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TESI DI LAUREA

DEFINING AND PREDICTING VERY EARLY RECURRENCE AFTER GASTRIC SURGERY FOR GASTRIC ADENOCARCINOMA: A MULTI-INSTITUTIONAL STUDY

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CONTENTS

SOMMARIO

Presupposti dello studio: Il carcinoma gastrico rappresenta la quinta neoplasia più frequente al mondo ed è la quarta causa di morte correlata al cancro. La resezione chirurgica è l'unica opzione terapeutica e, nonostante le strategie di trattamento perioperatorio basate su un approccio multimodale, la prognosi rimane infausta. Lo scopo di questo studio è di identificare le caratteristiche e i fattori predittivi di very early recurrence (VER) nei pazienti sottoposti a trattamento chirurgico a scopo curativo per carcinoma gastrico.

Metodi: È stato utilizzato un database di pazienti provenienti da 8 diversi istituti che si sono sottoposti a trattamento chirurgico a scopo curativo per adenocarcinoma gastrico in un arco di tempo compreso tra il 2000 e il 2020. VER è definita come ricorrenza di malattia localizzata o a distanza entro 6 mesi dal trattamento chirurgico. Per valutare il valore predittivo delle caratteristiche clinico-patologiche dei pazienti con VER è stato utilizzato il Modello dei rischi proporzionali di Cox univariato. Il modello della regressione di Cox regolarizzato è stato utilizzato per costruire un modello per predire VER e la recidiva entro un anno dal trattamento chirurgico.

Risultati: Complessivamente sono stati inclusi nello studio 1133 pazienti, i quali erano stati sottoposti a intervento chirurgico a scopo curativo per adenocarcinoma gastrico. Circa il 57% dei pazienti ha sviluppato una ricorrenza di malattia e in quasi il 20% si è riscontrata VER. È emerso che alcune variabili clinicamente rilevanti come l'età avanzata, la presenza di sintomi preoperatori, le comorbidità diverse dal diabete, le lesioni a livello del fondo gastrico, un tumore di grandi dimensioni, un tumore di alto grado, una malattia localmente avanzata e la presenza di metastasi a distanza sono correlate con VER.

Conclusioni: Sono stati identificati i fattori di rischio che predispongono all'insorgenza di VER in pazienti sottoposti a resezione chirurgica per carcinoma gastrico. Un nuovo strumento è stato sviluppato per predire VER e la ricorrenza entro un anno dal trattamento chirurgico. Questo nomogramma consente ai medici di

valutare il rischio di recidiva durante il follow-up in modo personalizzato per il paziente e regolare le strategie terapeutiche di conseguenza.

ABSTRACT

Background: Globally gastric cancer (GC) represents the fifth most common malignancies and the fourth leading cause of cancer-related death. Surgical resection is the only curative option and, despite perioperative treatment strategies based on a multimodal approach, prognosis remains dismal. The aim of the study was to identify pattern and predictor of very early recurrence (VER) in patients who underwent curative intent surgery for GC.

Methods: A multi-institutional database of patients undergoing curative-intent surgery for histology proved gastric adenocarcinoma was queried. Patients undergoing curative-intent surgery for GC between 2000 and 2020 at 8 major institutions were included. VER was defined as local or distant tumor recurrence within 6 months from curative-intent surgery. Univariable Cox Proportional Hazard Models was used to evaluate the predictive value of clinical-pathological features on VER. Regularized Cox regression model was employed to build a predictive model of VER and of recurrence within 1 year.

Results: Overall 1133 patients who underwent curative intent surgery for gastric adenocarcinoma were included in the study. Approximately 57% of patients developed recurrence of disease and almost 20% of patients experienced VER. Clinically relevant variables such as older age, presence of preoperative symptoms, comorbidities other than diabetes, fundic lesions, large tumor size, high tumor grade, locally advanced disease and presence of distant metastasis were found to be correlated with VER.

Conclusion: Predictive factors predisposing to VER in patients who underwent surgical resection for GC were identified. A new dynamic tool was developed to predict VER and recurrence within 1 year. This nomogram allows physicians to asses individualized recurrence evaluations during follow-up and to adjust the treatment strategies.

CHAPTER 1

Introduction

Gastric cancer (GC) the fifth most common malignancy worldwide [1, 2]. Even though the incidence is gradually decreasing in the last decades, in 2020 there has been more than 1 million cases of GC [1].

GC onset is insidious due to vague abdominal symptoms and patients are diagnosed at a late disease stage [2, 3]. Despite an accurate diagnosis and an appropriate multimodal approach consisting of curative-intent surgery and systemic treatment, GC represents the fourth most common cause of cancer-related death [1, 2]. Although radiotherapy and chemotherapy are often offered as adjuvant therapy [4], disease free survival in GC patient remains poor [5-8] and recurrence represents the leading cause of death in GC patients [7, 9, 10].

Recurrence rate after curative surgery occurs in 20% to 50% of patients and is more likely among those presenting with advanced stage at diagnosis [5,7-9]. Previous studies showed that around 90% of patients with recurrent disease died within 2 years [11]. For this reason, an early detection and a well-timed management of recurrence are needed.

Among patients- and tumor-specific characteristics correlated with recurrence we recognize: tumor size and grade, pathological stage and nodal status. Furthermore, patients with early recurrence have a poorer survival compared with those experiencing late recurrence after curative surgery [12]. In previous reports median survival times after recurrence ranges between 7.4 and 14.0 months in the early (recurrence within 1 year) and late (recurrence after 1 year) groups, respectively [12].

Very early recurrence, defined as a relapse of disease within 6 months from curative resection, might immediately affect survival, as shown for other malignancies such as intrahepatic cholangiocarcinoma, hepatic cell carcinoma and colorectal liver metastases [13-17]. Data on incidence and factors related to very early recurrence in GC patients remain limited. To our knowledge, no predictive tool exists to predict VER among patients undergoing curative-intent surgery for GC.

The aim of the study was to identify incidence and pattern of very early recurrence after curative intent surgery in GC and to characterize predictors of VER in patients undergoing curative-intent surgery. In addition, we developed a model to predict VER and recurrence within 1 year based on factors identified before and after surgery relying on a large, multi- institutional cohort of patients, in order to develop appropriate follow-up program and treatment strategy.

CHAPTER 2

Methods

2.1 Patient population and data collection

A multi-institutional database of patients undergoing curative-intent surgery for histology proved gastric adenocarcinoma was queried. Patients undergoing surgery between 2000 and 2020 at 8 major institutions (Johns Hopkins Hospital, Baltimore, MD; Emory University, Atlanta GA; Stanford University, Stanford, CA; Washington University, St. Louis, MO; Wake Forest University, Winston-Salem, NC; University of Wisconsin, Madison, WI; The Ohio State University, Columbus, OH; University of Padova, Italy) were identified. Patients undergoing palliative surgery and those with macroscopical residual disease were excluded. The institutional review board at each participating institution approved this study.

Standard demographic and clinicopathologic data were collected including age, gender, body mass index (BMI), presence of diabetes or other cardiological or pulmonary comorbidities, preoperative symptoms, family history of cancer, tumor size, tumor location, histological type and grade, depth of invasion, number of lymph nodes harvested, number of metastatic lymph nodes, lymph node ratio (LNR) and presence of lymphovascular invasion (LVI) or perineural invasion (PNI). Tumor stage was defined following the AJCC 8th edition staging manual [18].

Treatment details included extent of resection (partial vs. total gastrectomy), and lymphadenectomy (D1 vs. D2 vs. D3), as well as data on neoadjuvant and adjuvant chemotherapy and radiotherapy. Complications were also collected and graded according to Clavien Dindo classification.

Date of last follow-up or death, recurrence site and time, and vital status were also collected. Recurrence was defined as the presence of a biopsy-proven tumor showing adenocarcinoma cells or the presence of imaging highly suspicious for recurrence. The VER of gastric cancer was defined as the incidence of local or distant recurrence within 6 months after resection.

2.2 Statistical Methods

Descriptive statistics were reported as I quartile/median/III quartile for continuous variables and as percentages (absolute numbers) for categorical variables.

Univariable Cox Proportional Hazard Models were estimated to evaluate the impact of baseline clinical features on early recurrence.

A regularized Elastic Net Cox regression model was employed to build a predictive model of disease recurrence at follow-up. The model was chosen to account for the high number of candidate predictors in front of the number of events. Furthermore, regularized Cox models have been shown a better and more robust performance compared to traditional Cox regression in the predictive tasks. The predictors included in the model were selected according to the clinical judgment including, LNR, e.g., number of metastatic lymph nodes divided by the total number of nodes examined, recurrence, DFS, age, gender, BMI, diabetes, comorbidities, pre-operative comorbidities, site, tumor size (mm), grading, T stage, N stage and metastasis. Results were reported as Hazard Ratio.

Bootstrapped resampling to improve the stability, accuracy, and reducing overfitting of the algorithm selected was conducted, considering 2000 iterations. The discriminant ability of Cox regularized model has been evaluated by reporting a ROC curve together with the calibration plot, considering 200 runs.

To predict the 6 and 12 months DFS probability, two nomograms were developed.

Statistical analyses were performed with R version 4.0.4 (http://www.r-project.org), rms package (available from https://CRAN.R-project.org/package=rms) and glmnet (available here: https://cran.r-project.org/web/packages/glmnet/index.html).

CHAPTER 3

Results

3.1 Characteristics of Patients With or Without VER

A total of 1,133 patients met the inclusion criteria and were included in the analysis (Table 1). Median patient age was 67 years (IQR, 57-75years), 481 (42%) patients were female and 652 (58%) were men. The median BMI was 24.9 (IQR, 22.1-28.7). Overall, 211 (19%) patients had diabetes while 405 (36%) had cardiological and pulmonary comorbidities. The majority of patients (n=724, 64%) experienced preoperative symptoms such as bowel obstruction or bleeding. The antrum or pylorus were the most common tumor sites (n=502, 44%), followed by the gastric body (n=436, 38%) and the fundus (n=195, 17%). Median tumor size was 45 mm (IQR: 25-68). The majority of patients (n=785, 69%) had a G3-4 tumor. The median LNR was 0.12 (IQR: 0.00-0.47) and the majority of patients (n= 705, 62%) were AJCC 8th N positive sec. AJCC 8th ed. at final pathology. Similarly, the majority of patients (n=745, 66%) had locally advanced disease, defined at T3-4 sec. AJCC 8th ed., while only 9.1% (n= 103) had metastatic disease at final pathology, following a radical resection.

Overall, 212 patients (18.7%) had VER, define as recurrence within 6 months from the index operation, whereas 921 (81.3%) did not (non-VER group). Moreover, 385 patients (34%) had a recurrence within 1 year, 256 patients (23%) after 1 year and 492 patients (43%) did not experience a recurrence during the follow-up period. Differences in the characteristics of patients with and without VER are summarized in Table 1. Older age, higher BMI, presence of preoperative symptoms, comorbidities other than diabetes, fundic lesions, large tumor size, high grade, locally advanced disease, presence of lymph node metastases and presence of distant metastasis at final path were significantly correlated with VER (Table 1).

The median follow-up time was of 15 months (IQR, 7-38 months).

Variables		Overall, N = 1,133	Non VER, N = 921	VER, N = 212	Reference values	HR	CI Lower 95%	CI upper 95%
Age (years) *		67 (57, 75)	66 (57, 75)	70 (60, 78)		1.485	1.207	1.825
Gender	F	481 (42%)	396 (43%)	85 (40%)	F Vs. M	0.882	0.669	1.159
	M	652 (58%)	525 (57%)	127 (60%)				
BMI *		24.9 (22.1, 28.7)	25.0 (22.2, 28.7)	24.5 (21.6, 27.8)		0.844	0.716	0.996
Diabetes		211 (19%)	175 (19%)	36 (17%)	Yes Vs. No	0.895	0.625	1.280
Comorbidities		405 (36%)	313 (34%)	92 (43%)	Yes Vs. No	1.437	1.095	1.885
Pre-operative symptoms		724 (64%)	561 (61%)	163 (77%)	Yes Vs. No	1.988	1.445	2.736
Site	Antrum-Pylorus	502 (44%)	424 (46%)	78 (37%)				
	Body	436 (38%)	348 (38%)	88 (42%)	Body Vs. Antrum Pylorus	1.343	0.990	1.822
	Fundus	195 (17%)	149 (16%)	46 (22%)	Fundus Vs. Antrum Pylorus	1.586	1.102	2.283
Tumor size (mm) *		45 (25, 68)	40 (25, 65)	55 (35, 79)		1.392	1.217	1.593
Grading	G1+G2	348 (31%)	297 (32%)	51 (24%)	G1+G2 Vs. G3+G4	0.683	0.499	0.937
	G3+G4	785 (69%)	624 (68%)	161 (76%)				
LNR *		0.12 (0.00, 0.47)	0.09 (0.00, 0.39)	0.40 (0.06, 0.74)		2.096	1.753	2.504

AJCC T stage	T1+T2	388 (34%)	350 (38%)	38 (18%)	T1+T2 Vs. T3+T4	0.395	0.278	0.562
	T3+T4	745 (66%)	571 (62%)	174 (82%)				
AJCC N stage	N+	705 (62%)	539 (59%)	166 (78%)	N0 Vs. N+	0.427	0.307	0.591
	N0	428 (38%)	382 (41%)	46 (22%)				
Post-operative complications		478 (42%)	343 (37%)	135 (64%)	Yes Vs. No	2.706	2.045	3.579
AJCC M stage	M0	1030 (91%)	865 (94%)	165 (78%)	M1 Vs. M0	3.515	2.541	4.864
	M1	103 (9.1%)	56 (6.1%)	47 (22%)				

*Median and IQR for continuous variables has been considered.

Table 1. Sample characteristics according to VER status. The table presents the results of the univariable Cox regression models as Hazard Ratio, 95% Confidence Interval, and p-value.

3.2 Results of predictive model development and model performance

According to results of the regularized Elastic Net Cox regression, older age was associated with disease relapse, as shown by the Hazard ratio of 1.34. The model also demonstrates other important information about the likelihood of relapse, such as preoperative symptoms, that prove an increase of 12% for probability of recurrence. Cardiovascular disease and respiratory comorbidities, also, outlined a positive relationship with probability of relapse proven by an HR of 1.19. With the same strength, tumor size and grade showed a positive but small increase in probability of recurrence. In contrast, the lymph node ratio depicts a high association for the likelihood of relapse with an HR of 1.71. Patients with AJCC T3 or T4 tumors were more likely to experience recurrence (HR 1.54)

compared to T1 or T2 patiens. The model also showed that if a patient is affected by occult metastasis diagnosed at the time of surgery, the likelihood of relapse can double (HR 2.2; Table 2).

Variables		HR
Age	(years) 67 (57 - 75) *	1.342
Gender	F Vs. M	1.000
BMI	24.9 (22.1, 28.7) *	0.997
Diabetes	Yes Vs. No	1.000
Pre-operative symptoms		1.122
Comorbidities		1.192
Site	Body+Multicentric Vs. Antrum+Pylorus	1.094
	Body+Multicentric Vs. Gastric remnant Fundus	0.831
Tumor size	(mm) 45 (25, 68) *	1.108
Grading	G3+G4 Vs. G1+G2	1.065
LNR	0.12 (0.00, 0.47) *	1.706
AJCC T stage	T3+T4 Vs. T1+T2	1.538
AJCC N stage	N0 Vs. N+	0.834
AJCC M stage	M1 Vs. M0	2.137

*Median and IQR for continuous variables has been considered.

Table 2. Regularized Cox HR models results

The model predictive performance was good. At 6-month follow-up the value of the Area Under the Curve was of 73%, and increased with time, being 76% at 12-month, and 78% at 24-month (Figure 1). Furthermore, the agreement between the observed and estimated disease recurrence was evaluated with calibration plot (Figure 2) and revealed good prediction with minimal evidence of overfitting.

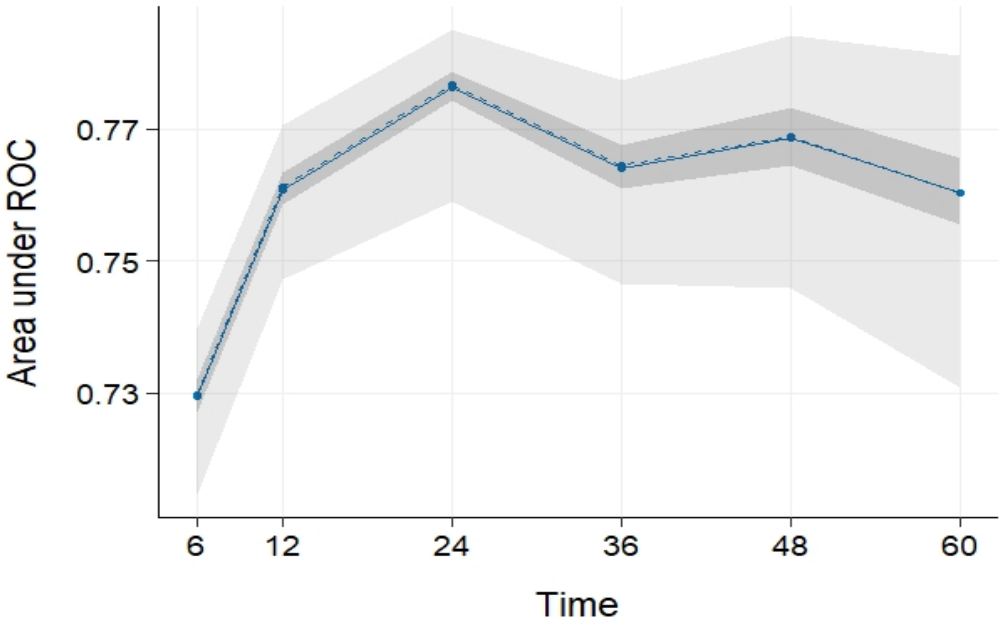

Figure 1. ROC values of the regularized Elastic Net Cox regression

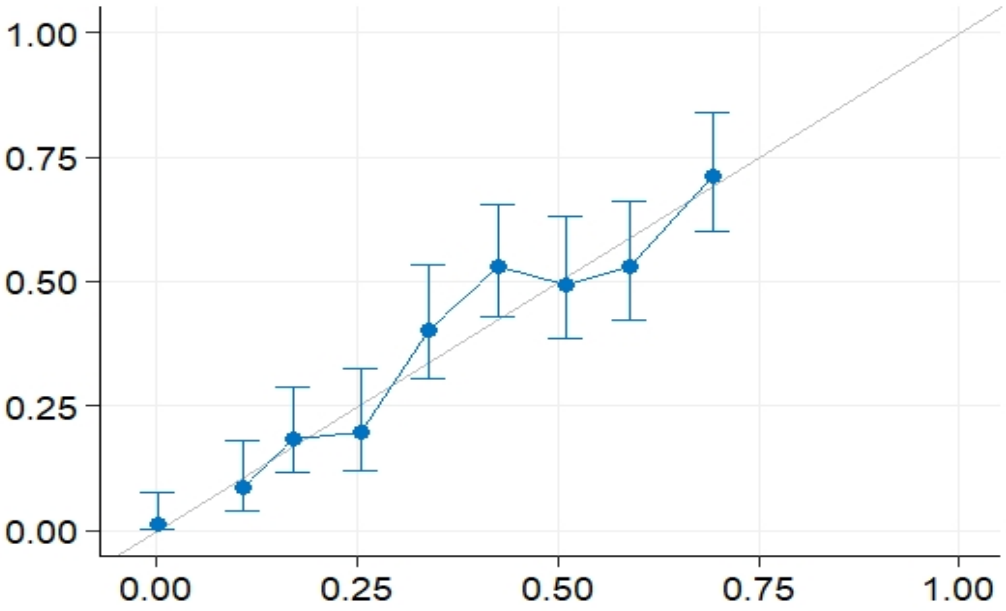

Figure 2. Calibration plot

3.3 Development of Nomogram to Predict VER and recurrence

Two nomograms, for the prediction of 6 (VER) and 12-month disease recurrence, were built based on the predictive model developed using the regularized Elastic Net Cox regression model (Figures 3 and 4, respectively).

Each factor in the nomogram was assigned a weighted number of points and the sum of points for each patient was associated with the outcome. Using the nomogram, a higher score was associated with worse prognosis. For example, at 6-month, a 70-year old man with a T2 stage gastric adenocarcinoma in the antrum with comorbidities and an LNR of 0.3 would have a total of 146 points, resulting in a probability of VER of 10%. Differently a 60-year old female in T4, G3 gastric adenocarcinoma in the pylorus, with comorbidities and LNR of 0.7 would have a total of 215 points, resulting in a probability of VER of 31%.

At 1-year (Figure 2), for example, a 70-year old man with a T2 stage gastric adenocarcinoma in the antrum with comorbidities and LNR of 0.3 would have a total of 146 points, resulting in a probability of recurrence at 1 year of 21%. Differently a 60-year old female in T4, G3 gastric adenocarcinoma in the pylorus, with comorbidities and LNR of 0.7 would have a total of 215 points, resulting in a probability of recurrence at 1 year of 47%.

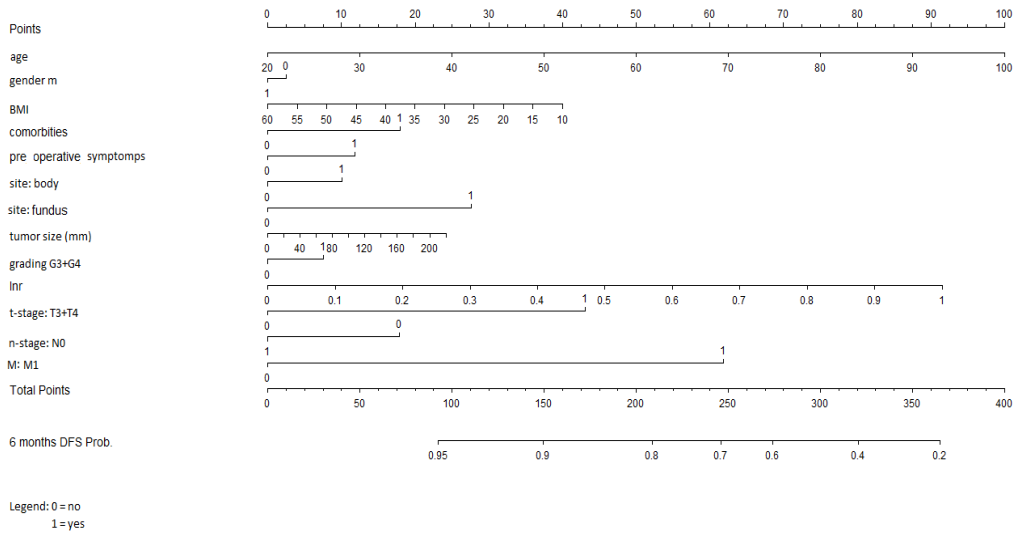

Figure 3. 6 months nomogram

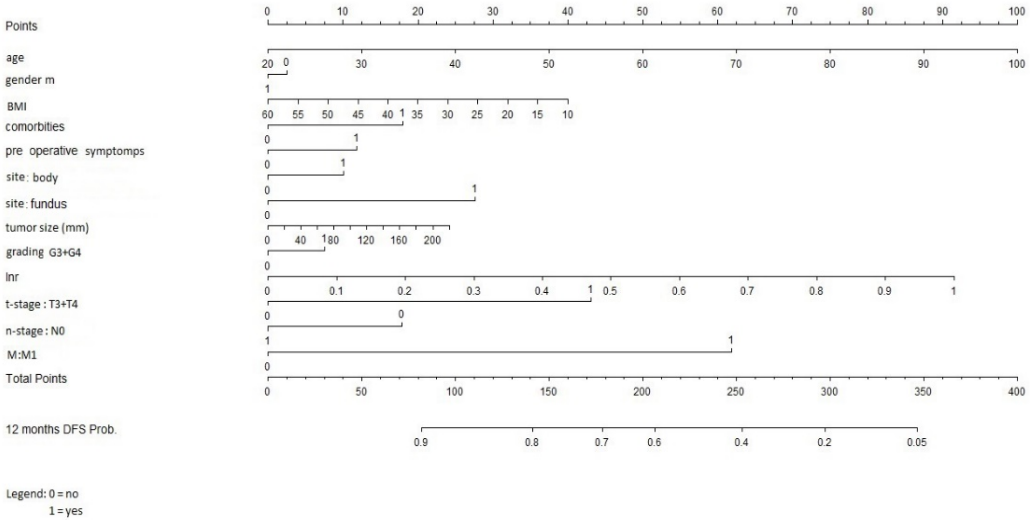

Figure 4. 12 months nomogram

CHAPTER 4

Discussion

Although the improvement in GC treatment with a multimodal approach, GC remains the fourth leading cause of cancer related death globally [1]. Despite surgery represents the only curative treatment for GC without metastasis [19], 20-50% of patients experienced recurrence of disease after surgery [7, 11, 19]. Recurrence is one of the factors that mostly affect cancer-related death in patients with GC. Moreover, patients experiencing an early recurrence tend to have a shorter survival time after diagnosis [7, 9, 10].

There is no consensus about the correct timing for defining early recurrence among GC patients. Previous studies defined early recurrence for GC as a disease relapse within 2 years from surgery [20, 21], however most patients tend to recur within 2 years from surgery [20, 22, 23]. Several studies employed the term VER to describe recurrence within 6 months following resection for hepatic cell carcinoma, intrahepatic cholangiocarcinoma, and colorectal liver metastases and demonstrated that VER is associated with a discouraging prognosis [13-17].

This study showed how almost one-fifth of patients developed recurrence within 6 months after surgical resection (VER). Considering the cut off of 1 year 34% experienced recurrence within 1 year and 23% after 1 year. Overall, more than half of patients developed recurrence after surgery. Previous studies, which analyzed pattern of early recurrence within 1 year from surgery, showed a lower incidence of early recurrence compared to the present study [24]. However, these studies were conducted from centers in Asia, while in the current study a Western cohort of patients were considered. Difference in epidemiology, time of diagnosis, natural history, and follow-up strategies of GC between Eastern and Western world, should explain the disparity in early recurrence rate.

To our knowledge this is the first study that analyze incidence and predictors of VER. In the current study older age, presence of preoperative symptoms, comorbidities other than diabetes, fundic lesions, large tumor size, high grade, locally advanced disease, and presence of distant metastasis were shown to be correlated with VER. Although no previous studies on VER were

conducted, in literature some study about recurrence of GC within 1 year from surgery demonstrated that similar variables, such as older age, tumor size, tumor stage and lymph node metastasis are associated with early recurrence [12, 21, 25].

Lymph node ratio (LNR) was found to be one of the strongest predictors for development of VER, consistently with previous studies from our group [26]. In literature were already demonstrated that LNR correlated with prognosis better than the simple number of metastatic lymph node [26-28].

In addition, a model to predict rate of VER and of recurrence within 1 year based on pre-operative and post-operative factors among patients affected by resectable GC was developed. A simple discrete scoring system, that can be easily utilized by physicians was elaborated. Several previous studies developed nomogram to predict OS and DFS after surgery in patients affected by GC [29-33] and only one study generate a scoring system to predict risk of recurrence of GC [34]. To our knowledge this is the first study to analyse the risk and the predictors of VER, defined as relapse within 6 months, and to produce a predictive tool to compare the risk of VER and of recurrence at 1 year among patients who underwent curative intent surgery for GC.

This study is remarkable for having used a large, multi-institutional contemporary cohort of patients to elaborate the nomogram. Based on factors such as age, gender, BMI, comorbidities, preoperative symptoms, tumor site, tumor size, grade, depth of invasion, LNR, N status and M status, our model is able to predict who are patients likely to experience VER and recurrence within 1 year, in order to asses who are patients with a more discouraging prognosis.

Previous studies used similar predictor variables to elaborate a nomogram to predict overall survival, disease free survival and recurrence after curative intent surgery [29, 31-33]. However, in the current study nomogram, also LNR, which has been noted to be superior in assessing prognosis after surgery for GC compared with simple lymph node status alone, was found to correlate with recurrence [26, 28, 35].

Defining which patients are at risk of VER is crucial because some consideration may be conducted about these patients. Identifying who are

patients likely to develop VER may guide the post-operative planning, determining a personalized follow-up setting and considering adjuvant treatment after curative-intent surgery for these group of patients. In addition, defining the risk of VER, enable physicians to have an accurate prognostication and to correctly inform patients and family members of prognosis. Although our nomogram requires external validation, the proposed nomogram had a very good predictive performance.

This study had several limitations. While the large multi-institutional design of the study may be a strength because of generalizability of data, it may be also a limit because of heterogeneity of patients' selection and treatment criteria. In addition, while the nomogram was internally validated using bootstrapped calibration and cross validation, further studies are needed to externally validate the proposed nomogram.

CHAPTER 5

Conclusion

Nearly one-fifth of patients who undergo curative intent surgery for GC experienced VER. A nomogram to predict risk of VER was developed, based on clinicopathological pre- and post-operative characteristics (age, gender, BMI, comorbidities, preoperative symptoms, tumor site, tumor size, grade, depth of invasion, LNR, N status and M status). The nomogram enabled to stratify patients into prognostic groups and performed well on internal validation. This project provide the physicians and the patients with a valid tool assisting physicians in determining the prognosis, in defining follow-up strategies and in evaluating correct treatment strategy in patients who underwent curative intent surgery for GC.

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