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Preoperative hiatal hernia in esophageal adenocarcinoma; does it have an impact on patient outcomes?☆,☆☆

Pénélope St-Amour [a], Styliani Mantziari [a,b,*], Clarisse Dromain [b,c], Michael Winiker [a], Sebastien Godat [b,d], Alain Schoepfer [b,d], Nicolas Demartines [a,b], Markus Schäfer [a,b]

[a] University Hospital of Lausanne, Department of Visceral Surgery, Lausanne, Switzerland
[b] Faculty of Biology and Medicine, University of Lausanne UNIL, Switzerland
[c] University Hospital of Lausanne, Institute of Radiodiagnosis and Interventional Radiology, Lausanne, Switzerland
[d] University Hospital of Lausanne, Division of Gastroenterology and Hepatology, Lausanne, Switzerland

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ABSTRACT

Background: The impact of hiatal hernia (HH) on oncologic outcomes of patients with esophageal adenocarcinoma (AC) remains unclear. The aim of this study was to assess the effect of pre-existing HH (≥3 cm) on histologic response after neoadjuvant treatment (NAT), overall (OS) and disease-free survival (DFS).
Methods: All consecutive patients with oncological esophagectomy for AC from 2012 to 2018 in our center were eligible for assessment. Categorical variables were compared with the X^2 or Fisher's test, continuous ones with the Mann-Whitney-U test, and survival with the Kaplan-Meier and log-rank test.
Results: Overall, 101 patients were included; 33 (32.7%) had a pre-existing HH. There were no baseline differences between HH and non-HH patients. NAT was used in 81.8% HH and 80.9% non-HH patients ($p = 0.910$), most often chemoradiation (63.6% and 57.4% respectively, $p = 0.423$). Good response to NAT (TRG 1–2) was observed in 36.4% of HH versus 32.4% of non-HH patients ($p = 0.297$), whereas R0 resection was achieved in 90.9% versus 94.1% respectively ($p = 0.551$). Three-year OS was comparable for the two groups (52.4% in HH, 56.5% in non-HH patients, $p = 0.765$), as was 3-year DFS (32.7% for HH versus 45.6% for non-HH patients, $p = 0.283$).
Conclusion: HH ≥ 3 cm are common in patients with esophageal AC, concerning 32.7% of all patients in this series. However, its presence was neither associated with more advanced disease upon diagnosis, worse response to NAT, nor overall and disease-free survival. Therefore, such HH should not be considered as risk factor that negatively affects oncological outcome after multimodal treatment of esophageal AC.

1. Introduction

Adenocarcinoma (AC) is the predominant histological type of esophageal cancer in the western world, with obesity and uncontrolled gastro-esophageal reflux disease (GERD) among the main risk factors [1]. Long-standing GERD may trigger a series of histopathologic changes of the esophageal mucosa, such as esophagitis, metaplasia and dysplasia, the latter predisposing to malignant transformation, in 1 out of 8 patients with Barrett's esophagus [2–4]. However, reflux symptoms are a poor predictor of the underlying mucosal damage, as 46% of patients with Barrett's and 80% with AC report no pre-existing reflux symptoms [5]. On its turn, the presence of a clinically significant hiatal hernia (HH) has been identified as a risk factor for Barrett's esophagus, high-grade dysplasia or AC, even in the absence of reflux [6,7].

No universally accepted cut-off for a clinically significant HH has been determined, since most studies do not provide precise definitions of

Abbreviations: HH, Hiatal Hernia; AC, Adenocarcinoma; NAT, Neoadjuvant Treatment; OS, Overall Survival; DFS, Disease-Free Survival; GERD, Gastro-Esophageal Reflux Disease; GEJ, Gastro-Esophageal Junction; EGD, Esogastroduodenoscopy; EUS, Endosonography; RCT, Radiochemotherapy; CT, Chemotherapy; TRG, Tumor Regression Grade; ECCG, Esophagectomy Complications Consensus Group; IQR, Interquartile Range.

☆ The study was approved by the Institutional Ethics Committee.☆☆ This work has been presented in parts in the Congress of Swiss Visceral Surgery Society (SSCV) in Interlaken, Switzerland, 9–11 September 2021.

* Corresponding author. University Hospital of Lausanne, Department of Visceral Surgery, Rue du Bugnon 46, CH 1011, Lausanne, Switzerland.
E-mail address: styliani.mantziari@chuv.ch (S. Mantziari).

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HH [8,9]. Patients with GERD and HH < 3 cm experience similar function as patients without HH, with comparable incidence of reflux symptoms, lower esophageal sphincter characteristics, esophageal peristalsis and acid exposure [10]; hence, we defined a clinically significant HH as ≥ 3 cm. The size of HH has been related to the severity of esophagitis and consequent mucosal changes [10]. Navab et al. reported that every cm of HH length increased the risk of Barrett's metaplasia by 19% [11].

Conversely, among patients who develop esophageal AC the impact of pre-existing HH on disease stage upon diagnosis and postoperative outcomes remain largely unknown. Gandon et al. reported that patients with a large (>5 cm) HH had higher risk of incomplete surgical resection and poor long-term survival, although they received comparable neoadjuvant treatment (NAT) as non-HH patients [12]. So far, this is the only study reporting poor oncological outcomes associated with the presence of a HH, while a clear pathophysiological explanation still lacks. As a preoperative HH remains a common finding in esophageal cancer patients, more robust data are needed to establish its potential relation, if any, with disease stage upon diagnosis, treatment efficacy and patient survival.

The aim of our current study was to assess the potential impact of a preoperative clinically significant HH (≥3 cm) on cancer stage upon diagnosis, histologic response to NAT, overall and disease-free survival of patients with esophageal AC.

2. Materials and methods

In this monocentric retrospective analysis, all consecutive patients undergoing curative esophagectomy for AC of the esophagus or gastro-esophageal junction (GEJ) (Siewert I-II) between January 2012 and December 2018, aged >18 years, were eligible for inclusion. Emergency surgery and other histological types were excluded from final analysis. Patient data were retrieved from our prospectively maintained institutional database. Patients who refused to participate in clinical research were excluded. The study was approved by the Institutional Ethics Committee (Protocol Number 2022-00064).

Baseline workup included endoscopic assessment with esogastroduodenoscopy (EGD) with endosonography (EUS) and biopsies, thoraco-abdominal CT-scan and whole-body 18-F-FDG-PET/CT-scan. Endoscopy reports and radiology images were respectively revised by a senior gastroenterologist and radiologist. An exploratory laparoscopy was performed for locally advanced tumors of the distal esophagus and GEJ (cT3 and/or N+) to exclude peritoneal spread. Gold standard for HH definition was endoscopy, when there was a ≥ 3 cm distance between the Z-line and the diaphragmatic hiatus [10]. For obstructive tumors or when the Z-line was not clearly identifiable because of tumor invasion, HH was assessed on baseline contrast-enhanced CT images as a ≥ 3 cm distance between the GEJ and the diaphragmatic hiatus.

All cases were discussed at a multidisciplinary tumor board. Upfront surgery was proposed for early-stage lesions (T1-2 N0), and NAT followed by surgery for locally advanced ones [1]. According to the current treatment guidelines, NAT consisted of radiochemotherapy (RCT) with 5FU/cisplatin or carboplatin/taxane and 41.4–50.4 Gy, or perioperative chemotherapy (CT), most often with ECF according to MAGIC study [13]. In our center, surgical intervention is systematically proposed to all 'fit-for-surgery' patients, even when clinical response to treatment was good or potentially complete. A totally minimal invasive approach was introduced in our department at the end of 2015.

Surgical specimens were histologically examined using the 8th TNM/UICC staging system [14]. Histologic response to NAT was defined with the Mandard score, tumor regression grade (TRG) 1 corresponds to pathologic complete response, whereas TRG5 to no response at all [15]. The Royal College of Pathologists definition was used for definition of R0 resection, as a >0.1 cm distance between the resection margin and the tumor [16]. Finally, based on previous results [12], a subgroup analysis of patients treated with neoadjuvant RCT was performed, to assess if HH was associated with higher RCT-related postoperative morbidity. Overall survival (OS) was defined as the interval (months) between surgery and death, or last follow-up if still alive. Disease-free survival (DFS) was determined with the earliest date of proven local or distant recurrence. In-hospital deaths after the index operation were excluded from survival analysis. Postoperative complications were recorded and graded with the Clavien-Dindo system, severe complications were defined as Clavien ≥ IIIa [17]. Anastomotic leakage was defined and classified according to Esophagectomy Complications Consensus Group (ECCG) [18,19].

Categorical variables were expressed as frequency (%) and compared with the $\chi 2$ or Fisher's exact test, and continuous variables were expressed as median [InterQuartile Range - IQR] and compared with the Mann-Whitney-U test. Time-to-event outcomes were expressed as 3-year overall (OS) and disease-free survival (DFS), as median survival was no reached for any of the groups. The Kaplan-Meier method and log-rank test were used for direct comparison of OS and DFS between the two groups. Statistical analyses were performed with the Rstudio (Version 1.1.383, Boston, USA) and SPSS (version 23.0, Chicago, USA) software.

3. Results

3.1. Baseline demographics, treatment details and morbidity

Among the included 101 patients with AC of the esophagus and GEJ, 33 had a pre-existing HH (32.7%) (Fig. 1). The majority of patients (84.2%) were men, with a median age of 62 years old [IQR 56–70]. No differences in baseline BMI or comorbidity status were observed (Table 1). A similar proportion of patients had preoperatively diagnosed GERD in both groups (48.5% HH patients versus 30.9% non-HH, p = 0.073), while Barrett's metaplasia was present in 42.4% HH and 30.9% non-HH patients (p = 0.154). Patients in the HH group had more proximally located tumors, the majority having an epicenter in the lower esophagus (66.7%), whereas non-HH patients had predominantly junctional lesions (58.8%) (p = 0.018). Median distance between the Z-line and the superior dental arch was 38 cm [IQR 34–42] in HH, and 39 cm [IQR 37–41] in non-HH patients (p = 0.004). No differences between HH and non-HH patients were observed in baseline cTNM stage, obstructive tumor on diagnosis (12.1% vs 7.4% respectively, p = 0.430), or metabolic activity of the primary tumor on PET-CT (SUVmax)

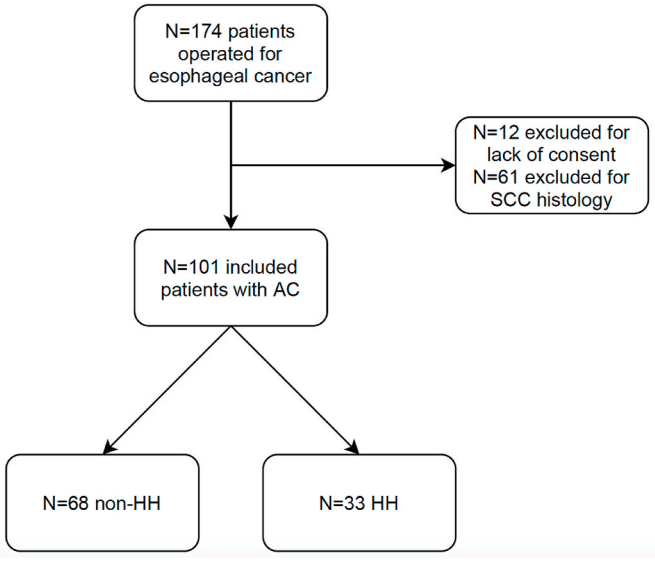


Fig. 1. Flow chart of the study.

Table 1
Baseline demographics.

	All population N = 101	HH patients N = 33	Non-HH patients N = 68	p-value
Male gender	85 (84.2)	29 (87.9)	56 (82.4)	0.475
Age, years	62 [56–70]	63 [48–78]	62 [49–75]	0.229
BMI (kg/m^2)	25 [22.6–28.1]	25.6 [21.9–29.5]	24.8 [22.6–28.1]	0.954
ASA class				0.610
I-II	65 (64.4)	20 (60.6)	45 (66.2)	
III-IV	36 (35.6)	13 (39.4)	23 (33.8)	
Active smoking	32 (31.7)	10 (30.3)	22 (32.4)	0.835
Diabetes	7 (6.9)	2 (6.1)	5 (7.4)	0.810
COPD	27 (26.7)	9 (27.3)	18 (26.5)	0.932
GERD	37 (36.6)	16 (48.5)	21 (30.9)	0.073
Barrett metaplasia/ esophagitis	35 (34.7)	14 (42.4)	21 (30.9)	0.154
Obstructive tumor	9 (8.9)	4 (12.1)	5 (7.4)	0.430
Z-line (cm)	39 [37–40]	38 [34–42]	39 [37–41]	0.004
Tumor location				0.018
GEJ	50 (49.5)	10 (30.3)	40 (58.8)	
Distal third	47 (46.5)	22 (66.7)	25 (36.8)	
Middle third	4 (4.0)	1 (3.0)	3 (4.4)	
cT stage				0.399
1	9 (8.9)	4 (12.1)	5 (7.4)	
2	13 (12.9)	2 (6.1)	11 (16.2)	
3	78 (77.2)	27 (81.8)	51 (75.0)	
4	1 (1.0)	0 (0.0)	1 (1.5)	
cN stage				0.694
0	34 (33.7)	10 (30.3)	24 (35.3)	
1	54 (53.5)	18 (54.5)	36 (52.9)	
2	9 (8.9)	4 (12.1)	5 (7.4)	
3	2 (2.0)	1 (3.0)	1 (1.5)	
Baseline SUVmax	12.4 [8.3–16.9]	13.3 [4.1–22.5]	11.2 [3.0–19.4]	0.273

TNM is based on the 8th edition of UICC classification [14]. Z-line is defined from superior dental arch. Categorial variables are expressed as N (%), and continuous variables as median [IQR].
HH= Hiatal Hernia, ASA = American Society of Anesthesists class, COPD = Chronic Obstructive Pulmonary Disease, GERD = Gastro-Esophageal Reflux Disease, GEJ = gastro-esophageal junction, SUVmax = Maximal Standardized Uptake Value on baseline (pre-treatment) PET-CT.

(Table 1).

Findings concerning surgery and short term post-operative outcomes are summarized in Table 2. The majority of the patients in both groups underwent NAT (81.8% HH, 80.9% non-HH, p = 0.910), most often RCT (63.6% HH versus 57.4% non-HH patients, p = 0.423). Surgical techniques were similar in the two groups, with thoracoabdominal Lewis resection being the procedure of choice in 87.9% HH and 94.1% non-HH patients (p = 0.177). A smaller proportion of HH patients had a minimally invasive approach (laparoscopy in 81.8% vs 91.2%, p = 0.041, thoracoscopy in 36.4% vs 57.4%, p = 0.048). Median operative time as postoperative complications were comparable between the two groups (Table 2).

3.2. Histopathologic analysis

No significant differences in ypTNM/pTNM stage were observed between the groups (Table 3). Lymphovascular and perineural invasion, as tumor differentiation were comparable. Negative margins (R0) were obtained in 90.9% HH versus 94.1% non-HH patients (p = 0.551). Finally, histologic response to treatment was similar in the two groups; 9.1% HH and 10.3% non-HH patients presented a complete pathologic response (TRG1), whereas 39.4% HH and 26.4% non-HH patients had poor response (TRG 4–5) (p = 0.297).

Table 2
Treatment details and post-operative outcomes.

	All population N = 101	HH patients N = 33	Non-HH patients N = 68	p-value
NAT	82 (81.2)	27 (81.8)	55 (80.9)	0.910
Type of NAT				0.423
RCT	60 (59.4)	21 (63.6)	39 (57.4)	
CT	22 (21.8)	6 (18.2)	16 (23.5)	
Surgical approach				0.177
Lewis	93 (92.1)	29 (87.9)	64 (94.1)	
Transhiatal	4 (4.0)	1 (3.0)	3 (4.4)	
Mc-Keown	4 (4.0)	3 (9.1)	1 (1.5)	
Minimally invasive approach				
Laparoscopy	89 (88.1)	27 (81.8)	62 (91.2)	0.041
Thoracoscopy	51 (50.5)	12 (36.4)	39 (57.4)	0.048
Operative time (min)	290 [260–323]	290 [224–356]	283 [216–350]	0.794
Severe complications (>Clavien IIIA)	34 (33.7)	13 (39.4)	21 (30.9)	0.396
Anastomotic leakage	33 (32.7)	10 (30.3)	23 (33.8)	0.723
Pneumonia	50 (49.5)	18 (54.5)	32 (47.1)	0.480
Atrial Fibrillation	27 (26.7)	10 (30.3)	17 (25.0)	0.572

Categorial variables are expressed as N (%), and continuous variables as median [IQR].
HH=Hiatal Hernia. NAT= Neoadjuvant treatment, RCT = Radiochemotherapy, CT = Chemotherapy.

Table 3
Histopathologic analysis.

	All population N = 101	HH patients N = 33	Non-HH patients N = 68	p-value
pT stage				0.656
0	12 (11.9)	3 (9.1)	9 (13.2)	
1	26 (25.7)	9 (27.3)	17 (25.0)	
2	9 (8.9)	3 (9.1)	6 (8.8)	
3	53 (52.5)	17 (51.5)	36 (52.9)	
4	1 (1.0)	1 (3.0)	0 (0.0)	
pN stage				0.658
0	62 (61.4)	21 (63.6)	41 (60.3)	
1	20 (19.8)	5 (15.2)	15 (22.1)	
2	11 (10.9)	5 (15.2)	6 (8.8)	
3	8 (7.9)	2 (6.1)	6 (8.8)	
Number of dissected LN	22 [18–30]	22 [9–35]	25 [16–34]	0.714
Differenciation grade (G)				0.700
1	5 (5.0)	1 (3.0)	4 (5.9)	
2	30 (29.7)	8 (24.2)	22 (32.4)	
3	44 (43.6)	16 (48.5)	28 (41.2)	
Lymphatic invasion (L1)	28 (27.7)	11 (33.3)	17 (25.0)	0.401
Vascular invasion (V1)	33 (32.7)	11 (33.3)	22 (32.4)	1.000
Perineural invasion (Pn1)	27 (26.7)	11 (33.3)	16 (23.5)	0.196
R0 resection	94 (93.1)	30 (90.9)	64 (94.1)	0.551
TRG				0.297
1	10 (9.9)	3 (9.1)	7 (10.3)	
2	24 (23.8)	9 (27.3)	15 (22.1)	
3	18 (17.8)	3 (9.1)	15 (22.1)	
4	29 (28.7)	13 (39.4)	16 (23.5)	
5	2 (2.0)	0 (0.0)	2 (2.9)	

TNM is based on the 8th edition of UICC classification [14]. Categorial variables are expressed as N (%), and continuous variables as median [IQR].
HH= Hiatal Hernia, LN = lymph nodes, R0 = clearance margins >0.1 cm, TRG = Tumor Regression Grade (Mandard) [15].

3.3. Long-term outcomes

Survival analyses showed no significant difference in terms of OS or DFS for patients with and without HH. Patients with a HH had a 3-year

OS of 52.4%, while non-HH patients 56.5% (p = 0.765) (Fig. 2). Patients with a HH had a 3-year DFS of 32.7%, while non-HH patients 45.6% (p = 0.283) (Fig. 3). Detailed analysis of recurrence patterns revealed a locoregional relapse in 18.8% of HH and 14.7% of the non-HH patients (p = 0.611). Similar rates of distant recurrence were also observed (50% HH vs 30.3% non-HH, p = 0.059). Among patients with distant metastases, the majority were found in bones (27.8%), liver (22.2%) and distant lymph nodes (19.4%), while less frequent recurrence sites included brain (13.9%), lungs (13.9%) and pleura (13.9%), supraclavicular lymph nodes (11.1%), adrenal glands (8.3%) and peritoneum (8.3%).

3.4. The impact of HH on patients undergoing RCT

Within the subgroup of patients treated with preoperative RCT (n = 60), severe postoperative complications occurred in 28.6% HH versus 33.3% non-HH patients (p = 0.705). Specifically, anastomotic leakage, pneumonia and cardiovascular complications did not present any significant differences between HH and non-HH patients. R0 resection rates and histologic response to treatment were also similar between HH and HH-patients (***Online appendix 1)***.

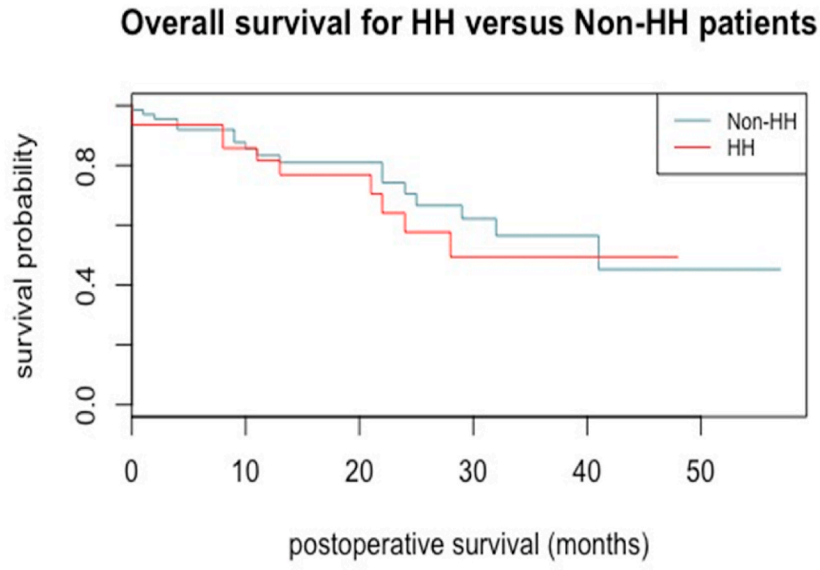
4. Discussion

In the present series, one third of esophageal AC patients had a preoperative HH ≥ 3 cm. The presence of HH did not correlate with more advanced tumor stages upon cancer diagnosis, worse post-operative outcomes, poorer response to NAT or worse long-term survival compared to the absence of HH.

Although the prevalence of GERD and HH in the general population is not yet well elucidated, estimated at 14.8% [20] for GERD, and up to 20.3% for HH [21]. In the present series, 36.6% of AC patients reported pre-existing GERD, and 32.7% had a HH in preoperative workup. Although there was a tendency towards higher GERD rates in the HH group (48.5% versus 30.9%, p = 0.073), these patients were not at higher risk to develop Barrett's metaplasia or more advanced disease stage at presentation.

Can the presence of HH have an impact on the choice of treatment strategy or treatment-related morbidity? Gandon et al. reported higher 30-day mortality for HH patients treated with neoadjuvant radiotherapy, attributed to potentially higher cardiac and pulmonary toxicity due to the larger radiotherapy field needed in the presence of a bulky HH and mediastinal ascension of the tumor [12]. This finding was not confirmed in our study, since preoperative RCT did not increase post-operative complications in HH patients. There is currently no evidence to avoid RCT and favoring perioperative chemotherapy in patients with a HH.

Although we found no differences in surgical procedure type in the present study between HH and non-HH patients, one important implication of the presence of HH could be the choice of surgical approach in

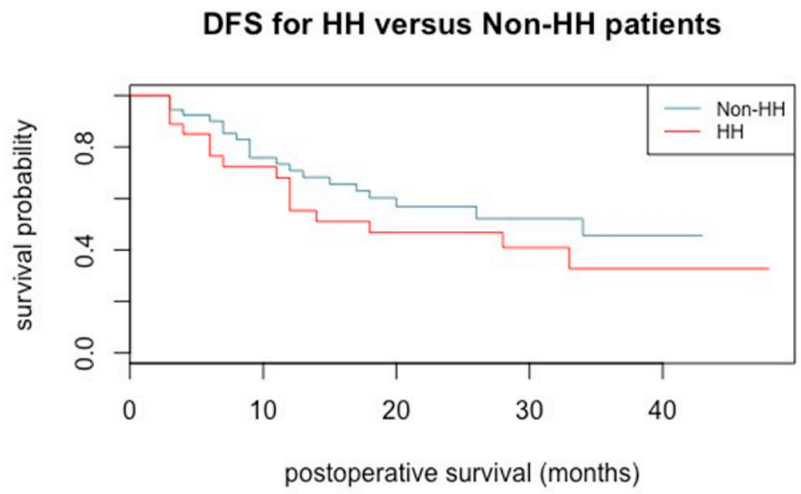


Nb at risk	0 mo	20 mo	40 mo	60 mo	80 mo
HH	31	12	0	0	0
Non-HH	68	24	5	0	0

Patients with a HH had a 3-year OS of 52.4%, similar to non-HH patients with 56.5% (p=0.765).

Non-HH: non-hiatal hernia subgroup; HH: hiatal hernia subgroup.

Fig. 2. Overall survival for all patients, according to the presence or not of HH.



Nb at risk	0 mo	20 mo	40 mo	60 mo	80 mo
HH	31	12	0	0	0
Non-HH	61	18	0	0	0

Patients with a HH had a 3-year DFS of 32.7%, similar to non-HH patients with 45.6% (p=0.283).

Non-HH: non-hiatal hernia subgroup; HH: hiatal hernia subgroup.

Fig. 3. Disease-Free survival for all patients, according to the presence or not of HH.

the specific case of Siewert II tumors. Indeed, in the current study, tumor epicenter in patients with HH was located higher up in the esophagus, whereas non-HH patients had mostly junctional tumors. Thus, in presence of a Siewert II lesion in a HH patient, mediastinal ascension of the junction precludes extended gastrectomy, which might be considered instead of esophagectomy in selected cases [22,23]. Of course, in many cases the exact epicenter of the tumour is difficult to diagnose precisely upon initial workup, and significant discrepancies may be observed among radiologic, endoscopic, and surgical intraoperative assessment. In presence of a HH, precise tumor location is even more difficult to assess, which may partly explain the difference in tumor location (distance from dental arch) between HH and non-HH patients in the present study. Thus, this additional staging challenge should be taken into account for patients with a clinically significant HH when planning the surgical strategy.

Pathologic complete response after NAT is associated with better prognosis in esophageal cancer [24]. In this study, the presence of a HH did not have an impact on the rates of complete pathologic response. As this was a series exclusively with AC, complete response rates were quite low (9.1% for non-HH, 10.3% for HH patients), poorer than the ones reported in the CROSS trial (23% of patients with AC) [25]. In the present study, we found similar rates of metastatic and locoregional recurrences in the two groups. Response to NAT and lymph node dissection was identical in both groups, while histopathologic analysis did not reveal any differences in TNM stage or other markers of biologic aggressiveness between the two groups.

The potential impact of HH on long-term survival after esophagectomy for cancer remains unknown. The previously mentioned French study including 367 patients with esophageal AC found that a >5 cm HH was associated with significantly lower rates of microscopically complete resection (50% reduction in R0 rates) and poorer survival [12]. They hypothesized local extension of an esophageal tumor in presence of a large HH may render surgical dissection more difficult, but also have an impact on the tumor's local growth and aggressiveness [12]. In that study, only large HH were included (>5 cm), and diagnosis was based on CT-scan or barium swallow but not endoscopy. Of note, HH group had more extensive lymph node involvement, which could be part of the explanation for worse long-term survival. This extensive lymphatic dissemination may have been a source of bias related to baseline differences in tumor stage, inherent aggressiveness in tumor biologic behavior of HH patients, or delayed cancer diagnosis due to long-lasting pre-existing symptomatic HH or GERD, masking cancer-related symptoms. Moreover, modification of local anatomy in the presence of a large HH could lead to inaccurate staging and suboptimal treatment. In the present study, we did not observe any differences in baseline cTNM staging or any other marker of biologic aggressiveness. Consequently, the presence of HH did not have any prognostic value in the long term.

Our study has some limitations that need to be mentioned. First, the relatively small number of included patients, as we excluded other histological types (e.g. squamous cell cancer), and analyzed only recent and well-documented cases. In this case, the small sample size may preclude clinically significant differences (e.x GERD and Barrett esophagus incidence) from reaching statistical significance. However, this shortcoming is compensated by a homogenous series, with standardized diagnostic workup and prospective data collection. Senior revision of radiologic

images and endoscopy reports to reliably identify the presence of a clinically significant HH added to the precision of HH diagnosis. As there is no universally accepted definition on sizes of HH considered clinically significant, we chose 3 cm as the threshold of a detectable HH on endoscopy and radiologic imaging [10].

5. Conclusion

In conclusion, in the present surgical series a preoperative HH $\geq$ 3 cm was observed in 32.7% of all AC patients, but it was not correlated with more advanced cancer stage upon diagnosis. Although the presence of a HH may indicate a higher location of the tumor epicenter and thus influence the choice of surgical strategy, it is not associated with poorer surgical outcomes, histologic response to treatment or long-term survival.

Declaration of competing interest

The authors have no financial disclosures or other conflicts of interest in relation to this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2023.101904.

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