survival			
		Univariate HR (95 % CI)	Stage-matched HR (95 % CI)	Multivariate stage-matched HR (95 % CI)	Univariate HR (95 % CI)	Stage-matched HR (95 % CI)	Multivariate stage-matched HR (95 % CI)
Q1 (≥144.6 cm^2)	125	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Q2 (93.2–144.5 cm^2)	130	1.11 (0.65–1.92)	0.97 (0.56–1.68)	1.09 (0.63–1.88)	1.40 (0.89–2.23)	1.25 (0.79–1.99)	1.03 (0.64–1.77)
Q3 (53.6–93.1 cm^2)	126	1.02 (0.58–1.79)	0.85 (0.48–1.50)	1.06 (0.58–1.95)	1.19 (0.74–1.94)	1.05 (0.65–1.75)	0.94 (0.54–1.67)
Q4 (<53.6 cm^2)	126	1.74 (1.05–2.95)	1.42 (0.86–2.42)	1.71 (0.88–3.36)	1.72 (1.10–2.74)	1.48 (0.94–2.34)	0.96 (0.51–1.85)
Q1–3 (≥53.6 cm^2)	381	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
Q4 (<53.6 cm^2)	126	1.73 (1.16–2.54)	1.58 (1.06–2.31)	1.61 (1.01–2.56)	1.43 (1.01–2.00)	1.34 (0.94–1.86)	0.98 (0.62–1.54)
p value		0.0075	0.026	0.047	0.044	0.10	0.85

HR hazard ratio; *CI* confidence interval

* Categorical variable with visceral fat binned into first quartile cases (Q1; ≥144.6 cm^2), second quartile cases (Q2; 93.2–144.5 cm^2), third quartile cases (Q3; 53.6–93.1 cm^2), and fourth quartile cases (Q4; <53.6 cm^2)

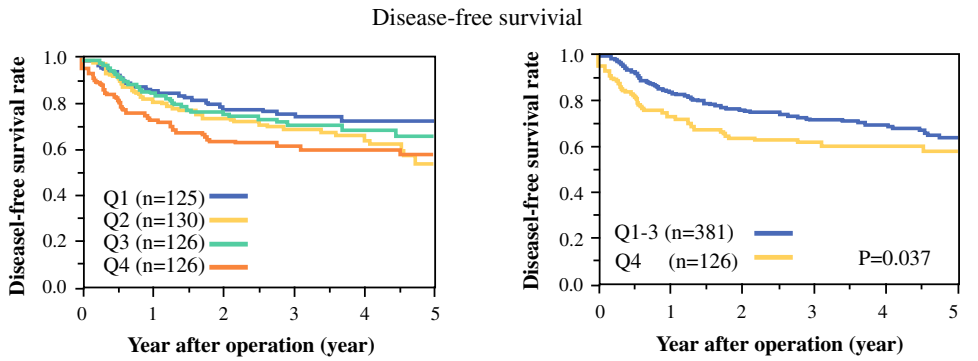


Number atrisk

Years	0	1	2	3	4	5
Q1	125	109	90	66	39	18
Q2	130	120	100	70	42	28
Q3	126	112	96	62	38	20
Q4	126	94	77	61	38	23

Number atrisk

Years	0	1	2	3	4	5
Q1-3	381	341	286	198	119	61
Q4	126	94	77	61	38	23



Number atrisk

Years	0	1	2	3	4	5
Q1	125	96	83	60	38	18
Q2	130	106	86	60	36	16
Q3	126	99	82	54	31	18
Q4	126	86	68	53	29	20

Number atrisk

Years	0	1	2	3	4	5
Q1-3	381	301	251	174	105	52
Q4	126	86	68	53	29	20

FIG. 2 Kaplan–Meier overall survival and disease-free survival, binned into quartiles (Q1–4) of visceral fat content in upper gastrointestinal cancer patients. In the right panels, Q4 represents the "low visceral fat group" and Q1, Q2, and Q3 collectively represent the "high visceral fat group"

nutritional status, the prognostic influence of visceral fat status was consistent across tumor stages and tumor depths (p of interaction = 0.94 and 0.84, respectively). Notably, the effect of low visceral fat seemed to differ between the tumor types [esophageal cancer (univariate HR 1.37; 95 % CI 0.73–2.33) and gastric cancer (univariate HR 2.30; 95 % CI 1.33–3.85)], although this difference was not statistically significant (p of interaction = 0.14).

DISCUSSION

This study examined the prognostic impact of visceral fat content among 507 patients with upper gastrointestinal cancers. We found an association between low visceral fat and poor prognosis, suggesting a potential role for visceral fat status as a biomarker to identify patients who will likely experience an unfavorable clinical outcome.

Recently, visceral fat has been implicated in the promotion of carcinogenesis and in cancer progression through several pathways, including adipocytokine-related inflammation and insulin resistance; the latter is associated with disturbances in insulin-like growth factor-1 (IGF-1) and hypoxia.[6,14] Adipocytokines secreted by visceral adiposity attract inflammatory cells, particularly macrophages and T cells, which produce cytokines, such as the tumor necrosis factor-a and interleukin-6, thus creating a proinflammatory, insulin-resistant, protumorigenic environment.[15,16] Excess visceral fat also decreases adiponectin. Adiponectin inhibits the proliferation, angiogenesis, and inflammatory properties of tumor cells, and promotes their apoptosis.[17–20] Excess visceral fat induces chronic hyperinsulinemia followed by insulin resistance, which reduces the expression of IGF binding protein and subsequently increases IGF-1 expression.[21,22] IGF-1 has protumorigenic properties and is linked

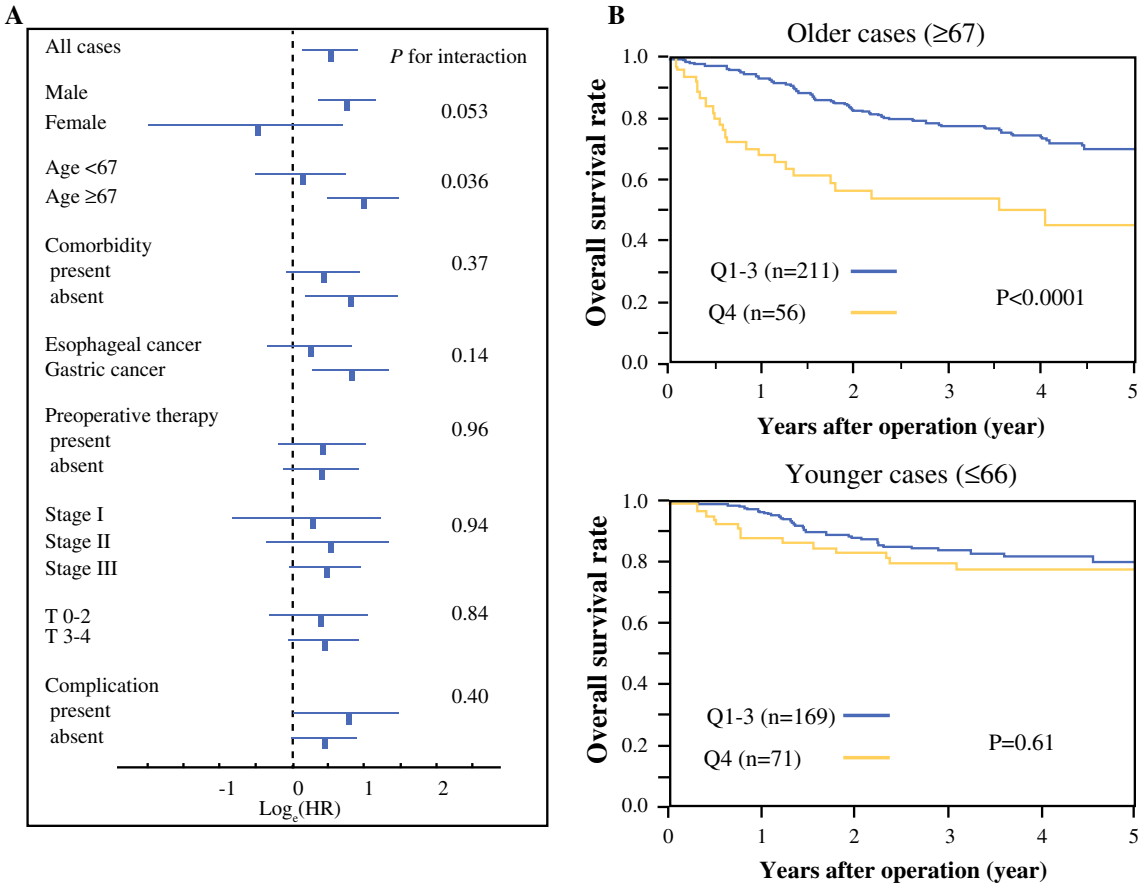


FIG. 3 Visceral fat status and overall survival in various strata. **a** Shown is the $\log_e$ (adjusted HRs) plot of overall survival rate in the low visceral fat group versus that in the high visceral fat group. 95 % CI also is indicated. **b** Kaplan–Meier curves of overall survival among older than 67 years (*upper panel*) and patients younger than 66 years (*lower panel*). Q4 represents the "low visceral fat group" and Q1, Q2, and Q3 collectively represent the "high visceral fat group"

to increased malignancy and progression of several gastrointestinal malignancies.[23–26] Hence, before conducting this study, we hypothesized a correlation between higher visceral fat content and poorer prognosis. Indeed, this correlation has been previously reported in several cancer types.[8–10,27–31] However, no positive association between higher visceral fat level and overall patient mortality was observed in this present study on upper gastrointestinal cancer patients.

The current "gold standard" for quantitative assessment of intra-abdominal adipose tissue is CT.[7] Collectively, these methods can adequately distinguish between visceral and subcutaneous adipose tissue compartments. Importantly, Kobayashi et al. demonstrated that single-slice estimates of visceral fat area at the umbilicus level strongly correlate with volumetric reconstruction.[32] Therefore, the visceral fat area should be reasonably evaluated from a single slice of CT imaged at the umbilical level.

An advanced-stage symptom of upper gastrointestinal cancer is oral ingestion disorder. In particular, deep tumors may lead to obstruction and dysphagia. Nutritional compromise caused by decreased intake, cachexia, or inflammation are associated with poor cancer prognosis.[33,34] Consistent with a previous report, the present study showed that the visceral fat content is lower in patients with advanced tumors than in patients with early-stage tumors, suggesting that visceral fat content is significantly impacted by tumor stage.[35] However, although our multivariate Cox model was adjusted for various clinical and pathological features, low visceral fat was nonetheless associated with a significantly higher overall mortality rate. Furthermore, we revealed that the influence of low visceral fat on overall survival was unmodified by tumor stage or tumor depth. Thus, the correlation between visceral fat content and stage of cancer progression does not sufficiently explain our present findings.

The relationship between prognosis and visceral fat content may be attributed to several factors. First, low visceral fat might reflect a malnutrition state. In the present study, low visceral fat was associated with preoperative weight loss, lower lymphocyte count and hypoalbumia. Furthermore, patients with low visceral fat content might

be pre-cachectic and thus respond less favorably to anticancer treatment.[35–38] Second, visceral fat is an energy store that correlates with physical capacity, suggesting that low visceral fat reserves affect cancer prognosis. Obese patients have a large energy store, which they can access in times of negative energy balance.[39] Conversely, the basic physical capacity is much reduced in patients with low visceral fat reserves and should present as a poor prognostic feature. Importantly, unlike older individuals, young individuals can compensate for an energy storage loss. Hence, we may adequately state that low visceral fat in the upper gastrointestinal cancers is associated with a poor prognosis, especially in elderly patients. This suggests a use for visceral fat content as a biomarker to identify patients who will experience an inferior outcome.

Our cohort included a relatively large number of patients ($n = 507$) in a single institution. Our sample size is sufficiently large to evaluate the prognosis factors. Moreover, the therapeutic strategy and surgical technique remained virtually unchanged throughout the study. However, the present investigation is somewhat limited, because it involved a cohort study rather than a prospective, controlled trial. Nonetheless, as mentioned above, the majority of patients were tracked in a prospective database. Additionally, it is not easily determined whether low visceral fat content reflects the precancer state or results from anorexia and cachexia.

In conclusion, we identified a correlation between low visceral fat in upper gastrointestinal cancer patients and poor prognosis, suggesting that low visceral fat may provide a biomarker for identifying patients likely to experience an inferior outcome. However, the influence of visceral fat content on the biological features of upper gastrointestinal cancer requires further analysis.

Disclosure None.

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