

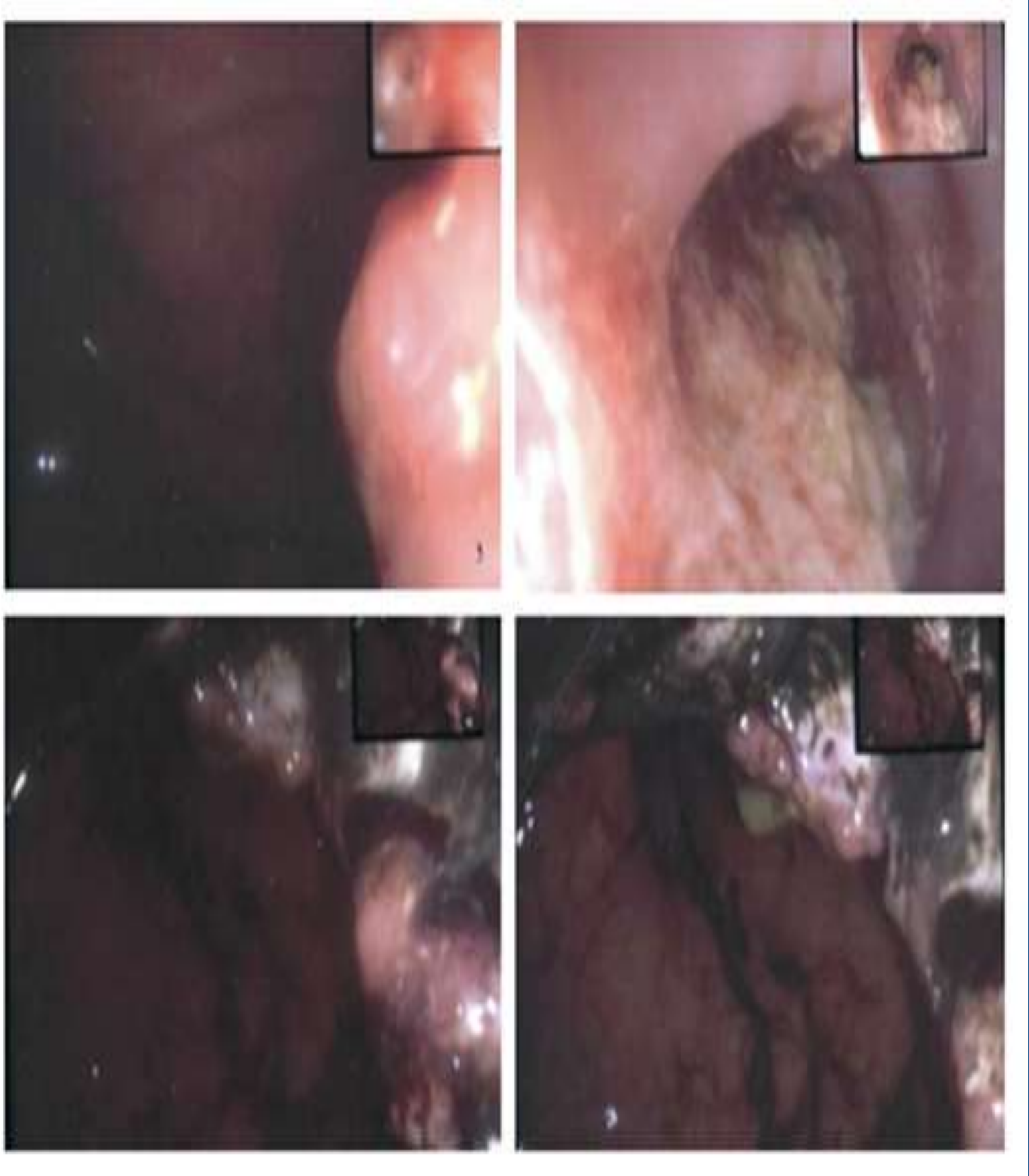
# Oligometastatic Mixed Neuroendocrine Adenocarcinoma of the Esophago-Gastric Junction: A Case of Successful Multidisciplinary Management, the Lessons Learnt and Review of the Literature

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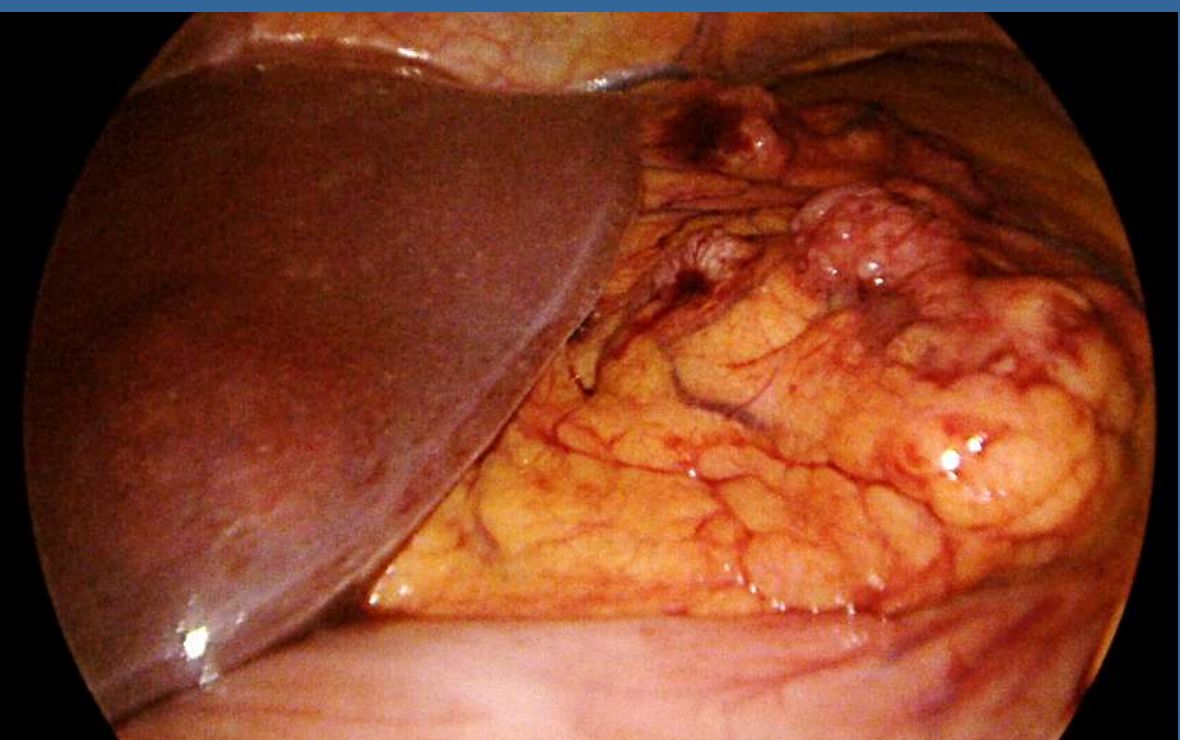
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**Background:** Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) of the esophago-gastric junction (EGJ) are rare aggressive malignant neoplasms, with, currently, limited evidence regarding the appropriate therapeutic approach.

**Methods:** Herein, we report the multimodal treatment management of a patient with oligometastatic MiNEN of EGJ (Siewert III), discuss the lessons learnt, and refer to the existent literature.

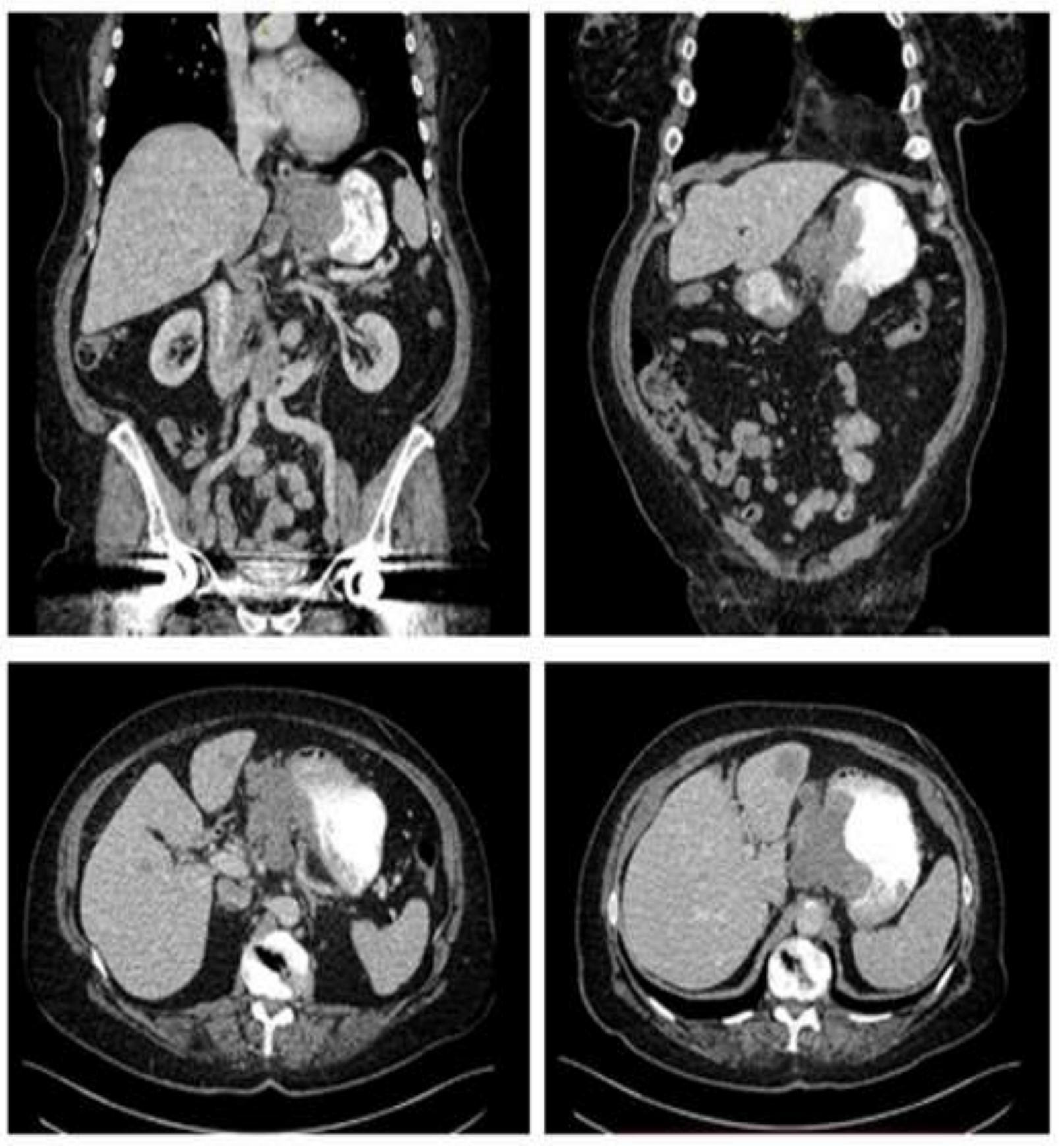


Initial gastroscopy findings depicting an ulcerous lesion at the gastroesophageal junction and the lesser curvature of gastric cardia

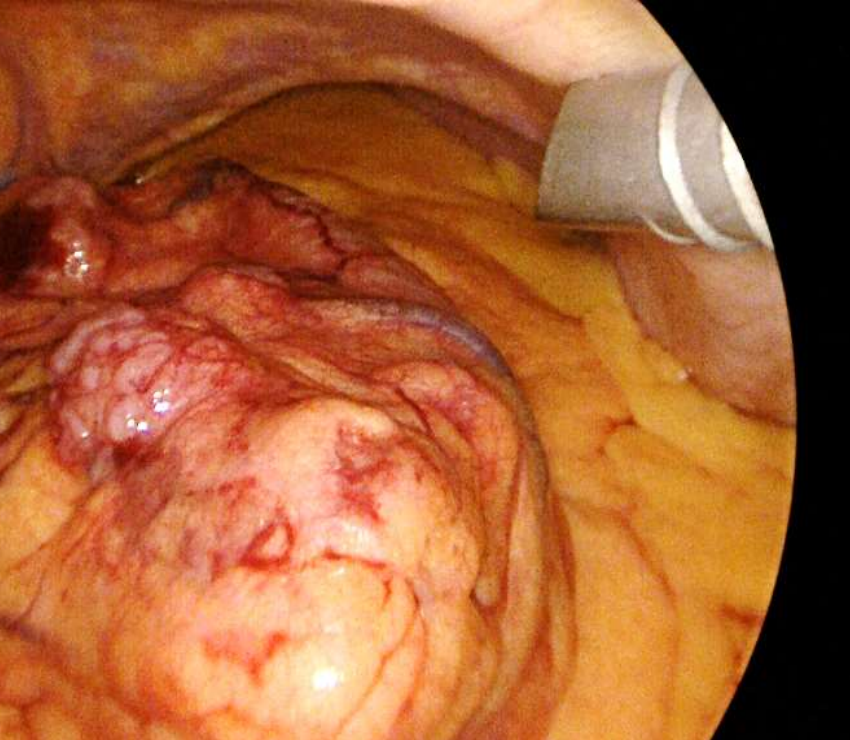


Initial exploratory laparoscopy findings with a visible liver metastatic lesion on the left hepatic lobe.

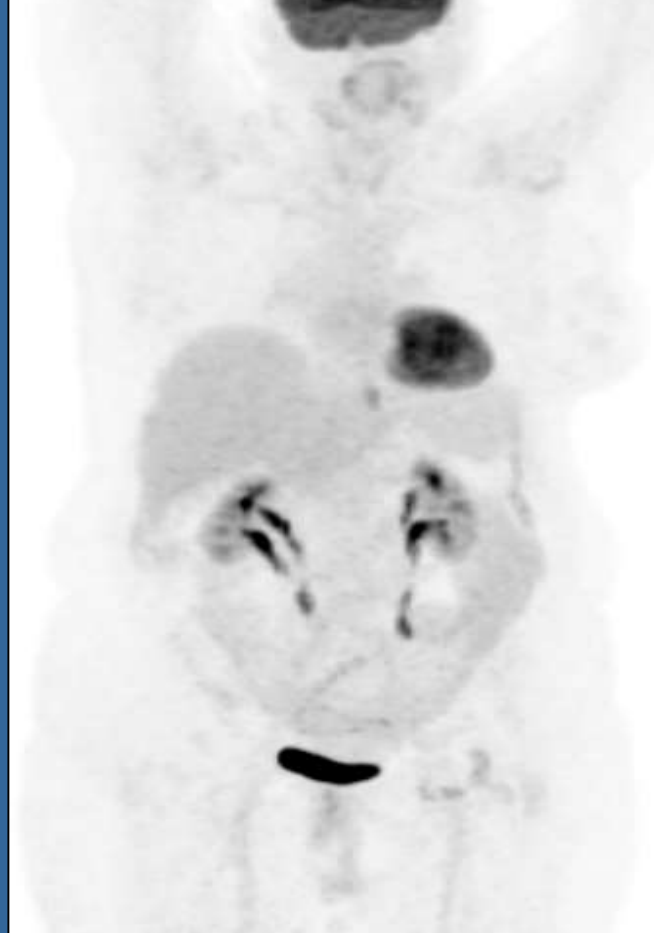
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Initial abdominal computed tomography in coronal and axial views, depicting the gastric lesion and liver metastatic lesions.



Initial exploratory laparoscopy findings with a visible liver metastatic lesion on the left hepatic lobe.



FDG PET-CT in coronal view, with high SUV noticed at the GEJ post neoadjuvant chemotherapy.

**Results:** A 69-year-old female with worsening dysphagia was diagnosed with a locally advanced EGJ tumor and three liver metastases (cT4, cN+, M1). As the initial histology from biopsy revealed a poorly differentiated HER2 negative adenocarcinoma, the patient was immediately set under a systemic chemotherapy protocol of combined fluorouracil, leucovorin, and oxaliplatin (FOLFOX). However, the histopathology of a lymph node biopsy from staging laparoscopy revealed infiltration of neuroendocrine carcinoma cells. Thus, the diagnosis of a mixed neuroendocrine adenocarcinoma was set, and systemic chemotherapy with etoposide and cisplatin was initiated to tackle the more aggressive and metastatic neuroendocrine component. A major clinical response post 6 cycles of chemotherapy led to conversion surgical resection of the primary tumor and metastases, following MDT discussion. Gastrectomy with D2 lymph node excision and atypical left hepatectomy with Radiofrequency ablation of liver scar tissue was performed. Histopathologic examination of the surgical specimen revealed the exclusive presence of residual adenocarcinoma of the primary lesion. Molecular analysis revealed a positive PD-L1-/CPS-Score of 6. Consequently, the patient received systemic chemotherapy with FOLFOX accompanied by immunotherapy with Nivolumab for three months, followed by maintenance therapy with Nivolumab monotherapy. The patient is free of disease and in good condition at the 3-year follow-up.

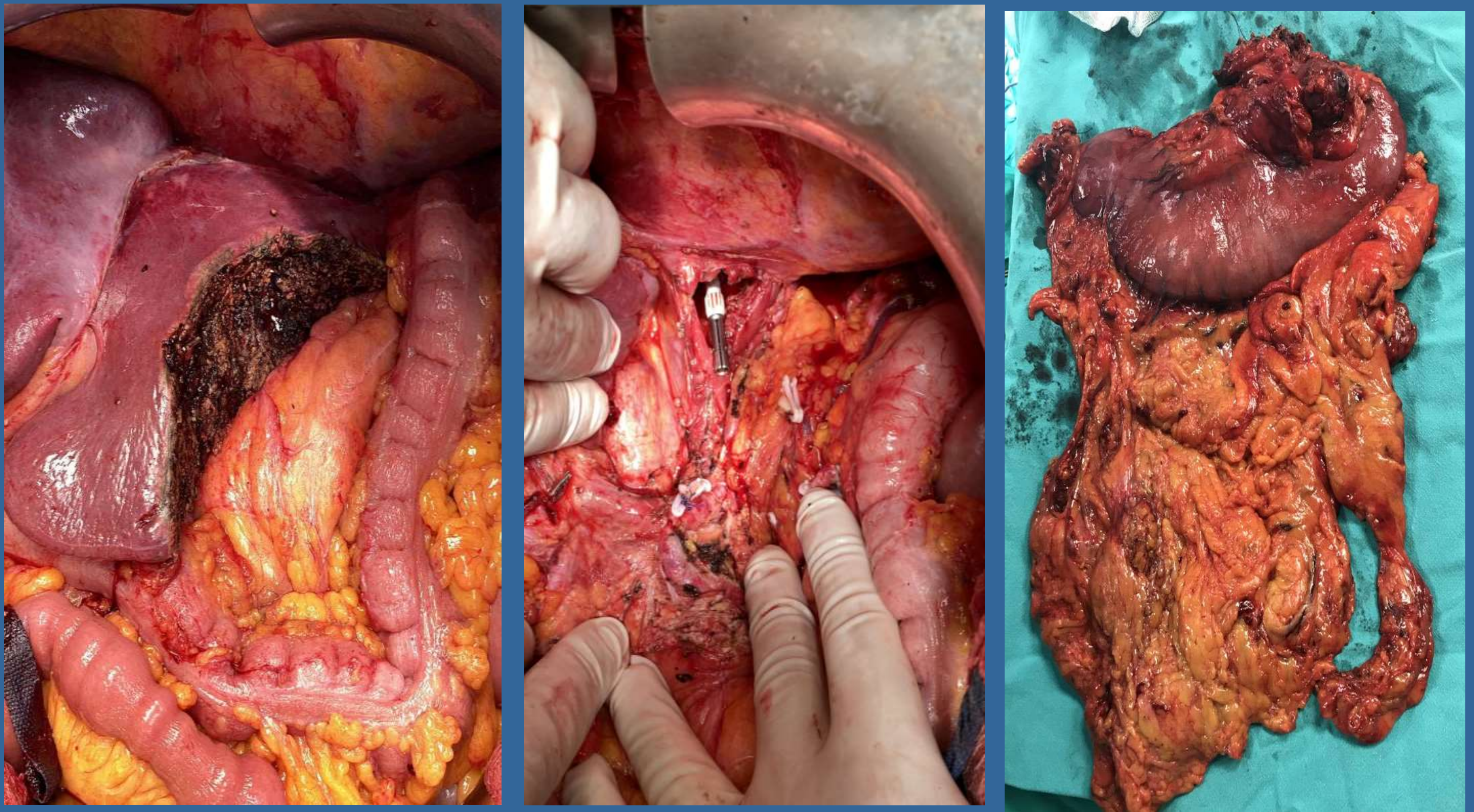
BEFORE INDUCTION THERAPY		POST INDUCTION THERAPY	
EGJ tissue Endoscopic biopsy	Lymph node laparoscopy	EGJ tissue Surgical specimen	Lymph node Surgical specimen
A 	B 	C 	D 
H-E stain (x40 magnification)	H-E stain (x20 magnification)	H-E stain (x20 magnification)	H-E stain (x20 magnification)
E 	F 	G 	H 
CKPAN marker, negative (x40 magnification)	AE1/AE3 marker, negative (x40 magnification)	CKPAN marker, negative (x40 magnification)	CKPAN marker, negative (x20 magnification)
I 	J 	K 	L 
Chromogranin A stain, positive (x40 magnification)	Chromogranin A stain, positive (x40 magnification)	CD68 marker, positive (x40 magnification)	Chromogranin A stain, negative (x20 magnification)
M 	N 	O 	P 
INSM-1 stain, positive (x40 magnification)	Synaptophysin stain, positive (x40 magnification)	Synaptophysin stain, negative (x40 magnification)	Synaptophysin stain, negative (x20 magnification)

Histologic images from primary EGJ tumor and lymph node, before and after induction chemotherapy showing regression of the neuroendocrine component.

A review of the literature on similar cases of EGJ or gastric MiNENs revealed a limited number of cases. All in all, it appears that current practices are in line with our suggestions and align with the latest European clinical practice guidelines for the definition, diagnosis, and treatment of oligometastatic esophagogastric cancer (OMEC-4). Regarding oligometastatic disease, platinum-based chemotherapy combined with etoposide or irinotecan is preferred as the induction regimen. Performance status is crucial in deciding whether patients are eligible to commence chemotherapy. Conversion surgery could be a potential choice following significant tumor burden remission.

## Conclusions:

- Our case and the existing literature on MiNENs of EGJ underline the need for a personalized treatment approach following thorough interpretation of comprehensive pretherapeutic staging.
- The key to successful management is the early detection of the mixed nature of the malignant tumor.
- Immunostaining of at least one neuroendocrine marker on endoscopic biopsies in EGJ tumors should facilitate early diagnosis.
- Conversion radical surgery with curative intent could be considered in cases of major or complete clinical response to induction chemotherapy with potentially favorable outcomes.
- Further research on the field of oligometastatic MiNENs is required, in order to standardize a therapeutic protocol with the most favorable outcome for the patients.



Surgical situs post-gastrectomy and atypical left hepatectomy, impression of the celiac trunk post-resection showing the D2-lympadenectomy and ligation of left gastric artery and impressed en bloc resected surgical specimen.

**References:** Sotiropoulou, A.; Avgoustidou, M.; Milionis, V.; Papadimitriou, I.; Vergadis, C.; Schizas, D.; Arkadopoulos, N.; Lyros, O. Oligometastatic Mixed Neuroendocrine Adenocarcinoma of the Esophago-Gastric Junction: A Case of Successful Multidisciplinary Management, the Lessons Learnt and Review of the Literature. J. Clin. Med. 2025, 14, 1503. <https://doi.org/10.3390/jcm14051503>