Liver Resection for Metastases from Gastrointestinal Stromal Tumors: Does it Improve Long-Term Survival?

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Rezumat

Supraviețuirea pe termen lung este prelungită după rezecția hepatică pentru metastazele tumorilor gastrointestinale stromale?

Introducere și Scop: Apariția inhibitorilor tirozin kinazei a modificat radical managementul tumorilor gastrointestinale stromale și a ridicat controverse privind rolul rezecției hepatice în tratamentul metastazelor. Prezentul studiu își propune: să cerceteze existența unei prelungiri în supraviețuirea pe termen lung a pacienților cu metastaze hepatice ale tumorilor gastrointestinale stromale, supuși rezecției în contextul terapiei multimodale, în comparație cu pacienții abordați numai prin terapie sistemică.

Materiale și Metode: Folosind o bază retrospectivă, am identificat 57 pacienți tratați în centrul nostru pe o perioadă de 12 ani: grupul A (n=31) supuși rezecției hepatice alături de terapie sistemică și grupul B (n=26) care a urmat doar terapie sistemică. Pentru a obține un lot robust, necesar unei analize elocvente a supraviețuirii, am utilizat calculul unui scor de propensitate cu matching și o selecție bootstrapping cu corecția erorilor Jackknife, astfel am creat un lot de studiu extins ce a cuprins 1000 pacienți virtuali.

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Rezultate: Supraviețuirea globală determinată pentru întreg lotul a fost de 47 luni (95%CI:34-60); semnificativ crescută pentru grupul A (56 luni, 95%CI:37-75) în comparație cu grupul B (38 luni, 95%CI:19-56), ($p=0.007$, Log Rank test). Analiza multivariată a identificat un factor de risc: existența metastazelor hepatice sincrone la momentul diagnosticului tumorii primare.

Concluzii: Considerăm că rezecția hepatică precedată de terapia cu inhibitori ai Tirozin Kinazei este strategia terapeutică actuală ce aduce șansele adecvate spre o posibilă vindecare și prelungirea supraviețuirii, la pacienții selectați corespunzător, evaluați în cadrul unei comisii oncologice multidisciplinare.

Cuvinte cheie: tumori gastrointestinale stromale, hepatectomie, terapie multimodală, scor de propensitate cu matching, selecție bootstrapping cu corecția erorilor Jackknife, supraviețuire

Abstract

Background & Aims: The emergence of tyrosine kinase inhibitors, radically altered the management of GISTs and sparked controversy regarding the role of hepatic resection for metastatic tumors. This study aims to identify whether there is improvement in the overall survival of patients with gastrointestinal liver metastases, undergoing hepatic resection in the context of multimodal treatment strategy, as to those approached only by systemic therapy.

Methods: Using a retrospective database, we identified 57 patients treated at our center over a 12-year period: Group A ($n=31$) underwent hepatic resection alongside systemic therapies, and B ($n=26$) only systemic therapies. In order to obtain a more robust sample, needed for the survival analysis, we performed a propensity score matching and a bootstrapping selection with Jackknife correction for errors; thus, we created an extended sample of 1000 virtual patients.

Results: The overall survival measured in all patients was 47 months (95%CI:34-60); significantly higher for group A (56 months, 95%CI:37-75) compared to group B (38 months, 95%CI:19-56), ($p=0.007$, Log Rank test). Multivariate analysis identified one risk factor: the presence synchronous liver metastases upon diagnosis of primary.

Conclusions: Liver resection following TKI therapy is the current mainstay of treatment strategy for potential cure and prolonged survival, in appropriately selected patients evaluated in an multidisciplinary tumor board.

Key words: gastrointestinal stromal tumors, hepatectomy, combined modality therapy, propensity score matching, bootstrapping selection with Jackknife correction for errors, survival

Introduction

Gastrointestinal stromal tumours (GISTs) arise from the interstitial cells of Cajal and are the most common type of mesenchymal tumours in the gastrointestinal tract (1), with an estimated incidence of 11.0–21.0 per million worldwide (2).

The incidence of distant metastases from GISTs has been reported to be as high as 23–47% (3,4). The most common sites of GIST

metastases are the liver and peritoneum. Among the different sites, the liver accounted for 20–60% of all distant metastases (3,5). GIST metastases to the liver (GLM) occur both synchronously and metachronously and are present at initial diagnosis between 15 and 20% of the time (6).

To treat liver metastases from GISTs, prior to 2000, hepatic resection was the only possible treatment option, which had a poor median survival of 15 months (7). The

emergence of tyrosine kinase inhibitors (TKIs), such as imatinib mesylate, radically altered the management of GISTs and sparked controversy regarding the role of hepatic resection for metastatic tumours. TKIs significantly improved prognosis, achieving high disease control: 80% response rate and a significantly prolonged median survival time that has increased to 5 years (8).

Nowadays, Imatinib, a tyrosine kinase inhibitor (TKI), is the first-line treatment for advanced GIST (9). However, despite its potent efficacy, complete responses are rare, and at least half of the patients develop resistance to imatinib within 2 years of initiating treatment because of secondary gene mutations (10). The limitation of TKI therapy has prompted the reassessment of surgery for advanced GIST, but opinions differ. Some suggested that only patients with stable or limited progression disease on TKI therapy could benefit from debulking surgery (11), whereas others found that when complete resection could be achieved, even those with progressing disease would benefit (12). From an anatomical perspective, GLM are easier to define and assess than those in the peritoneum. This feature gives the first, greater possibility of complete resection, revealing a special subset of advanced GIST where surgery has a greater role to play: by the means of the liver-directed therapies available, leading to the importance of establishing a coordinated approach to GLM (6).

Nowadays, there is a lack of randomised clinical trials that target the therapy model composed of hepatic resection with TKIs. Thus, leading to a controversy regarding the influence of liver resection within a multimodal treatment plan, concerning: efficacy (13), as well as timing (14).

This study aims to identify whether there is improvement in the overall survival of patients with GLM, undergoing hepatic resection in the context of multimodal treatment strategy, as to those approached only by systemic therapy.

Methods

This retrospective cohort study was performed at a tertiary referral centre for hepato-bilio-pancreatic surgery and liver transplant. No ethical concerns were raised by the institution's Ethics Committee.

Patients

Using a retrospective institutional database, we identified 57 patients undergoing multimodal treatment for histologically diagnosed GLM at our centre over a 12-year period, between 1st of January 2007 and 31st of December 2018. We categorised patients in two groups, based on their treatment approach: Group A (n = 31) underwent hepatic resection alongside systemic therapies, and Group B (n = 26) underwent only systemic therapies. For each and every one of the patients, the treatment approach was determined by a multidisciplinary team (hepato-bilio-pancreatic surgeon, digestive oncologist, interventional radiologist).

Patients declared unfit for surgery, were directed to the systemic therapy group because of the following reasons: in 6 patients the liver resection was technically unfeasible (due to high metastases burden: multiple, disseminated, great dimensions), in 8 patients the metastases resection was unfeasible, due to presence of extrahepatic metastases with high burden (multiple, disseminated), resection of the primary tumour was unfeasible among 3 patients, 7 patients refused the surgical act, and 1 patient was declared unfit for surgery due to comorbidities.

In order to reduce the bias of patient selection, we excluded from the study:

- those patients (n = 7) from Group B, considered as "end stage disease" upon admission in our institute, due to the high tumour burden and great extent of the metastatic disease.
- those patients (n = 3) from Group A, that underwent other forms of liver-directed therapies besides resection (radio-frequency ablation, whole liver trans-

plantation), or as a complement to liver resection (resection and ablation);

Analyzed Variables

1. Standard demographic and clinico-pathologic data were collected, including: gender, age, ASA class, comorbidities [scored using the Charlson Comorbidity Index], and ECOG performance status.
2. For primary tumor characteristics: origin of primary tumor (foregut: esophagus, stomach, liver, gallbladder, pancreas, caudal portion of the duodenum, midgut: distal duodenum, jejunum, ileum, cecum, appendix, ascending colon, proximal 2/3 of transverse colon, and hindgut: distal transverse colon, descending colon, sigmoid, anorectum), presence of symptoms, and existence of synchronous liver, or extrahepatic metastases.
3. Resection of primary tumor: resection status, tumor grading, NIH risk group, presence of lymph node metastases.
4. GIST liver metastases data included: number, size, location, hepatic involvement, grading, number of mitoses, Ki-67 index, and presence of extrahepatic metastases.
5. For patients undergoing liver resection, we collected the following data: number of synchronous resections (of both primary and liver metastases), minimally invasive approach, portal vein embolisation, intra-operative ultrasound, extent and type of resection (non-anatomic wedge, single segmentectomy, bi-segmentectomy, right hepatectomy, left hepatectomy, extended right hepatectomy, extended left hepatectomy, and extended central hepatectomy), resection margin status, intent of treatment, type of postoperative complications and their management, and mortality rates.
Postoperative complications: were scored according to the Clavien-Dindo classification as no complication or complication grades I to V (15).
6. For patients undergoing systemic therapy

we collected: the type of therapy administered, response of liver metastasis; related morbidity. Tyrosine kinase inhibitor therapy included: Imatinib, Sunitinib and Regorafenib. Patients undergoing chemotherapy received: ifosamide, taxotere, and gemcitabine.

7. Upon long-term results we collected: the date of death.

Study Endpoints and Baseline Definitions

The endpoint of the study was Overall Survival (OS), defined as the time from randomisation until death from any cause (16); measured from the baseline: date of GLM diagnosis, until: date of death - obtained officially from the "Directorate for People's Registry and Databases Management", on the 13th of April 2019. Follow-up evaluation results were obtained by review of the patient's medical records and/or by personal telephone interview conducted during April 2019. The response to the systemic treatment was classified according to the Response Evaluation Criteria in Solid Tumors (RECIST) (17).

Statistical Analyses

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 23.0, IBM, Chicago, IL). Categorical variables were described in frequencies and percentages. Continuous variables were represented as mean $\pm$ SD or median and range. Categorical variables were compared using the Chi-Square test and Fisher's exact test. Continuous variables with quasi-normal distributions were compared using Student's T test and those with a severe deviation from normality, with appropriate nonparametric tests.

Overall survival (OS) was estimated using a Kaplan-Meier survival analysis considering the time-to-event in months. The differences in survival were tested using the log-rank test.

A propensity score matching was performed to reduce the patient selection bias. This methodology has been shown to greatly

reduce effect size bias and gives non-randomised studies experimental design characteristics. However, its main drawback is: that due to the reduction in sample size, the studies will likely develop a decrease in terms of the statistical power analysis. The propensity score matching was performed with Python extension for SPSS. Covariates used to calculate the propensity score were: not only those based upon previously published studies (8), but also upon the ones that we considered adequate. At first, the propensity score was estimated using logistic regression. The covariates used in this step were: age, Charlson Comorbidity Score, ECOG Performance Status, NIH risk group, hepatic involvement at diagnosis, grading of liver metastasis, and presence of extrahepatic metastases. After estimating the propensity score, we matched the patients originating from the two groups using a one-to-one nearest neighbour matching with a caliper of 0.15. After employing this procedure, we have obtained a 49% matching of cases from the sample (28 patients, 14 from each group).

In order to obtain a more robust sample, needed imperatively for the analysis of the differences in survival between the two groups and for identifying the factors associated with improved survival, we performed a bootstrapping selection with Jackknife correction for errors (18,19). Thus, we created an extended sample of 1000 virtual patients, on which we performed again the propensity score matching, using the same covariates and caliper as previously mentioned, obtaining a 49% matching of cases (488 virtual patients in total, 244 from each group). The survival analysis was conducted on the extended matched sample (488 virtual patients).

Factors potentially associated with improved survival were analyzed using the Cox proportional hazard model with forward stepwise selection (on the original sample and on the matched sample). All variables were included in a univariate analysis and those with a p-value of less than 0.05 were used in the multivariate analysis. Results were expressed as hazard ratio (HR) with a 95% confidence interval

(CI). For all analyses, p-values < 0.05 were considered statistically significant.

Results

The baseline characteristics of the unmatched sample (57 patients) are presented in *Table 1*.

Quality Assessment of Propensity Scores

In determining the propensity score we used the following covariates: (1) age, (2) Charlson Comorbidity Score, (3) ECOG Performance Status, (4) NIH risk group, (5) hepatic involvement at diagnosis, (6) grading of liver metastasis, and (7) presence of extrahepatic metastases. Using these covariates we performed a logistic regression, saving predicted probabilities and logit transformations given the fact that they are used in the matching process (propensity score). The dependent variable was specified as the patient's treatment group. Afterwards, we examined the logistic regression model in order to assess the quality of propensity scores. First, we compared the correct classification of participants to groups to the null hit rate, and we discovered a 29% improvement (79% versus 50%). An inferential goodness-of-fit test (Hosmer–Lemeshow) was also performed and suggested good model fit Chi-square = 3.377 (p = 0.848). This apparently implied that the treatment approach was not determined randomly, and therefore can be reasonably predicted by the result of the covariates used in the estimation of propensity scores. The differences in the likelihood of undergoing hepatic resection or not (i.e. selection bias) were compared afterwards using an independent samples t-test. This initial assessment is important for evaluating the magnitude of bias and any improvement after the propensity score matching. Results indicated the groups were statistically different in their propensity scores or initial likelihood of being selected into group A (p<0.001, SMD=1.316). This difference in SMD (standardized mean difference) suggests that the two groups should not be directly compared when estimating treatment effects.

Table 1. Baseline characteristics of the patients before score matching

Categorical covariates	Total (%) (n=57)	Group A (%) (n=31)	Group B (%) (n=26)	p-value*
Gender (male)	47%	45%	50%	0.793
ASA score (>=3)	14%	7%	23%	0.078
Charlson Comorbidity Score				
6-7	37%	48%	23%	0.029
8-9	51%	48%	54%	
≥10	12%	4%	23%	
ECOG Performance Status				
0	35%	26%	46%	0.076
1	51%	64%	35%	
2	12%	7%	19%	
3	2%	3%	0%	
Origin of Primary Tumor				
Foregut	40%	45%	35%	0.407
Midgut	53%	52%	54%	
Hindgut	7%	3%	11%	
Symptomatic Primary Tumor (yes)	93%	94%	92%	0.855
Resection of Primary Tumor (yes)	88%	97%	77%	0.039
Primary Tumor Grading				
G1	37%	36%	39%	0.816
G2	63%	64%	61%	
NIH Risk Group				
Low	12%	13%	12%	0.987
Intermediate	19%	19%	19%	
High	69%	68%	69%	
Lymph Node Metastasis upon Resection of Primary (yes)	21%	19%	26%	0.499
Synchronous Liver Metastases upon Diagnosis of Primary (yes)	49%	61%	35%	0.040
Synchronous Extrahepatic Metastases upon Diagnosis of Primary (yes)	23%	13%	35%	0.050
Number of Hepatic Metastases Upon Diagnosis				
Solitary	30%	45%	12%	0.020
2-4	14%	13%	15%	
>4	56%	42%	73%	
Hepatic Involvement at Diagnosis				
<25%	62%	61%	61%	0.902
25-50%	33%	32%	35%	
50-75%	5%	7%	4%	
Location of Liver Metastases Bilobar	63%	52%	77%	0.044
Grading of Liver Metastasis				
G1	32%	29%	35%	0.777
G2	68%	71%	65%	
Ki-67 of Liver Metastases				
<8	4%	3%	4%	0.789
≥8	19%	16%	23%	
Unknown	77%	81%	73%	
Extrahepatic Metastases upon Diagnosis of the Liver Metastases (yes)	40%	32%	50%	0.138
Continuous covariates				
Age in years (mean±SD)	56±13	52±13	62±12	0.005
Size of the Largest Liver Metastasis (cm) (mean ± SD)	5.54±4.85	6.96±5.73	3.85±2.78	0.011
Number of Mitoses of Liver Metastasis (mean±SD)	8.79±5.96	10.35±7.19	6.92±3.29	0.022

*Chi-square test for categorical variables and T-test for continuous variables (comparisons between the two groups)

Nearest Neighbor Matching Within a Specified Caliper

Therefore, propensity scores were used to match the patients from group A to those in group B. Because, even in a large sample, an exact match is almost impossible to obtain, we decided to specify a priori: a distance measure (a caliper). Specifically, we used a caliper of 0.15 standard deviations of this score, as a reasonable distance for reducing bias between groups (a larger value of the caliper will lead to more pairs matched, but with a less power of bias reduction).

Post-matching Analyses to Evaluate Balance

In order to evaluate balance as a result of the propensity score matching model, literature (20-22) suggests that: the standardised difference in the mean propensity score between the two groups should be less than 0.20 and the ratio of the propensity score variances in both groups should be near one (the recommended limits are 0.80 – 1.20). For covariates, continuous or categorical, statistical differences should not be significant in the matched sample. The results of balance evaluation is presented in *Table 2.1.* and *Table 2.2.* Once balance is achieved on the propensity scores and covariates, groups can be directly compared on the outcome of interest (overall survival and factors potentially associated with better survival).

The characteristics of the administered liver-directed and systemic therapy before and after matching, are shown in *Table 3.*

Liver Resection Characteristics in the Matched Sample

36% of patients in Group A underwent resection of the primary tumor and resection of synchronous liver metastases during the same operative procedure, 7% of patients were approached by the means of minimally invasive surgery, 3% were subjected to portal vein embolization, prior to the surgical intervention, and 32% received ultrasonographically guided liver resection. 71% of patients underwent minor resections, 29% whereas received major resections. 71% received a wedge resection, single, and/or bi-segmentectomy. 13% received a right hemihepatectomy; 7% a left hemihepatectomy; 3% an extended right hemihepatectomy; 3% an extended left hemihepatectomy; 3% an extended central hepatectomy.

R0 resection was achieved in 97% of patients, in spite of the fact that 13% underwent hepatic resection with the plan of surgical debulking.

Postoperative complications occurred in 42% of patients. Dindo-Clavien Grade I or II complications were encountered in 19% of patients, whereas complications greater than Grade IIIa, occurred in 23% of patients, thus leading to the need of management, performed by: endoscopic, or radiologic reinterventions on 10% patients, whereas 13% patients required reoperation. Postoperative mortality rate was 3%, due to hepatic failure.

Survival Comparison for the Unmatched Sample

The OS measured in all patients was 51 months (95% CI: 40-62). There was a signifi-

Table 2.1. Propensity score balance before and after matching

	Before matching (57 patients)				After matching on extended sample (488 virtual patients)			
	Group A (n=31)	Group B (n=26)	SMD	Variance ratio	Group A (n=244)	Group B (n=244)	SMD ratio	Variance
Propensity score (Mean $\pm$ SD)	0.717 $\pm$ 0.260	0.337 $\pm$ 0.241	1.25	1.07	0.485 $\pm$ 0.204	0.455 $\pm$ 0.199	0.14	1.02

Table 2.2. Covariates score balance before and after matching

Categorical covariates	Before matching (57 patients)			After matching on extended sample (488 virtual patients)		
	Group A (%) (n=31)	Group B (%) (n=26)	p-value*	Group A (%) (n=244)	Group B (%) (n=244)	p-value*
ASA score (≥ 3)	7%	23%	0.078	14%	22%	0.500
Charlson Comorbidity Score						
6-7	48%	23%	0.029	29%	29%	0.822
8-9	48%	54%		64%	57%	
>10	4%	23%		7%	14%	
ECOG Performance Status						
0	26%	46%	0.076	35%	29%	0.620
1	64%	35%		43%	43%	
2	7%	19%		15%	28%	
3	3%	0%		7%	0%	
Origin of Primary Tumor						
Foregut	45%	35%	0.407	28%	14%	0.435
Midgut	52%	54%		64%	65%	
Hindgut	3%	11%		7%	21%	
Symptomatic Primary Tumor (yes)	94%	92%	0.855	100%	93%	0.309
Resection of Primary Tumor (yes)	97%	77%	0.039	100%	72%	0.098
Primary Tumor Grading						
G1	36%	39%	0.816	29%	36%	0.686
G2	64%	61%		71%	64%	
NIH Risk Group						
Low	13%	12%	0.987	14%	7%	0.591
Intermediate	19%	19%		14%	29%	
High	68%	69%		72%	64%	
Lymph Node Metastasis upon Resection of Primary (yes)	19%	26%	0.499	22%	28%	0.511
Synchronous Liver Metastases upon Diagnosis of Primary (yes)	61%	35%	0.040	43%	43%	1.000
Synchronous Extrahepatic Metastases upon Diagnosis of Primary (yes)	13%	35%	0.050	22%	50%	0.115
Number of Hepatic Metastases Upon Diagnosis						
Solitary	45%	12%	0.020	14%	22%	0.881
2-4	13%	15%		14%	14%	
>4	42%	73%		72%	64%	
Hepatic Involvement at Diagnosis						
<25%	61%	61%	0.902	71%	50%	0.381
25-50%	32%	35%		29%	43%	
50-75%	7%	4%		0%	7%	
Location of Liver Metastases Bilobar	52%	77%	0.044	71%	71%	1.000
Grading of Liver Metastasis						
G1	29%	35%	0.777	22%	28%	0.663
G2	71%	65%		78%	72%	
Ki-67 of Liver Metastases						
<8	3%	4%	0.789	-	7%	0.236
≥ 8	16%	23%		21%	43%	
Unknown	81%	73%		79%	50%	
Extrahepatic Metastases upon Diagnosis of the Liver Metastases (yes)	32%	50%	0.138	36%	57%	0.256
Continuous covariates						
Age in years (mean $\pm$ SD)	52 $\pm$ 13	62 $\pm$ 12	0.005	57 $\pm$ 9	59 $\pm$ 14	0.643
Size of the Largest Liver Metastasis (cm) (mean $\pm$ SD)	6.96 $\pm$ 5.73	3.85 $\pm$ 2.78	0.011	4.78 $\pm$ 4.11	4.11 $\pm$ 3.46	0.641
Number of Mitoses of Liver Metastasis (mean $\pm$ SD)	10.35 $\pm$ 7.19	6.92 $\pm$ 3.29	0.022	10.36 $\pm$ 5.28	6.86 $\pm$ 2.71	0.040

*Chi-squared test for categorical covariates and T-test for continuous covariates

Table 3. Characteristics of the administered liver-directed and systemic therapy before and after matching

Categorical covariates	Before matching (57 patients)			After matching on extended sample (488 virtual patients)		
	Group A (%) (n=31)	Group B (%) (n=26)	p-value*	Group A (%) (n=244)	Group B (%) (n=244)	p-value*
Systemic Therapy						
Yes	65%	100%	0.047	71%	100%	0.098
No	35%	-	-	29%	-	-
Response of GLM to Systemic Therapy						
Progressive disease	-	27%	-	-	21%	-
Stable disease	22%	27%	0.976	21%	21%	1.000
Partial response	10%	46%	<0.001	7%	58%	<0.001
Complete response	68%	-	-	72%	-	-
Systemic Therapy Related Morbidity (n=46)						
Yes	15%	15%	1.000	10%	21%	0.437
No	85%	85%		90%	79%	

*Chi-square test or Fisher's exact test

cantly higher OS for group A (65 months, 95%CI: 47-82) compared to group B (35 months, 95%CI: 22-47), ($p=0.031$, Log Rank test) (*Fig. 1*).

Survival Comparison for the Matched Sample

The OS measured in all patients was 47 months (95% CI: 34-60). There was a significantly higher OS for group A (56 months, 95%CI: 37-75) compared to group B (38 months, 95%CI: 19-56), ($p=0.007$, Log Rank test) (*Fig. 2*).

Estimating Treatment Effects on the Matched Sample

All the baseline characteristics were included in a univariate analysis in order to identify the factors associated with improved survival. Afterwards, the multivariate analysis was performed upon those factors that recorded a p -value < 0.05 in the univariate analysis. After multivariate analysis, only one factor remained independent risk factor: synchronous liver metastases upon diagnosis of primary. Details of the analysis are shown in *Table 4*.

Figure 1. Kaplan-Meier survival for unmatched groups **Figure 2.** Kaplan-Meier survival for matched groups

Table 4. Cox proportional hazard model for factors influencing survival after propensity score matching (n=488)

Factors	Univariate			Multivariate		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Age (in years)	1.032	0.983-1.082	0.203	-	-	-
Primary Tumor Location						
Foregut	0.521	0.116-2.340	0.395			
Midgut	1.069	0.338-3.376	0.910	-	-	-
Hindgut	3.062	0.589-15.93	0.183			
Symptomatic Primary Tumor (no)	5.440	0.607-48.78	0.130	-	-	-
Resection of Primary Tumor (no)	2.698	0.511-14.26	0.243	-	-	-
Primary Tumor Grading						
G1	1.920	0.620-5.945	0.258	-	-	-
G2	0.521	0.168-1.613	0.258			
Synchronous Liver Metastases upon Diagnosis of Primary (yes)	4.923	1.269-19.09	0.021	4.245	1.034-17.427	0.045
Synchronous Extrahepatic Metastases upon Diagnosis of Primary (yes)	0.625	0.223-1.751	0.371	-	-	-
Lymph Node Metastasis upon Resection of Primary (no)	0.624	0.222-1.758	0.372	-	-	-
NIH Risk Group						
Low	1.079	0.130-8.978	0.944			
Intermediate	1.937	0.645-5.815	0.238	-	-	-
High	0.539	0.184-1.576	0.258			
Number of Hepatic Metastases Upon Diagnosis						
Solitary	6.424	1.395-29.57	0.017	3.716	0.565-24.426	0.172
2-4	1.777	0.367-8.612	0.475			
>4	0.217	0.056-0.838	0.027	0.600	0.105-3.431	0.566
Size of the Largest Liver Metastasis (cm)	0.934	0.765-1.141	0.506	-	-	-
Hepatic Involvement at Diagnosis						
<25%	1.248	0.423-3.681	0.688	-	-	-
25-50%	0.854	0.290-2.514	0.774			
Location of Liver Metastases (unilobar)	2.189	0.733-6.538	0.160	-	-	-
Grading of Liver Metastasis						
G1	2.295	0.750-7.023	0.145	-	-	-
G2	0.436	0.142-1.333	0.145			
Number of Mitoses of Liver Metastasis	0.933	0.834-1.044	0.227	-	-	-
KI-67% of Liver Metastasis (≥ 8)	1.785	0.414-7.690	0.437	-	-	-
Systemic Therapy after Liver Resection (yes)	1.036	0.280-3.836	0.958	-	-	-
Extrahepatic Metastases upon Diagnosis of the Liver Metastases (no)	0.665	0.235-1.881	0.442	-	-	-
Response of Liver Metastasis to Systemic Therapy						
Stable disease	1.682	0.566-5.00	0.350			
Partial response	0.650	0.205-2.054	0.463	-	-	-
Complete response	0.533	0.168-1.687	0.284			
Systemic Therapy Related Morbidity (yes)	0.882	0.175-4.438	0.879	-	-	-

Discussion

Our study focused on a special subset of GIST patients originating from a single centre and offered an insight into the role of surgery in this setting, the results suggest that GLM who undergo liver resection following TKI therapy

show improved OS compared with those who undergo TKI therapy alone.

In the pre-TKI period, surgical resection alone was associated with 5-year survival of 30–60 % and a median overall survival of only 15 months (7). High liver recurrence rates of up to 60% were registered (23). With the intro-

duction of first line TKI therapy, improved patient survival was encountered especially in this advanced disease patient population, therefore the surgical decision-making was modified. Nowadays, the principles of patient selection for liver resection are based primary on tumor biology and patient performance status; and secondly on the disease-free interval, response to medical therapy, presence of extrahepatic disease, the number and size of the metastases, tumor location(s), and the patient level of fitness for surgery. If the patient is fit for surgery and the resection is technically feasible, surgical margin status and TKI response will determine the outcome (6).

Literature reports that margin-negative (R0) resection is associated with a better progression-free survival and 1-year overall survival, as compared with margin-positive resection (29 months vs. 7 months, $p = 0.002$) (24), respectively (100% vs. 37.5%, $p = 0.001$) (25). In the present study, R0 resection was achieved in 97% of group A patients.

It is widely considered that a sustained preoperative response to TKI therapy portends improved benefit from surgical therapy, thus a reduced tumour volume may improve surgical margins (26) (11). NCCN guidelines recommend surgical resection in order to obtain microscopically negative margins, although the need for extensive margins is not specified (27).

The baseline characteristics of both groups were similar. We encounter however a difference that involves: ECOG performance status, Charlson comorbidity score and the number of hepatic metastases upon diagnosis. These differences are to be expected given current clinical practices: group A patients might have presented with conditions that made them more likely candidates for surgery (e.g. better performance status, lower tumour burden) than group B patients. In fact, these factors result from a limitation of this retrospective study: a potential patient selection bias.

To minimise the impact of selection bias on the clinical outcomes in our current study

cohort, we used various statistical methods: at first, a propensity score was determined, afterwards the matching function was performed: this methodology has been shown to greatly reduce effect size bias and gives non-randomised studies experimental design characteristics. However, it's main drawback is: that due to the reduction in sample size, the studies will likely develop a decrease in terms of the statistical power analysis (we obtained a 49% matching of cases: 28 patients matched, 14 from each group, insufficient for analysis). Covariates used to calculate the propensity score were not only the ones based upon previously published studies (8), instead in order to compare similar patients we considered adequate to introduce: Charlson Comorbidity Score, NIH risk group, hepatic involvement at diagnosis, and grading of liver metastasis.

Secondly, in order to obtain a more robust sample, needed imperatively for the analysis of the differences in survival between the two groups and for identifying the factors associated with improved survival, we performed a bootstrapping selection with Jackknife correction for errors (18,19). Thus, we created an extended sample of 1000 virtual patients, that have identical characteristics as the original sample, on which we performed again the propensity score matching, using the same covariates and caliper as previously mentioned, obtaining a the same matching of cases. It's proper to underline another limit of the study: the fact that the statistical analysis was conducted on a virtual extended matched sample of patients. Never the less, this a proven method in statistical literature (18,19) that implies that the virtual extended sample has the identical characteristics as the original sample. Although it was not employed in medical literature; we consider it feasible in order to reach a sufficient sample size when reporting a single centre experience that involves low-incident tumours. Of course, the best way to eliminate selection bias is a randomised controlled trial, but given that the benefit of surgery has already been strongly suggested in literature, this makes its implementation ethically challenging. This fact was

evidenced by the 2009 phase III clinical trial (EORTC-62063) performed by the European Organisation for Research and Treatment of Cancer, which evaluated the role of surgery in treating patients with metastatic GIST who responded to imatinib. It was terminated early, due to low participant accrual, reflecting the mixed attitudes of treating physicians to the role of surgery in the treatment of GISTs. In addition, often the results of randomised controlled trials demonstrate insufficient power, and may not necessarily be generalised to a broader patient population. In the future, non-randomised observational data from databases remain a viable option, which could reflect widespread clinical practice, and complement the results of clinical trials.

Thirdly, factors potentially associated with improved survival were analysed using the Cox proportional hazard model with forward stepwise selection (on the original sample and on the matched sample). With multivariate analysis, we found that only one factor affected the patient outcome: synchronous liver metastases upon diagnosis of primary.

Literature agrees nowadays that preoperative TKI therapy for surgically resectable and borderline resectable metastatic GIST is a standard approach, that should be continued up until the time of surgery with resumption in the postoperative period (6).

The optimal timing of surgery continues to be debated. Some recommend to wait, for 3–9 months after the initiation of TKI therapy, since this is the time frame of greatest radiological response (28). Several studies are suggesting that operating during periods of responsive disease or stable disease, compared to progressive disease will improve outcome (11,25,29). In the contrary, despite the positive response to TKI therapy, the delay of resection leads frequently to the development of secondary mutations, resulting in resistance to imatinib (30). The time of greatest response is considered the moment of successful intervention; therefore the surgeon must closely follow the radiological response (6). The removal of either whole residual tumors or partially resectable tumors, residual after TKI

therapy, is considered to bring benefit, because the macroscopic residual lesions usually contain viable tumor cells, and possibly imatinib-resistant clones (8).

Conclusions

Once the bias of patient selection was reduced by the means of obtaining a more robust sample, and afterwards performing the propensity score matching, patients with hepatic resection as part of the therapeutic strategy show significant improvement in overall survival compared to those undergoing only systemic treatment.

The heterogeneous genetic population of liver metastases from GIST primary tumors leads to the differential success with TKI therapy and resection in achieving prolonged overall survival.

Based on these results, we consider that hepatic resection of GLM following TKI therapy is the current mainstay of treatment strategy for potential cure and prolonged survival, in appropriately selected patients evaluated in an multidisciplinary tumor board.

Also, we consider that patients with stable, or progressive disease following TKI therapy, benefit from surgery (even if complete cytorreduction could not be achieved) in terms of OS, by lowering the risk of developing secondary gene mutations and therefore resistance to TKI therapy.

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metastases arising from non-colorectal neoplasia”, developed at “Titu Maiorescu” Doctoral School of Medicine, Bucharest, Romania, with Irinel Popescu, University Professor, PhD, as thesis coordinator.

Conflict of Interest

The authors declare no conflicts of interests.

Ethics of Approval

For performing this study ethical approval was obtained.

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