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Adipokines and Clinical Outcomes in Upper Gastrointestinal Cancer: Protocol for a Prospective Cohort Study

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ABSTRACT

Obesity is associated with upper gastrointestinal (GI) malignancies, with particularly strong epidemiological links to oesophageal adenocarcinoma and gastric cardia cancer. Adipose tissue is biologically active, and adipokines may provide one of the links between excess adiposity, inflammation, and tumour progression. Clinical evidence, however, remains limited. Most studies have examined one or a small number of circulating adipokines, often in relatively small cohorts, while tissue expression and long-term oncological outcomes have received much less attention. This prospective cohort study will be conducted at two tertiary university hospitals in Athens, Greece, with a 36-month recruitment period and a total study duration of 48 months. Adults with histologically confirmed oesophageal or gastric cancer undergoing curative-intent surgery will be eligible. Preoperative serum adipokines will be measured using enzyme-linked immunosorbent assays, while subcutaneous and omental adipose tissue will be collected during surgery for tissue-level assessment. Clinical, nutritional, metabolic, pathological, and oncological data will be recorded prospectively. The primary objective is to examine whether circulating and tissue adipokine profiles are associated with tumour stage, clinicopathological characteristics, and prognosis. Postoperative morbidity, recurrence, disease-free survival, and overall survival will also be evaluated. By examining serum and two adipose tissue compartments within the same patients, this study will address whether circulating adipokine changes reflect tissue-level findings and whether particular adipokine patterns are associated with tumour behaviour or clinical outcome. Findings from this cohort may help identify signals that warrant further evaluation in larger, disease-specific studies.

Key words: *Adipokines; upper gastrointestinal cancer; obesity; prognosis; prospective cohort study*

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BACKGROUND

Upper gastrointestinal (GI) malignancies, including oesophageal and gastric cancer, remain major causes of cancer-related mortality worldwide and continue to carry a poor prognosis despite advances in treatment. Among these malignancies, oesophageal squamous cell carcinoma and adenocarcinoma differ substantially in their epidemiology and risk factors, while gastric cancer presents a biologically

and clinically heterogeneous group of tumours [1,2].

Obesity is increasingly recognised as a risk factor for certain upper GI malignancies, with an established association with oesophageal and gastric cardia adenocarcinoma [3,4]. In contrast, oesophageal squamous cell carcinoma is primarily associated with tobacco smoking and alcohol consumption, rather than obesity [1]. Beyond its association with increased cancer risk, adiposity is thought to influence tumour biology through the endocrine activity of adipose tissue and the release of bioactive mediators [5-7]. Among these, adipokines have attracted interest because of their involvement in metabolic regulation, inflammation, angiogenesis, and cell proliferation [6,7]. Several adipokines, including leptin, adiponectin, resistin, visfatin, chemerin, and omentin, have been linked to pathways involved in tumour development and progression [6,7]. Among these, leptin and adiponectin have been studied more extensively, while evidence for other adipokines in oesophageal and gastric cancer remains limited [6-9].

The aim of this study is to investigate the association between circulating and adipose tissue adipokine profiles and tumour characteristics, prognosis, and clinical outcomes in patients with oesophageal and gastric cancer.

OBJECTIVES

Primary Objectives

The primary objectives of the proposed study protocol are:

1. To assess the association between preoperative serum concentrations of selected adipokines, including leptin, adiponectin, resistin, visfatin, chemerin, and omentin, and tumour stage and prognosis in patients with oesophageal and gastric cancer.
2. To evaluate the expression of these adipokines in subcutaneous and omental adipose tissue and correlate tissue expression with clinicopathological characteristics and clinical outcomes.

Secondary Objective

To investigate the relationship between nutritional and metabolic status and prognosis in patients with upper gastrointestinal cancer.

METHODS AND DESIGN

Study Design and Setting

This is a prospective cohort study that will be conducted at two tertiary university hospitals in Athens, Greece. Patients will be eligible if they are aged ≥18 years, have histologically confirmed oesophageal or gastric cancer, and are scheduled for elective surgical resection with curative intent. Written informed consent will be required before inclusion. Patients with another active malignancy and those unable to provide informed consent or comply with study procedures will be excluded. Patients found to have unresectable or metastatic disease during surgery will remain in the observational cohort, while analyses requiring pathological staging after resection or disease-free survival will be restricted to patients who undergo tumour resection and meet the criteria for the respective analyses.

Sample Size and Recruitment

The participating centres have a combined annual surgical volume of approximately 150 patients with oesophageal or gastric cancer. Over the planned 36-month recruitment period, approximately 450 patients are expected to be assessed for eligibility. Assuming an enrolment rate of 80%, the anticipated study population will comprise approximately 360 patients.

Given the exploratory nature of the study, the sample size is primarily based on anticipated recruitment feasibility. Allowing for 10% incomplete data, approximately 324 patients are expected to be available for analysis. For a representative comparison of circulating adipokine concentrations between two groups with a 30:70 distribution, this sample would provide 80% power to detect a standardised mean difference of approximately 0.34, using a two-sided significance level of 0.05. This calculation represents an illustrative sensitivity analysis rather than a formal power calculation for all planned biomarker–outcome associations.

The study is intended to explore associations between adipokines and clinical outcomes rather than provide definitive validation of individual biomarkers. Analyses involving smaller subgroups or less frequent outcomes may have limited statistical power and will be interpreted accordingly.

Data Collection

Demographic and clinical data will include age, sex, type of malignancy, treatment received, type of surgery, American Society of Anesthesiologists (ASA) physical status, Eastern Cooperative Oncology Group (ECOG) performance status, and follow-up. Medication use, including antidiabetic agents, statins, and corticosteroids, will also be recorded. Routine blood tests, inflammatory markers, tumour markers, and lipid parameters will also be recorded.

Nutritional and metabolic status will be assessed using changes in body weight and body mass index (BMI),

along with validated nutritional assessments including the Patient-Generated Subjective Global Assessment (PG-SGA), Prognostic Nutritional Index (PNI), Geriatric Nutritional Risk Index (GNRI), Controlling Nutritional Status (CONUT), and Global Leadership Initiative on Malnutrition (GLIM) criteria. Anthropometric and body-composition assessment will include skeletal muscle and sarcopenia indices, with CT-derived measurements obtained from available staging examinations, while functional assessment will include handgrip strength and gait speed.

Pathological variables will include histological type, tumour grade, TNM classification, and disease stage. Clinical stage before treatment and pathological stage after surgery will be recorded separately, including post-neoadjuvant pathological staging (ypTNM), where applicable. Neoadjuvant treatment regimens and the interval between treatment completion and surgery will also be documented. Postoperative outcomes will include length of stay and any complications graded using the Clavien-Dindo classification. Clinical and oncological follow-up will be performed at 3, 6, and 12 months after surgery and annually thereafter, with additional assessments according to clinical indications. Disease recurrence, disease-free survival, and overall survival will be recorded using clinical records and available follow-up information.

Patient recruitment and biological sample collection will take place over 36 months, with an anticipated enrollment of approximately 360 patients. An additional 12 months will be allocated for completion of follow-up, laboratory analyses, and statistical evaluation, resulting in a total study duration of 48 months. Primary results are expected to become available by the end of this period, while longer-term oncological follow-up will continue beyond study completion.

Biological Sample Collection and Laboratory Analyses

Preoperative venous blood samples will be obtained within one week before surgery. Sampling will follow a standardised protocol across both participating centres, including consistent collection, processing, and storage procedures. Serum will be separated by centrifugation and stored at −80°C until analysis. Approximately 0.5–1 g of tissue will be collected from each compartment, with subcutaneous samples obtained from the abdominal incision site and omental samples obtained from macroscopically unaffected areas of the greater omentum. Tissue collection will be attempted in all enrolled patients whenever anatomically feasible, and unavailable or inadequate samples will be documented. Samples intended for molecular analysis will be stored at −80°C. Samples intended for histological assessment will be fixed in 10% neutral-buffered formalin and processed as formalin-fixed, paraffin-embedded tissue.

Serum leptin, adiponectin, resistin, visfatin, chemerin, and omentin concentrations will be measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits. Samples from both participating centres will be distributed across batches to minimise intercentre analytical variability. Adipokine protein expression in adipose tissue will also be examined by immunohistochemistry (IHC), using antibodies validated for human formalin-fixed, paraffin-embedded tissue, with standard positive and negative controls. Immunohistochemical expression will be assessed semi-quantitatively based on staining intensity, classified as negative (0), weak (1+), moderate (2+), or strong (3+), and the percentage of positively stained cells. Furthermore, tissue expression will be assessed by two independent observers blinded to clinical outcomes. Interobserver agreement will be assessed using weighted Cohen's kappa, and discrepancies will be resolved by consultation with a senior pathologist. Finally, relationships between serum adipokine concentrations and expression in subcutaneous and omental adipose tissue will also be investigated.

Statistical Analysis

Baseline characteristics will be summarised using appropriate descriptive statistics. Associations between individual adipokines and tumour stage, histological characteristics, and postoperative outcomes will be examined using univariable analyses. Continuous outcomes will be analysed using linear regression, binary outcomes using logistic regression, and ordered categorical outcomes using ordinal logistic regression where appropriate. Multivariable analyses will be performed to account for relevant clinical and demographic factors, including age, sex, BMI, tumour type, and treatment characteristics. Given the exploratory nature of the study, analyses involving multiple biomarkers and outcomes will be considered hypothesis-generating. The Benjamini–Hochberg method will be used to adjust for multiple comparisons, while statistical significance will be set at a two-sided p value of <0.05, with adjusted p values reported for analyses involving multiple comparisons.

Overall survival and DFS will be estimated using Kaplan-Meier analysis. Overall survival will be defined as the interval from surgery to death from any cause, while DFS will be defined as the interval from curative resection in patients without residual disease to documented disease recurrence or death, whichever occurs first. Patients without an event will be censored at their last available follow-up. Cox proportional hazards regression will be

used to associate adipokine concentrations and survival after adjustment for covariates, including age, sex, BMI, tumour stage, and comorbidities. Oesophageal and gastric cancers will be analysed separately where sample size permits, with further subanalyses according to histological or anatomical subtype. In addition, patients receiving neoadjuvant treatment and treatment-naïve patients will be evaluated in separate strata to account for potential treatment-related effects on adipokine concentrations. Clinical and pathological tumour stages will be analysed separately, with post-neoadjuvant pathological staging considered in patients who received preoperative treatment.

The primary analyses will focus on the associations between adipokine profiles, tumour stage, and survival outcomes. Additional evaluation will examine associations with clinicopathological, postoperative, nutritional, and metabolic outcomes.

Relationships among circulating adipokine levels and between serum levels and tissue expression will also be assessed. Correlations between serum concentrations and adipokine expression in subcutaneous and omental adipose tissue will be investigated separately using appropriate correlation coefficients.

Ethical Considerations

The study protocol will be submitted for approval to the Ethics Committees of both participating institutions. Written informed consent will be obtained from all participants before enrolment, including consent for biological sample collection and analysis. Patient data will be pseudonymised and handled in accordance with applicable data protection regulations.

DISCUSSION

Obesity is increasingly recognised as an important factor in the development and progression of several malignancies, including upper gastrointestinal cancers. One suggested link between excess adiposity and aggressive tumour biology is the activity of adipose tissue, which contributes to metabolic, inflammatory, and endocrine signalling through the release of adipokines [5-7]. These mediators have been linked to pathways involved in cell proliferation, angiogenesis, immune regulation, and tumour progression [6,7]. Among them, leptin and adiponectin have been studied more extensively in gastrointestinal malignancies, while the roles of resistin, visfatin, chemerin, and omentin remain less clearly defined [6-8].

The role of adipokines in upper gastrointestinal malignancy remains unclear. Most of the available data has focused on circulating biomarkers, and findings have not always been consistent. For instance, in oesophageal adenocarcinoma, a systematic review of obesity-related inflammatory and metabolic biomarkers found inconsistent associations across several circulating markers [9]. Additionally, evidence relating broader adipokine profiles to adipose tissue expression, pathological characteristics, recurrence, DFS, and OS is less developed [7,8]. It therefore remains uncertain whether alterations in adipokines primarily reflect obesity, systemic inflammation, nutritional deterioration, or tumour burden, or whether particular profiles are more closely associated with tumour behaviour and prognosis.

The proposed protocol was designed to address several of these gaps. Rather than examining individual adipokines in isolation, a broader panel will be assessed in parallel. Circulating concentrations will also be examined alongside expression in subcutaneous and omental adipose tissue obtained from the same patients. This permits comparison of systemic adipokine levels with two distinct adipose compartments. Omental adipose tissue is of particular interest as a visceral depot within the upper abdominal tumour environment, while subcutaneous tissue provides a different adipose compartment for comparison.

Adipokine measurements will further be interpreted alongside clinical, nutritional, pathological, and oncological data. Their associations with TNM stage, histological characteristics, postoperative morbidity, recurrence, DFS, and OS will be examined together with nutritional and metabolic parameters. This may help clarify whether particular adipokine patterns are associated with specific tumour characteristics or subsequent clinical outcomes.

A major strength of the protocol is the prospective and simultaneous collection of biological samples and clinical data within a defined surgical population. The assessment of several adipokines in parallel, together with paired serum and tissue measurements, provides the opportunity to examine both systemic and tissue-level patterns. Sampling both subcutaneous and omental adipose tissue also allows differences between adipose compartments to be explored and provides the opportunity to assess the same biomarkers across distinct tissue environments. In addition, assessment of nutritional status, body composition, inflammatory indices, functional status, and pathological characteristics should allow adipokine findings to be interpreted within the broader clinical and metabolic context of each patient.

Several limitations should also be considered. The observational design cannot establish causality, and preoperative adipokine concentrations may be influenced by tumour burden, cancer-related weight loss, systemic

inflammation, nutritional status, or previous neoadjuvant treatment. In patients receiving neoadjuvant therapy, preoperative adipokine concentrations will reflect the post-treatment state, which may differ from that of treatment-naïve patients. These groups will therefore be evaluated separately. A single preoperative serum measurement will also not capture changes occurring during treatment or follow-up. Oesophageal and gastric cancers each include biologically distinct histological and anatomical subtypes, and the number of patients within individual subgroups may limit the power of disease-specific analyses. In addition, the evaluation of several biomarkers and multiple outcomes increases the possibility of chance associations. Accordingly, findings will be considered exploratory and will require confirmation in independent cohorts.

Overall, this prospective investigation aims to clarify the relationship between circulating and adipose tissue adipokines and the clinical and pathological features of upper gastrointestinal cancer. Comparing serum, subcutaneous adipose tissue, and omental adipose tissue within the same cohort may help identify patterns associated with tumour behaviour or prognosis and determine which adipokines warrant further investigation in larger, disease-specific populations.

CONCLUSION

This prospective study will investigate the relationship between circulating and adipose tissue adipokine profiles and the clinicopathological and oncological characteristics of oesophageal and gastric cancer. By assessing serum concentrations together with subcutaneous and omental adipose tissue expression, it aims to provide a clearer picture of adipokine profiles across different biological compartments. The findings may help determine whether specific adipokine patterns are associated with tumour stage, recurrence, or survival and identify those that warrant further investigation in larger, disease-specific cohorts.

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