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GAME-SCORE PREDICTS PATHOLOGICAL AND RADIOLOGICAL RESPONSE TO CHEMOTHERAPY IN PATIENTS WITH COLORECTAL LIVER METASTASES

S.S.D. MED/18

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SUMMARY

1. **Abstract……...3**
2. **Introduction……....4**
3. **Methods……..….5**
4. **Results. ……8**
5. **Discussion……..10**
6. **References……12**
7. **Table 1. ……..18**
8. **Table 2……20**
9. **Table 3……21**
10. **Table 4……22**
11. **Figure 1……..23**
12. **Figure 2……..24**

Abbreviations

GAMEs: Genetic And Morphological Evaluation score

CRLMs: colorectal liver metastases

TRG: tumor regression grade

NAC: neoadjuvant chemotherapy

CEA: carcinoembrionic antigen

Abstract

Background: GAME score is the newest prognostic model for patient with colorectal liver metastases (CRLMs). Pathological and radiological responses to NAC are key factors that can stratify the prognosis of these patients. Aim of the present study is to evaluate the ability of Genetic And Morphological Evaluation (GAME) score to predict pathological and radiologic responses to neoadjuvant chemotherapy (NAC).

Methods: Patients with CRLMs who underwent liver resection after NAC between January 2010 and December 2021 were divided into three groups according to GAME scores: low risk (LR, 0–1), moderate risk (MR, 2–3), and high risk (HR, ≥4). Correlations between groups with radiological and pathological features were analyzed.

Results: In total, 448 of the 1054 liver resections for CRLMs were included. GAME scores were grouped as follows: LR: 80 (18%), MR: 228 (51%), and HR: 140 (31%). HR-GAME scores were associated with lower pathological response assessed by Tumor Regression Grade 4–5 (LR: 67.1%, MR: 74.9%, HR: 82.6%; p=0.010). Radiologic progressive disease was found in 10% of HR patients, which was significantly higher than in the other groups (LR: 3.8%, MR: 3.5%; p=0.011). These findings were confirmed at multivariable analysis. HR-GAME scores were also associated with higher rates of mucinous differentiation (LR: 3.8%, MR: 8.8%, HR: 13.1%; p=0.021), satellitosis (LR: 27%, MR: 40.4%, HR: 53%; p=0.001), vascular invasion (LR: 73.8%, MR: 81%, HR: 87.5%; p=0.011), and perineural invasion (LR: 8.8%, MR: 10.6%, HR: 19.7%; p=0.010).

Conclusions: GAME score category should be considered into planning of therapeutic strategy of patients with CRLMs.

Introduction

Liver resection has been widely demonstrated to be a potentially curative strategy for patients with colorectal liver metastases (CRLMs) and has a 5-year survival rate of up to 60%[1]. Improved results over recent years have been attributed not only to advances in surgical technique[2] but also to more effective chemotherapeutic regimens[3] and targeted therapies[4-5]. Neoadjuvant chemotherapy (NAC) is now a well-established treatment in combined therapeutic strategies, that is used not only to downsize lesions and ensure surgical resectability[6] but also to control micrometastases[7] and prolong progression-free survival[8].

Chemotherapy efficacy is generally evaluated, first of all, from radiological aspects (i.e., CRLM size reduction), which are reported according to the Response Evaluation Criteria in Solid Tumors (RECIST)[9]. Secondly, histopathological response from resected specimens of CRLMs are evaluated according to Tumor Regression Grade (TRG) classification[10].

Many clinical factors have been used to predict survival of patients with CRLM after hepatectomy, including the number and diameters of liver metastasis[11], carcinoembryonic antigen (CEA) level, primary tumor location[12], node-positive primary disease, *RAS* mutational status[13], mucinous differentiation[14], and involvement of resection margin. With the development of preoperative chemotherapy, new clinicopathological factors have emerged, such as degree of radiological and pathological response[15,16].

Genetic And Morphological Evaluation (GAME)[17] score is a new prognostic tool that combines clinical and biological factors including tumor burden score (TBS)[11], preoperative CEA levels >/= 20 ng/mL, primary lymph-nodes metastases, *KRAS* mutational status, and extrahepatic disease. The sum of each item creates the total GAME score, which appears to perform well for prognostic stratification of patients with CRLMs. External validation was made using over 2000 patients from Johns Hopkins Hospital and Memorial Sloan Kettering Cancer Center, which confirmed reliable prognostic stratification[18].

In contrast to other prognostic scores, all data included in the GAME score are available preoperatively; therefore, it could be used also not only as a prognostic tool but also in a preoperative setting to guide treatment strategies for in patients with upfront resectable CRLMs[19]. The aim of this study was to investigate correlations between GAME score and radiological and pathological responses to NAC.

Methods

Approval for data collection and analysis for this study was obtained from our institutional review board. Prospectively collected data of consecutive patients who underwent laparoscopic and open liver resections at General and Oncological Surgery Department of Mauriziano Hospital between January 2010 and December 2021 were retrospectively reviewed. Patients who did not receive preoperative chemotherapy and with incomplete data to calculate GAME scores were excluded.

Objectives

The association between GAME scores and radiological and pathological response was explored by stratify population as previous described by Sasaki et al[18] into three groups according to GAME score risk: Low Risk (LR 0-1), Moderate Risk (MR 2-3), and High Risk (HR ≥4). The primary objective of the study was the association between GAME score category and response to neoadjuvant chemotherapy, evaluated by RECIST criteria and TRG. As secondary objectives, the prognostic value of GAME score and TRG was tested on this cohort and additional correlation between GAME score and pathological characteristic of poor prognosis (i.e., satellitosis, mucinous differentiation, grading) were investigated.

Data collection

Demographics, operative details, and postoperative data were collected from medical records. Preoperative characteristics included age, sex, body mass index (BMI, kg/m2), comorbidities, primitive site, synchronous disease, type, and lines of chemotherapy. Intraoperative data of major and associated resection, laparoscopic approach, blood loss and perioperative blood transfusion, pringle

maneuver and its time were retrieved. Postoperative details of mortality, morbidity and length of hospital stay were reported.

Patient Management

Management of patients with colorectal liver metastases at our Institution has been previously reported[20]. Treatment strategies were decided by a multidisciplinary board. Chemotherapy before liver resection was administered to initially unresectable patients (conversion therapy) and to selected resectable patients (NAC) if they met the following criteria: four or more CRLMs, simultaneous extrahepatic disease, or possibility to perform more conservative liver resection after tumor shrinkage. In such cases, a short treatment was scheduled (4–6 cycles) and surgery was planned at response. In patients with synchronous CRLMs from rectal cancer with a high tumor burden, liver-first strategy followed by radiotherapy was applied when indicated. The multidisciplinary board's decision was also based on other factors including age, performance status, vascular relationship of the liver lesions, and risk of remnant disease after surgery. *KRAS* mutations were tested at codons 12 and 13. Hepatic resection was only planned when radical resection (Resection R0/R1) was achievable. Residual liver function after chemotherapy was routinely investigated[20]. Portal vein occlusion (PVO) was performed if future remnant liver volume was less than 30% after long course (>6 cycles) chemotherapy[21]. In this case, CT scans with volumetry were analyzed four weeks after PVO, and surgery was scheduled only after adequate hypertrophy was obtained. Hepatic surgery was performed at least 30 days after interruption of chemotherapy and 40 days after administration of the last dose of bevacizumab. Intraoperative liver ultrasonography was routinely performed to confirm the stage and guide liver resection. Pathological analysis was routinely performed, with data collected for differentiation grade, mucinous differentiations, necrosis, vascular micro- and macro-invasion, perineural and bile duct invasion, presence of satellitosis, and tumor regression grade.

Follow-up schedule provides a quarterly physical examination, carcinoembryonic antigen level test, and abdominal ultrasonography. Thoraco-abdominal CT scan was performed annually. Follow-up was performed at outpatient clinics or by contacting the patients' general practitioner, and it was

updated to December 2022 or at the time of death. Disease-free survival was measured from the date of hepatic resection until the date of radiographic detection of recurrence. Overall survival was measured from the date of hepatic resection until the date of death or last follow-up.

Definitions

Comorbidities were described using Charlson Comorbidity Index[22]. Radiological response was classified according to RECIST criteria[9] during multidisciplinary board. Liver resections were defined according to Brisbane 2000 terminology[23], with major hepatectomy designed resection of three or more Couinaud's segments[24]. Morbidity included all postoperative complications and was graded according to Dindo-Clavien classification[25] and Comprehensive Complication index[26]. Postoperative mortality was determined as death within 90 days after surgery or before discharge from the hospital. Post-hepatectomy liver failure and biliary leakage were both defined according to International Study Group of Liver Surgery[27-28]. R1 resection was defined as surgical margin < 1 mm and satellitosis as a metastatic nodule separated by >1 mm from the leading nodule[29]. Definition of mucinous differentiation was based on the World Health Organization criteria according to the presence of a mucinous component of more than 50%[30]. Tumor Burden Score was defined as previously reported by Sasaki et al[11]. TRG was categorized in high-TRG (0-3) and low-TRG (4-5) according to Takahashi et al.[3,11,29.]

Statistical Analysis

All statistical analyses were performed using SPSS Italy (v20.0; IBM, Armonk, NY, USA). Categorical variables were compared using the chi-square test, Fisher's exact test, or Pearson's test as appropriate. As appropriate, continuous variables were compared using unpaired t-tests or Mann–Whitney U tests. Pairwise comparisons were performed using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons in cases where significant differences observed among the three groups. Adjusted p values are presented. Continuous variables were compared between groups using the unpaired t-test or Mann–Whitney U test, as appropriate.

The Kaplan–Meier method was used to estimate survival probabilities, which were compared using the log-rank test. Multivariate analysis was performed using a Cox proportional hazard model to identify independent prognostic factors of overall and disease-free survival after liver resection. All p-values were two-sided, and $p<0.05$ was considered statistically significant. A Multiple regression analysis was performed to assess predictive factors of radiological response and tumor regression grade (TRG). Multivariate analysis was completed for factors with a P value of 0.05 or less in the univariate analysis. A P value of less than 0.05 was considered significant for all tests.

Results

From January 2010 to December 2021 at author's institution, 378 (448 liver resections) out of 712 patients (1054 liver resections) fulfilled inclusion criteria. Excluded from the analysis were 232 patients (419 liver resections) that did not received NAC and 102 patients (187 liver resections) because one or more parameters needed to calculated GAME score lacked. Patients were divided into three groups based on their GAME score: 58 patients (15.3%) (80 liver resections, 17.9%) in the low-risk (LR) group, 195 patients (51.6%) (228 liver resections, 50.9%) in the moderate risk (MR) group and 125 patients (33.1%) (140 liver resections, 31.3%) in high-risk (HR) group.

Comparison of preoperative and intraoperative characteristics

Table 1 summarizes perioperative and postoperative characteristics of the three groups. Patients in the HR group had higher proportion of right-sided colon cancers (LR: 17.5%, MR: 21.5%, HR: 30.7%; p=0.017) and synchronous liver metastases (LR: 56.3%, MR: 74.1, HR: 73.6%; p=0.019). Patients in the HR group also received a higher median number of NAC cycles (6 vs. 7 [MR and LR vs. HR groups]; p=0.009). Radiological response to NAC appeared significatively correlated to GAME scores: patients in the HR group had higher proportion of progressive disease according to RECIST criteria (LR: 3.8%, MR: 3.5%, HR: 10%; p=0.011). Furthermore, HR patients underwent laparoscopic liver resection less often (LR: 25%, MR: 21.1%, HR: 12.1%; p=0.012), whilst a

significantly higher proportion received associated extrahepatic surgery (LR: 35%, MR: 38.6%, HR: 56.4%; p=0.001)

Comparison of pathological details

Pathological details among three groups are summarized in Table 2. No differences in presence of necrosis and biliary invasion were found. As GAME score increased, presence of satellitosis (LR: 26.9%, MR: 40.4%, HR: 53%; p=0.001), vascular invasion (LR: 73.8%, MR: 81%, HR: 87.5%; p=0.011), perineural invasion (LR: 8.8%, MR: 10.6%, HR: 19.7%; p=0.010) and mucinous differentiation (LR: 3.8%, MR: 8.8%, HR 13.1%; p=0.021) increased at pathological analysis. TRG data were available on 434 liver resections. Low TRG (4-5) was found in significantly higher proportion of patients in the HR group compared with the other two groups (LR: 67.1%, MR: 74.9%, HR: 82.6%; p=0.010).

Survival analysis

Median follow-up time was 79 months (95% IC 59 – 99). GAME scores stratify patients according to risk of death (median overall survival: HR: 27 months, MR: 44 months, LR: 87 months, p<0.001) and recurrence (median disease-free survival: HR: 7 months, MR: 15 months, LR: 20 months, p<0.001) (Figure 1). Similarly, TRG values confirmed prognostic value and correlation with long-term results (Figure 2).

Predictors of radiological and pathological response

At multivariable analyses of factors affecting pathological response after NAC (Table 3), the use of biological agent (bevacizumab, cetuximab and panitumab) and the number of cycles of NAC >6 (OR 0.556 , p=0.038) emerged as protective factors while age higher than 70 years (OR 2.111, p=0.022), irinotecan-based NAC (OR 3.066, p<0.001) and HR-GAME (OR 1.843, p=0.025) were independent risk factors of poor pathological response. The HR-GAME score (OR 2.77, p=0.016) was the only independent factor able to predict radiological progression disease after NAC at multivariate analysis (Table 4).

Discussion

Prognostic scores represent a key point for medical research as predictors of long-term outcomes. Nevertheless, their use in clinical practice still remains controversial[31]. The biggest limitation is that most of provided scores[32-33-34] for patients with CRLM include pathological data of liver specimen that are only available after surgery. GAME score is the first prognostic model based only on genetic and morphological data of liver and primary disease. GAME score can stratify CRLMs population into different risk categories better than other pre-existing scores[17] even in large and external cohort[18]. NAC can led to radiological and pathological response in high proportion of patients, however survival benefits still remain controversial[35-36], especially regarding specific clinical scenarios (cfr. single and/or metachronous CRLM[37]). Currently, ability by surgeons and oncologists to predict radiological and/or pathological response to NAC remains poor as it is based on few elements (e.g. *KRAS* status[38-] and primitive tumor location[39,40]).

At multivariable analysis high-risk category of GAME score was correlated with radiological progressive disease and worse pathological response, in particular HR-GAME category had a more than double risk of radiological progressive disease and a 50% reduced likelihood of good pathological response. Therefore, the median number of NAC-cycles in these patients was significantly higher than in the LR and MR groups. Prolonged NAC exposes to higher risk of chemotherapy-associated liver injury as highlighted by the higher rate of postoperative ascites in the HR-GAME group compared to the other groups, despite the same rate of major hepatectomy.

Consistent with what has already emerged from previous evidences[17,18], HR-GAME group was also associated with higher rates of right-sided colon cancers, mucinous differentiation, satellitosis, and vascular and perineural invasions, which are all recognized determinants of worse prognosis.

Right colon cancer is recognized to have a different biology and more aggressive behavior than left colon and rectum cancer due to different frequencies of mutational status and external exposure[41,42]. These characteristics correlate with different chemosensitivities and lower pathological responses to NAC[42]. Also mucinous differentiation in CRLMs has been already recognized to be less

chemosensitive[14] partially due to different genetic arrangements[43]. Thus, higher proportion of right-sided colon cancer and mucinous differentiation in HR-GAME group partially explains lower chemosensitivity occurred. However, liver resections have recently been demonstrated to achieve the same outcome for mucinous and non-mucinous CRLMs[44], although chemosensitivity remains low[45] and new molecular targets are still being investigated[46].

Presence of satellitosis has been recognized to be a sign of pathological non-response to NAC[29] but also an independent prognostic factors of overall survival[47].

Present study highlighted ability of GAME scores to catch all these pathological unfavorable prognostic factors and chemosensitivity at the beginning of CRLMs history. According to the present results new therapeutical strategies can be considered.

In high-risk patients the most effective NAC available should be chosen, for example triplet chemotherapy (FOLFOXIRI)[48] with or without target therapy or intra-arterial chemotherapy[49,50]. Patients in the HR group, due to the high tumor burden, underwent complex liver surgery (more often with open approach) and required associated extrahepatic resections. For these reasons is important to reduce the risk of developing chemotherapy-associated liver injuries[51] using the most effective NAC for the shortest time possible.

At the other extreme, in patients with easily resectable liver metastases and low risk GAME category, the possibility of upfront surgery should be evaluated.

This study has some limitations. Even if data were prospectively collected, patients without assessed RAS mutation were excluded and final cohort could not be representative of all this kind of patients. Other inherent drawback is the non-intention-to-treat structure and exclusion of patients who underwent to NAC but surgically missed for massive progressive diseases. Even if further studies are needed on this topic, the present data come from a high-volume center with a reasonably large sample size and it can be considered a good starting point for external validation.

In conclusion, GAME score can be used not only to predict survival but also the likelihood of pathological and radiological response to NAC. Consequently, GAME score categories should be considered when planning of therapeutic strategies for patients with CRLMs.

Figure legends

Figure 1. Survival after liver resection according to GAME score category. A. overall survival ($p<0.001$); B, disease-free survival ($p<0.001$)

Figure 2. Survival after liver resection according to Tumor Regression Grade Category. A. overall survival ($p<0.001$); B. disease-free survival ($p=0.008$).

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Conflicts of interest

None to declare.

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TABLE 1. Patient Characteristics, Treatment Details and Surgical Results stratified according to GAME score categories

		GAME SCORE			
Parameters		**LOW RISK (n = 80) N (%)**	**MODERATE RISK (n = 228) N (%)**	**HIGH RISK (n = 140) N (%)**	**P**
Male	M	46 (57.5)	130 (57)	77 (55)	0.690
Age (median, IQC)		61,5 (12)	63 (13)	60 (14)	0.150
ASA Score	1	2 (2.6)	15 (6.8)	12 (9.1)	0.417
	2	47 (61.8)	125 (56.6)	75 (56.8)	
	3	26 (34.2)	78 (35.3)	42 (31.8)	
	4	1 (1.3)	3 (1.4)	3 (2.3)	
Body Mass Index (median, IQC)		25.3 (5)	25.2 (5.4)	24,9 (5)	0.695
Charlson Comorbidity Index (median, IQC)		8 (2)	8 (5)	8 (2)	0.575
Right sided colon cancer		14 (17.5)	49 (21.5)	43 (30.7)	**0.017**
Synchronous colorectal – liver disease		45 (56.3)	169 (74.1)	103 (73.6)	**0.019**
Type of preoperative chemotherapy					
	Oxaliplatin – based	49 (61.3)	156 (68.4)	96 (68.6)	0.328
	Irinotecan – based	27 (33.8)	78 (34.2)	52 (37.1)	0.568
	Oxa-Iri – based	6 (7.5)	12 (5.3)	10 (7.1)	0.944
	Biological therapy	48 (60)	141 (61.8)	90 (64.3)	0.512
Number of lines					
	1	66 (82.5)	190 (83.3)	102 (72.9)	0.102
	2	10 (12.5)	27 (11.8)	30 (21.4)	
	3	4 (5)	11 (4.8)	8 (5.7)	
Number of Cycles (median, IQC)		6 (6)	6 (6)	8 (7)	**0.009**
Radiological response					
	Partial Response	52 (65)	146 (64)	74 (52.9)	**0.011**
	Stable Disease	25 (31.3)	74 (32.5)	52 (37.1)	
	Progressive Disease	3 (3.8)	8 (3.5)	14 (10)	
Surgical Details					
Major liver resection		15 (18.2)	41 (18)	36 (25.7)	0.140
Extrahepatic associated resection		28 (35)	88 (38.6)	79 (56.4)	**0.001**
Laparoscopic resection		20 (25)	48 (21.1)	17 (12.1)	**0.012**
Perioperative blood transfusion		9 (11.3)	24 (10.5)	14 (10)	0.772
Pringle Maneuver		50 (62.5)	147 (64.5)	101 (72.1)	0.107
Pringle clampoing time (median, IQC)		28.5 (57.7)	32 (84)	36,5 (60.2)	0.080
Intraoperative blood loss (median, IQC)		240 (260)	300 (275)	268 (315)	0.151
Postoperative Outcomes					
Mortality rate		1 (1.3)	0 (0)	1 (9.7)	0.783
Overall morbidity rate		25 (31.3)	62 (27.2)	52 (37.1)	0.214
Postoperative ascites rate		3 (3.8)	11 (4.9)	16 (11.8)	**0.012**
Post-hepatectomy liver failure rate		3 (3.8)	8 (3.6)	6 (4.4)	0.755
Biliary Leakage rate		3 (3.8)	10 (4.5)	11 (8.2)	0.125
Clavien-Dindo ≥ 3		8 (10)	23 (10.1)	19 (13.6)	0.348

Comprehensive Complication Index (median, IQC)	20.9 (12.6)	20.9 (12.6)	20.9 (23.3)	0.146
Length of hospital stay (median, IQC)	7 (4,75)	8 (5)	8 (5,7)	0.085

NAC neoadjuvant chemotherapy: continuous variables are reported as median or mean value and interquartile range IQR, in bold significant factors

TABLE 2. Pathological Outcomes stratified according to GAME score categories

Variables		GAME SCORE LOW RISK (n = 80) N (%)	MODERATE RISK (n = 228) N (%)	HIGH RISK (n = 140) N (%)	P
Parenchymal R1		7 (10.3)	18 (10.1)	20 (17.5)	0.099
TRG*	1-3	26 (32.9)	56 (25.1)	23 (17.4)	**0.010**
	4-5	53 (67.1)	167 (74.9)	109 (82.6)	
Grading	1	0 (0)	1 (0.5)	0 (0)	0.099
	2	30 (40.5)	68 (31.1)	39 (28.7)	
	3	44 (59.5)	150 (68.5)	97 (71.3)	
Mucinous differentiation		3 (3.8)	20 (8.8)	18 (13.1)	**0.021**
Necrosis		73 (91.3)	205 (91.9)	129 (93.5)	0.523
Vascular invasion		59 (73.8)	183 (81)	119 (87.5)	**0.011**
Perineural invasion		7 (8.8)	24 (10.6)	27 (19.7)	**0.010**
Biliary invasion/infiltration		6 (7.9)	22 (10.2)	18 (13.8)	0.116
Satellitosis		21 (26.9)	91 (40.4)	71 (53)	**0.001**
Cirrhosis		1 (1.3)	1 (0.5)	1 (0.8)	0.759
Steatosis		50 (64.9)	148 (67.3)	96 (71.1)	0.328

TRG: Tumor Regression Grade; 1data available on 434 liver resections; in bold significant factors.

TABLE 3. Univariate and Multivariate Analysis of predictive factors of pathological responses according to tumor regression grade

	# Patients 434	**Univariate Analysis**		**Multivariate Analysis**	
Variables		TRG 4 – 5 *N (%)*	P	P	RR (95% CI)
Age > 70 years			**0.015**	**0.022**	2.111 (1.114 – 4.004)
Y	95	81 (85.3)			
N	339	248 (73.2)			
Right colon			0.068	-	
Y	103	85 (82.5)			
N	331	244 (73.7)			
N stage Primitive Cancer			0.711.	-	
N+	312	238 (76.3)			
N0	122	91 (74.6)			
KRAS mutated			0.327	-	
Y	179	140 (78.2)			
N	255	189 (74.1)			
Number of cycles NAC			**0.010**	**0.038**	0.556 .319-0.967)
> 6	290	209 (72.1)			
≤ 6	144	120 (83.3)			
Number of Lines NAC			0.079	-	
1	346	256 (74)			
> 1	88	73 (83)			
Biological agents			**0.012**	**0.025**	0.538 (0.313 – 0.923)
Y	269	193 (71.7)			
N	165	136 (82.4)			
Oxaliplatin-based scheme			0.182		
Y	291	215 (73.9)			
N	143	114 (79.7)			
Irinotecan-based scheme			**< 0.001**	**< 0.001**	3.066 (1.784 – 5.269)
Y	154	131 (85.1)			
N	280	198 (70.7)			
Oxa-Irinotecan-based scheme			0.252	-	
Y	27	18 (66.7)			
N	407	311 (6.4)			
GAME Score			**0.029**	**0.025**	1.843 (1.079 – 3.151)
Low/Moderate Risk	302	220 (72.8)			
High Risk	132	109 (82.6)			

Y yes; N no; TRG tumor regression grade; NAC neoadjuvant chemotherapy; In bold significant factors

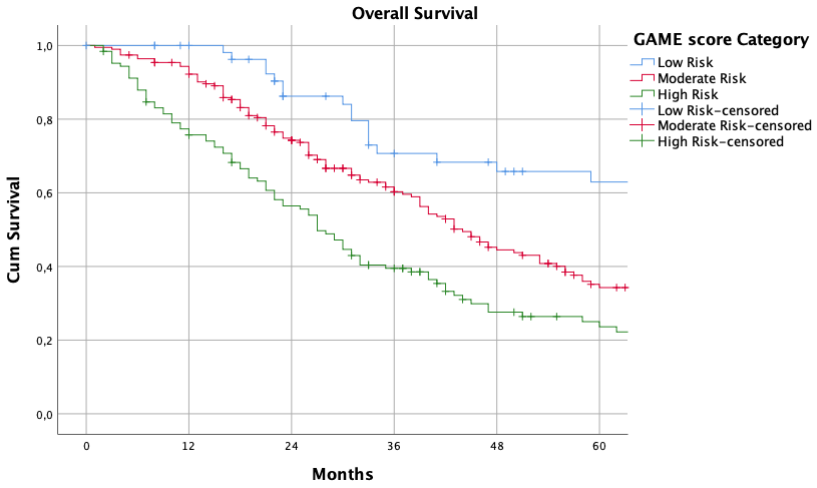
TABLE 4. Univariate and Multivariate Analysis of predictive factors of radiological progressive disease according to RECIST criteria

	# Patients 448	**Univariate Analysis**		**Multivariate Analysis**	
Variables		PD *N (%)*	P	P	RR (95% CI)
Age > 70 years			0.465	-	
Y	98	4 (4.1)			
N	350	21 (6)			
Right colon			0.599	-	
Y	342	7 (6.6)			
N	106	18 (5.3)			
N stage Primitive Cancer			0.318	-	
N+	319	20 (6.3)			
N0	129	5 (3.9)			
KRAS mutated			0.777	-	
Y	185	11 (5.9)			
N	263	14 (5.3)			
Number of cycles NAC			0.323	-	
> 6	300	19 (6.3)			
≤ 6	148	6 (4.1)			
Number of Lines NAC			**0.041**	0.099	
1	90	9 (10)			
> 1	358	16 (4.5)			
Biological agents			0.855	-	
Y	279	16 (5.7)			
N	169	9 (5.3)			
Oxaliplatin-based scheme			0.096	-	
Y	301	13 (4.3)			
N	147	12 (8.2)			
Irinotecan-based scheme			0.067	-	
Y	157	13 (8.3)			
N	291	12 (4.1)			
Oxa-Irinotecan-based scheme			1.000	-	
Y	28	1 (3.6)			
N	420	24 (5.7)			
GAME Score			**0.006**	**0.016**	2.77 (1.213 – 6.325)
Low/Moderate Risk	308	11 (3.6)			
High Risk	1140	14 (10)			

Y yes; N no; NAC neoadjuvant chemotherapy; In bold significant factors

Figure 1. Survival after liver resection according to GAME score Category. A. overall survival (p<0.001); B, disease-free survival (p<0.001).

A

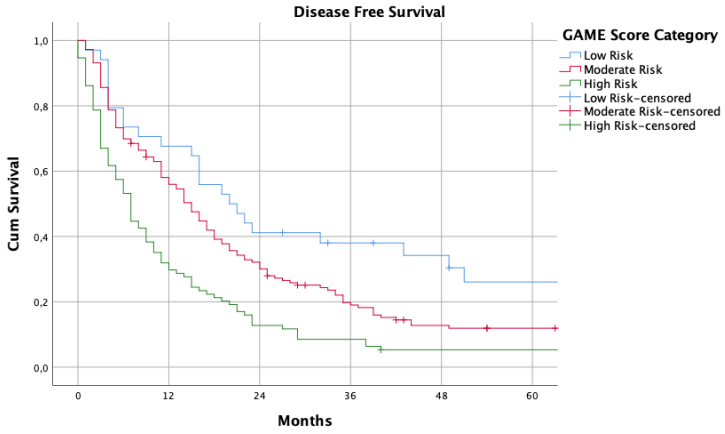


Patients at risk overall survival

	MONTHS					
At risk	0	12	24	36	48	60
LR – GAME	58	53	40	30	26	22
MR – GAME	195	179	132	93	61	40
HR - GAME	125	94	67	43	24	17

	MEDIAN OF OVERALL SURVIVAL AFTER LIVER RESECION (MONTHS ± ES) (95% I.C.)
All	41 (± 2,628) (36 – 46)
Low Risk (58) (15,3%)	87 (± 15,475) (57 – 117)
Moderate Risk (195) (51,6%)	44 (± 2,989) (38 – 50)
High Risk (≥4) (125) (33,1%)	27 (± 2,080) (23 – 31)

B



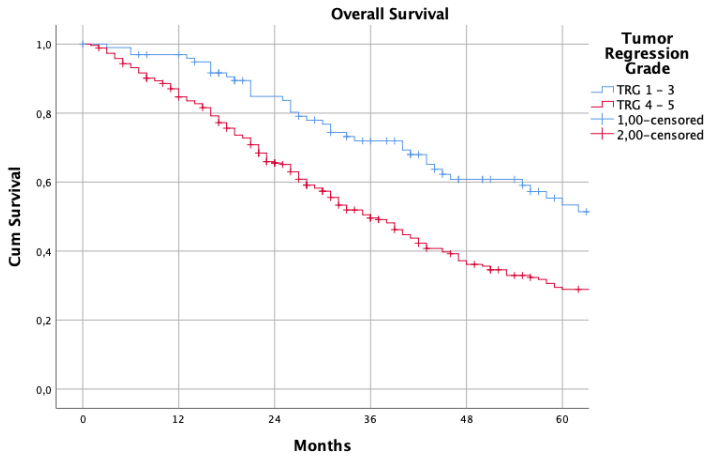
Patients at risk overall survival

	MONTHS					
At risk	0	12	24	36	48	60
LR – GAME	34	23	14	11	8	6
MR – GAME	146	82	45	25	14	11
HR - GAME	94	29	12	7	4	3

	MEDIAN OF DISEASE-FREE SURVIVAL AFTER LIVER RESECION (MONTHS ± ES) (95% I.C.)
All	12 ± 1,320 (9 – 15)
Low Risk (58) (15,3%)	20 ± 4,373 (12 – 18)
Moderate Risk (195) (51,6%)	15 ± 1,486 (14 – 24)
High Risk (≥4) (125) (33,1%)	7 ± 0,803 (6 – 10)

Figure 2. Survival after liver resection according to Tumor Regression Grade Category. A, overall survival (p<0.001); B, disease-free survival (p=0.008).

A

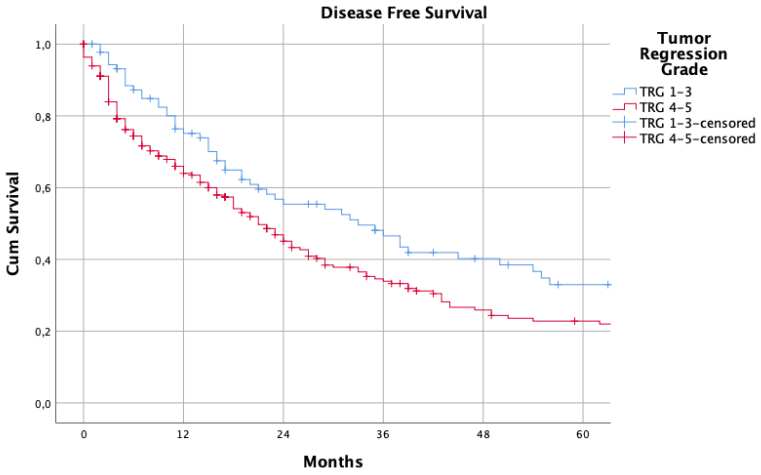


Patients at risk overall survival

	MONTHS					
At risk	0	12	24	36	48	60
TRG 1 – 3	90	78	66	54	42	30
TRG 4 – 5	249	237	225	213	201	189

	MEDIAN OF OS AFTER LIVER RESECION (MONTHS ± ES) (95% I.C.)
All	42 ± 2,392 (37 – 47)
TRG 1-3 (58) (15,3%)	65 ± 16,005 (34 – 96)
TRG 4-5 (195) (51,6%)	36 ± 2,692 (31 – 41)

B



Patients at risk overall survival

	MONTHS					
At risk	0	12	24	36	48	60
TRG 1 – 3	90	61	40	30	23	170
TRG 4 – 5	249	133	79	52	33	28

	MEDIAN OF DFS AFTER LIVER RESECION (MONTHS ± ES) (95% I.C.)
All	23 ± 2,447 (18 – 28)
TRG 1-3 (58) (15,3%)	33 ± 6,703 (20 – 46)
TRG 4-5 (195) (51,6%)	21 ± 1,972 (17 – 25)