Surgical Resection Predicts Overall Survival even in Frail Patients with IDH- wildtype Glioblastomas

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Research Article

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Abstract

Purpose

The aim of this study was to evaluate the role of frailty required in the surgical risk assessment in old patients with IDH-wildtype glioblastoma on surgical outcome, overall survival, and functional dependency.

Methods

We reviewed records of old and frail patients surgical treated at our institution between January 2018 to May 2021. Inclusion criteria were : 1) neuropathological diagnosis of IDH-wildtype glioblastoma; 2) patient older than 65 years at the time of surgery; 3) available data to assess the frailty index according to the 5-mFI.

Results

A total of 47 patients were included. The 5-mFI was at 0 in 11 cases (23.4%), at 1 in 30 cases (63.83%), at 2 in 2 cases (4.25%), at 3 in 2 cases (4.25%), at 4 in 2 cases (4.25%). A GTR was performed in 26 patients (55.3%), a STR was performed in 13 patients (27.6%), and a B was performed in 8 patients (17.1%). The rate of 30-day postoperative complications was higher in B and in the 5-mFI = 4 subgroup ($p > 0.05$). GTR and age ≤ 70 years were independent predictors of a longer overall survival ($p < 0.005$). Sex, 5-mFI, postoperative complications, and preoperative KPS status did not independently influence overall survival and functional dependency.

Conclusion

In aged patients with IDH-wildtype glioblastoma, GTR is still an independent predictor of longer survival and good postoperative functional recovery whatever the frailty index. The 5-mFI score does not influence surgery and outcomes. Further confirmatory analyses are required.

Introduction

Poor clinical condition and age, that are frequently intermixed, impact the management of patients harboring a IDH-wildtype glioblastoma [1]. Age alone appears as a predictor affecting morbidity and mortality for malignant gliomas patients [2, 3]. However, older patients with preserved clinical conditions and harboring a IDH-wildtype glioblastoma still benefit of aggressive and iterative treatments, even at disease progression [4]. A wide analysis is required in the surgical risk assessment in this population and the assessment of frailty has been proposed. Several studies have suggested that frailty correlates with morbidity and mortality in multiple surgical disciplines, including neurosurgery [5–8]. Therefore, frailty represents a promising factor to assess surgical risk, particularly in the elderly. Different scores have been proposed to assess frailty in surgical patients basing upon different criteria [9],[10]. Among them, the five-item modified frailty index (5-mFI) computes five co-morbidity factors[10]. Previous studies have addressed the association between frailty and postoperative morbidity and mortality in oncological neurosurgery. However, no clear distinction has been proposed between primary and secondary malignant brain neoplasms [8, 11, 12]. Therefore, the management of frail and old patients with an IDH-wildtype glioblastoma is still controversial and no standardized therapeutic approach has been recommended.

The aim of this study, focused on old patients harboring an IDH-wildtype glioblastoma, was to evaluate the role of frailty evaluation on: 1)surgical outcome related to the extent of resection, 2) preoperative risk assessment, 3) overall survival and; 4) functional dependency.

Materials And Methods

Data source

We reviewed records of old and frail patients who underwent a brain surgery for the diagnosis of a cerebral neoplasm at our institution between January 2018 to May 2021 using a protocol designed for the study. Inclusion criteria were : 1) neuropathological diagnosis of IDH-wildtype glioblastoma according to the 2016 World Health Organization Classification of Tumors of the Central Nervous System; 2) patient older than 65 years at the time of surgery; 3) available data to assess the frailty index according to the 5-mFI [10]. The five-item modified frailty index was calculated assigning a point to the following co-morbidity: functional dependent status, history of diabetes mellitus, hypertension, chronic obstructive pulmonary disease or pneumonia, and congestive heart failure.

According to the inclusion criteria, 47 out of 60 screened patients were included in the final analysis. We excluded 11 patients with a diagnosis different from IDH-wildtype glioblastoma, while two patients were lost to follow-up.

Informed consent

was acquired from all patients. Consent for publication was obtained from the patients and this study received required authorizations of the Ethics Committee of A.O. “SS Antonio e Biagio e Cesare Arrigo” – Alessandria (date 30/03/2022/ n° 0007012). This article follows STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Guidelines[13].

Data collection

Data at surgery included: sex, age, Karnofsky performance status (KPS) score, past medical history (diabetes mellitus, hypertension, chronic obstructive pulmonary disease or pneumonia, and congestive heart failure), surgical treatment, histopathological diagnosis, postoperative KPS score, clinical complications (new and permanent focal neurological deficit, epileptic seizures, signs of raised intracranial pressure, postoperative hematoma requiring surgical evacuation, infection, systemic thromboembolic event), surgical outcome on early postoperative MRI (extent of resection) and overall survival. To assess the functional impairment, the KPS score was used at diagnosis, at hospital discharge, and at final follow-up.

Surgical procedure

The decision as to whether to perform a particular surgical procedure was decided on an individual basis by the treating neurosurgeon according to his own preferences. For cases amendable to surgery, neurosurgeons favored ultrasonography-guided and MRI-based neuronavigation-guided (Stealth Station S7, Medtronic) resections without intraoperative functional brain mapping under asleep conditions. All cases deemed too risky for tumor resection received stereotactic biopsies under general anesthesia.

The tumor volume (cm3) was calculated using manual segmentation of abnormal signal on post-contrast T1-weighted sequence for every tumor. The extent of resection was quantified using an early postoperative MRI (within 48 hours) and performing manual segmentation of residual enhancing tumor. A total resection corresponded to the complete absence of the enhancing signal on post-contrast T1-weighted sequence. A subtotal resection corresponded to a residual enhancing signal on post-contrast T1-weighted sequence less than 10%.

Endpoints

The safety of the surgery was defined as the surgery-related morbidity: postoperative recovery (defined as a KPS score increase > 10 points in the immediate postoperative period in relation to preoperative KPS score), postoperative complications (hemorrhage, seizures, hydrocephalus, infections, and acute renal failure), and death within the first postoperative month.

Statistical Analysis

Continuous variables were described as mean ± standard deviation. Categorical variables were described as percentages. Univariable analyses were carried out, computing unadjusted odds ratios, and using the chi-square or Fisher’s exact test for comparing categorical variables, and the unpaired t-test or Mann–Whitney U test for continuous variables, as appropriate. Variables associated at the $P < 0.05$ level in unadjusted analysis were entered into logistic regression models. We performed a backward stepwise selection of variables, removing the least significant variables one after the other, and defining the least significant variable as having the highest p-value in the model. Unadjusted survival curves for overall survival were plotted by the Kaplan-Meier method, using log-rank tests to assess significance for group comparison. A Cox proportional hazard model was constructed using a backward stepwise approach, adjusting for predictors previously associated at the $p < 0.100$ level with mortality in unadjusted analysis.

The final models retained only the variables significant at the $P < 0.05$ level.

Statistical analyses were performed using JMP software (Version 16.1.0; SAS® Institute Inc., Cary, North Carolina, USA).

Results

Population

A total of 47 patients (65.9% men, mean age 72.9 ± 5.1-year-old, range 65–82) were included. Demographic and clinical characteristics are detailed in Table 1. The 5-mFI was at 0 in 11 cases (23.4%), at 1 in 30 cases (63.83%), at 2 in 2 cases (4.25%), at 3 in 2 cases (4.25%), at 4 in 2 cases (4.25%). No patient resulted with a 5-mFI at 5. A gross total resection was performed in 26 patients (55.3%), a subtotal resection was performed in 13 patients (27.6%), and a biopsy was performed in eight patients (17.1%).

Surgical-related morbidity and mortality

Surgical-related morbidity is detailed in **Table 2**. Overall, 30-day postoperative complications included surgical site hematoma managed conservatively in six cases (12.8%), epileptic seizures in two cases (4.3%), pneumonias in two cases (4.3%), hydrocephalus in one case (2.1%), and acute renal failure in one case (2.1%). The rate of 30-day postoperative complications was higher following biopsy than following subtotal and total resection (37.5%% and 23.1% vs 25.9%, respectively, $p = 0.5$). The rate of 30-day postoperative complications was higher in the 5-mFI = 4 subgroup than in the 5-mFI = 0 and 5-mFI = 1 subgroup (50% vs 20% and 30%, $p = 0.67$). No post-operative complications were recorded in the other 5-mFI subgroups.

In univariate analyses, no significant predictor of postoperative complications or surgical-related death was identified.

Surgical-related functional outcome analysis

In univariate analysis (**Table 4**), total resection (OR 4.36, [95% CI 1.22–15.54], $p = 0.02$) and the absence of postoperative complications (OR 4.54, [95% CI 0.85 – 23.80], $p = 0.07$) were independent predictors of a KPS score increase ≥ 10 points postoperatively. The 5-mFI did not influence the KPS score increase ≥ 10 points postoperatively ($p = 0.37$). Similar resulted were observed for sex, age and pre-operative KPS ($p > 0.05$).

In multivariable analysis, only total resection was an independent predictor of a KPS score increase ≥ 10 points postoperatively (aOR 4.91, [95%CI 1.29–18.71], $p = 0.010$] (**Table 4**).

Survival analysis

No patient fulfilled the criteria to receive the adjuvant standard radio-chemotherapy[14, 15]; they rather received radiotherapy alone and adjuvant Temozolomide. Twenty-five patients (53.2%) died over the follow-up period. The median overall survival was 9.0 months [range: 1–25 months]. Kaplan-Meier curves are shown in Fig. 1.

Unadjusted Hazard Ratios (HR) for overall survival in the whole series are detailed in **Table 5**. The median overall survival was longer in patients ≤ 70 years, than in patients > 70 years (12.5 months, and 7.0 months, respectively, p = 0.003). The median overall survival was longer following gross total resection, than partial resection and biopsy (11.4 months, 5.0 months, and 7.0 months, respectively, p = 0.001). The 5-mFI did not influence overall survival (p = 0.249). After multiple adjustments using Cox models (Table 5), gross total resection (aHR = 3.51, [95% CI, 1.42–8.63], p = 0.006), and age ≤ 70 years (aHR = 4.98, [95% CI, 1.74–14.16], p = 0.002) were independent predictors of a longer overall survival. Conversely, 5-mFI, was not an independent predictor of overall survival.

Discussion

Key results

In this retrospective monocentric cohort of 47 patients ≥ 65 year-old and harboring an IDH-wildtype glioblastoma, we show that: 1) gross total resection was feasible with low complication rates, even in frail patients ; 2) surgical treatment, age, sex, preoperative KPS and the 5-mFI score did not independently influence surgical-related mortality and morbidity; 3) gross total resection was an independent predictor of a KPS score increase ≥ 10 points postoperatively; 4) gross total resection and age ≤ 70 were independent predictors of a longer overall survival; 5) sex, 5-mFI, postoperative complications, and preoperative KPS status did not independently influence overall survival.

Interpretation

The role of frailty on general surgery outcomes has been widely reported and is associated with higher complication and reoperation rates, longer hospital stay, loss of independence, higher readmission rates, and mortality [16–21]. Concerning neurosurgery, only few studies assessed the postoperative outcomes of frail patients, and even fewer studies focused on glioblastoma patients [22, 22–24]. The present results, focused on IDH-wildtype glioblastoma patients ≥ 65-year-old, suggest that the extent of resection remains a strong predictor of longer overall survival and better functional outcomes, even in frail patients. Indeed, gross total resection was feasible despite frailty and was an independent predictor of KPS score increase postoperatively. These results suggest that an aggressive resection using required intraoperative tools to maximize the safety of procedure could be proposed in frail IDH-wildtype glioblastomas patients ≥ 65-year-old.

In the present series, the 5-mFI score was not a predictor of both survival and functional outcomes (p < 0.05). These results differ from previous reports [2, 3, 11, 22–24]. These differences should be related to several aspects. First, our study focused on patient harboring a IDH-wildtype glioblastoma while previous studies included a wider but more heterogeneous population, including all brain tumors. Second, the score used to evaluate the frailty varied. Several authors reported an equally effectiveness of mFI-5 compared to the mFI-11 to predict surgical outcomes [22, 25, 26]. Here, we decided to adopt the 5-mFI score, which was easier to adopt in clinical practice than conventional 11-item modified frailty index. Bonney et al. used the Johns Hopkins Adjusted Clinical Groups (JHACG) to prove the role of frailty as independent predictive factors for a poor outcome following brain tumor surgery. They found an association between frailty and postoperative outcomes, including surgical complications, mental status changes, pulmonary insufficiency, and venous thromboembolism and also longer lengths of stay [12]. However, any distinction between benign or malignant tumor, such as between primary or secondary, lesions was performed. Cloney et al. included only glioblastoma patients and used the mFI-11 score [23]. They found that an increased frailty is directly related to higher morbidity and mortality rates. However, authors decided to include the frailty score as a factor addressing the choose of surgical treatment (resection versus biopsy). Consequentially, frail patients were preferentially addressed to biopsy, thereby affecting the surgical efficacy. Similar results are reported also by Krenzlin and colleagues [24]. They retrospectively reviewed data of 104 patients aged > 70 years harboring a glioblastoma and used the G8 Questionnaire and the 15-item Groningen Frailty Index to estimate frailty. They observed that frail patients had a shorter overall survival than not-frail patients (median overall survival of 7.1 months vs 14.3 months; $p = 0.0025$) and a higher postoperative complication rate (OR 3.913, 95%CI 1.0515–14.5620, $p = 0.0419$). However, the German group used the 15-item Groningen Frailty Index combined to the G8 Questionnaire to estimate frailty, resulting a more comprehensive but articulate and complex score to use in clinical practice. Zouaoui et al. retrospectively analyzed 265 elderly patients with glioblastoma [27]. They suggested that patients aged > 70 years have a survival benefit with increasing treatment: the reported median survival for untreated patients was 2.0 months vs 8.8 months and 12.2 months in those treated by surgery plus radiotherapy and comprehensive multi-modality treatment, respectively.

Gross total resection still remains the strongest predictor of better survival and functional outcome in old patients harboring a IDH-wildtype glioblastoma, despite frailty, therefore an overall preoperative evaluation should be considered for a better risk stratification.

Generalizability

This real-life practice series evaluates the efficacy and safety of the surgical management of IDH-wildtype glioblastoma in frail patients ≥ 65-year-old. In previous studies, the evaluation of frailty score impacted the surgical treatment decision making. The present study controlled for this bias by analyzing all patients whatever their 5-mFI score. This cohort reflects the real-life surgical management of aged and frail patient harboring an IDH-wildtype glioblastoma and could help: 1) envision a particular surgical technique based on clinical requirements without increasing complications rates and envision the surgery despite frailty score; 2) identify preoperatively cases at risk of poor clinical outcomes postoperatively by evaluating age, performance status and comorbidities through easy and clinically feasible scores.

Limitations

These findings should be interpretated with caution, given the retrospective and monocentric design, the exploratory design of statistical analyses, the lack of control group and the lack of an external validation set, all limiting the generalizability of the results. In addition, the low number of patients limited the number of predictive variables to be entered in multivariable models. Further confirmatory analyses are required.

Conclusion

In patients ≥ 65-year-old harboring an IDH-wildtype glioblastoma, gross total resection is still an independent predictor of longer survival and good postoperative functional recovery whatever the frailty index. In this series, the patient's frailty, evaluated using the 5-mFI score does not have a significant role to address surgical treatment and outcomes.

Abbreviations

aHR
adjusted Hazard Ratios
B
biopsy
GTR
gross total resection
HR
Hazard Ratios
KPS score
Karnofsky Performance Status score
STR
subtotal resection.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dr Angela Elia and Prof Johan Pallud. The first draft of the manuscript was written by Dr Angela Elia and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Patient and clinical characteristics at diagnosis (n=47)

Parameters	n (%)
Sex	
Male	31 (65,9)
Female	16 (34,0)
Age, years (median, mean±SD, range)	Median 73, mean 72,95 (± 5,1), range 65-82
≤ 70	19 (40.4)
> 70	28 (57.8)
Pre-operative Karnofsky Performance Status (median, mean±SD, range)	Median 75, mean 74,2 (±18,4), range 30-100
≤ 70	20 (42.5)
> 70	27 (57,5)
5 -modified Frailty Index (median, mean±SD, range)	
0	11 (23.4)
1	30 (63,8)
2	2 (4.2)
3	2 (4.2)
4	2 (4.2)
5	0
30-days post-operative complications	
No	36 (76,6)
Yes	11 (23,4)
Treatment	
B	8 (17.1)
STR	13 (27.6)
GTR	26 (55,3)
Other (STR or B)	21 (44,6)
Post-operative Karnofsky Performance Status (median, mean±SD, range)	Median 80, mean 78,7(±18,8), range 20-100
≤ 70	17(36,2)
> 70	30 (63,8)

Increase of KPS>10	
No	27 (57,4)
Yes	20 (42,5)

Table 2. Overall post-operative complications according to treatment and 5-mFI subgroups

Treatment	5-mFI=0	5-mFI=1	5-mFI=2	5-mFI=3	5-mFI=4	5-mFI=5
Gross total resection	7 (26.9%)	17 (65.4%)	1 (3.85%)	0	1 (3.85%)	0
Hematoma	1	4	-		-	
Seizures	0	0	-		-	
Pneumonia	0	1	-		-	
Hydrocephalus	0	0	-		-	
Acute Renal Failure	0	1	-		-	
Subtotal resection	4 (30.8)	6 (46.1%)	1 (7.7%)	2 (15.4%)	0	0
Hematoma	1	0	0	0	0	0
Seizures	-	-				
Pneumonia	-	-				
Hydrocephalus	-	1				
Acute Renal Failure	-	-				
Biopsy	0	7 (87.5%)	0	0	1 (12.5%)	0
Hematoma		-			-	
Seizures		2			-	
Pneumonia		-			1	
Hydrocephalus		-			-	
Acute Renal Failure		-			-	

Tab 3. Independent risk factors of post-operative complications

Parameters		Unadjusted Odds Ratio			Adjusted Odds Ratio *		
30-days Post-operative Complications		**OR**	**CI95%**	**p-value**	**aOR**	**CI95%**	**p-value**
Sex	M	1 (ref)					
	F	1.50	0.33 – 6.69	0.58			
Age (years)	>70	1 (ref)					
	≤70	1.25	0.30 – 5.04	0.75			
Preoperative KPS score	≤ 70	1 (ref)					
	> 70	3.09	0.76 – 12.60	0.11			
5-mFI	> 0	1 (ref)					
	≤ 0	3.33	0.37 – 29.77	0.28			
Extent of resection	Subtotal resection or biopsy	1 (ref)					
	Gross total resection	1.04	0.26 – 4.04	0.95			
30-days Post-operative Death		**OR**	**CI95%**	**p-value**			
Sex	M	1 (ref)					
	F	1.03	0.08 – 12.35	0.97			
Age (years)	>70	1 (ref)					
	≤70	1.38	0.11 – 16.44	0.79			
5-mFI	≤ 0	1 (ref)					
	> 0	3,08	0 – .	0.99			
Preoperative KPS score	≤ 70	1 (ref)					

	> 70	1.42	0 – .	0.99
Extent of resection	Subtotal resection or biopsy	1 (ref)		
	Gross total resection	2.63	0.22 – 31.21	0.44
Complication onset	Yes	1 (ref)		
	No	7.77	0.63 – 95.67	0.1

Tab 4. Independent risk factors of Surgical-related Functional Outcome

Parameters		Unadjusted Odds Ratio			Adjusted Odds Ratio *		
Post-operative KPS increase ≥10		**OR**	**CI95%**	**p-value**	**aOR**	**CI95%**	**p-value**
Sex	F	1 (ref)					
	M	2.33	0.68 – 8.01	0.17			
Age (years)	>70	1 (ref)					
	≤70	1.48	0.45 – 4.89	0.51			
Pre-operative Karnofsky Performance Status	≤ 70	1 (ref)					
	> 70	1.19	0.36 – 3.82	0.77			
5-mFI	> 0	1 (ref)					
	≤ 0	1.98	0.44 – 8.88	0.37			
Treatment	GTR	1 (ref)			1 (ref)		
	STR or B	4.36	1.22–15.54	**0.02**	4.91	1.29 – 18.71	**0.01**
30-days-post-operative complications	No	1 (ref)			1 (ref)		
	Yes	4.54	0.85 – 23.80	**0.07**	5.32	0.91 – 30.98	0.06

Tab 5. Independent risk factors of Survival

Parameters		Unadjusted Hazard Ratio for death			Adjusted Hazard Ratio * for death		
		HR	CI95%	p-value	aHR	CI95%	p-value
Sex	F	1 (ref)					
	M	1.07	0.47 – 2.43	0.86			
Age (years)	>70	1 (ref)			1 (ref)		
	≤70	3.71	1.38 – 9.94	**0.009**	4.98	1.75 – 14.16	**0.002**
Preoperative Karnofsky Performance Status	≤ 70	1 (ref)					
	> 70	1.85	0.84 – 4.11	0.12			
5-mFI	0	1 (ref)					
	1	1.83	0.76 – 4.44	0.17			
	2	0.66	0.07 – 5.57	0.7			
	3	0.33	0.06 - 1.63	0.17			
	4	1.28	0.15 – 10.39	0.81			
Extent of resection	STR or B	1 (ref)			1 (ref)		
	GTR	3.30	1.44 – 7.53	**0.004**	3.51	1.42 – 8.63	**0.006**
30-day postoperative complications	Yes	1 (ref)					
	No	2.2	0.94 – 5.12	0.067			
Postoperative Karnofsky Performance Status score	≤ 70	1 (ref)			1 (ref)		
	> 70	2.56	1.15 – 5.70	**0.02**	2.20	0.96 –	0.06

				5.03
Postoperative Karnofsky Performance Status score increase ≥10	No	1 (ref)		
	Yes	2.43	1.00 – 5.93	0.05

Figures

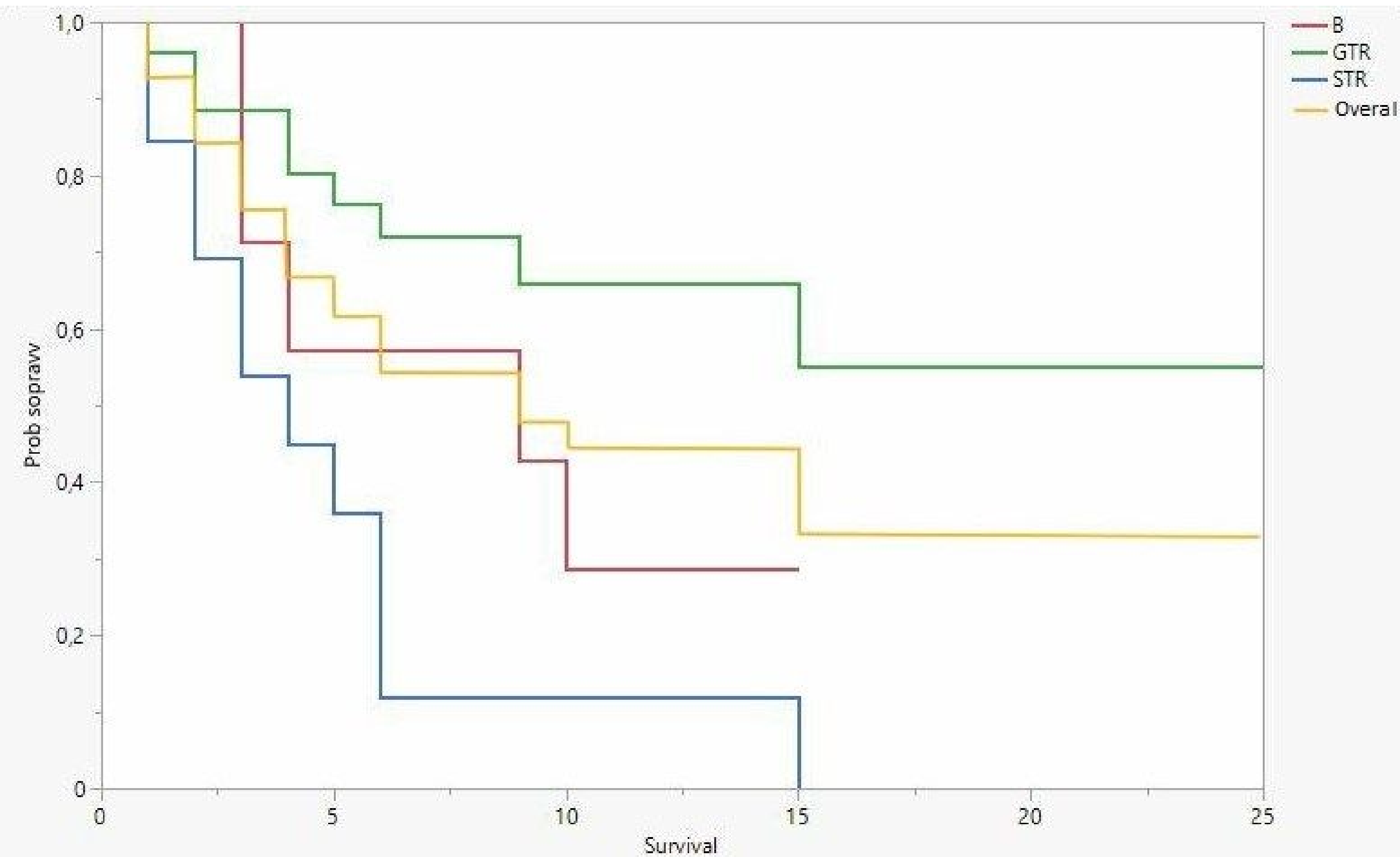

Figure 1

Kaplan-Meier curves of median overall survival (*yellow*) and related to biopsy group (*red*), subtotal resection (*blue*) and gross total resection (*green*). The median overall survival was 9.0 months [range: 1-25 months]. The median overall survival of GTR group was 11.4 months, 5.0 months for STR, and 7.0 months for B (p=0.001).