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Original Article

Gastrointestinal Stromal Tumors: Recurrence and Survival Analysis of 49 Patients

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Abstract

Background: Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor originating from the gastrointestinal tract and have a broad spectrum of clinicopathological features affecting disease management regarding the treatment modalities.

Methods: A retrospective study of 49 patients who underwent surgery for gastrointestinal tumors between 2008 and 2016 was conducted. Clinical, pathological, and immunohistochemical features of patients with and without recurrence were statistically analyzed.

Results: Twenty-nine (59.1%) patients had gastric; 16 (32.6%) had small intestinal; 3 (6.1%) had mesenteric; and 1 (2.2%) had rectal GISTs. Microscopic tumor necrosis and tumor ulceration were also significant for disease recurrence ($P=0.005$, $P=0.049$). High-risk patients according to Miettinen's risk classification were more likely to develop a recurrence ($P<0.001$). Additionally, high-grade tumors were also a risk factor for recurrence ($P<0.001$). Ki-67 levels were available in 40 patients and the mean Ki-67 level was 16.8 in patients with recurrence, which was a significant risk factor in regression analysis (HR: 1.24, 95%, CI: 1.08-1-43). Five-year disease-free survival rates of non-gastric and gastric GISTs were 62.3% and 90%, respectively ($P=0.044$).

Conclusion: Larger tumors and higher mitotic rates are more likely to develop recurrence. High Ki-67 levels were also associated with recurrence.

Keywords: Gastrointestinal stromal tumors, Mesenchymal tumors, Recurrence, Survival, GIST

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Introduction

Gastrointestinal stromal tumors (GISTs) constitute 1-2% of gastrointestinal neoplasms.[1-3] They present as a subepithelial mesenchymal tumor arising from Cajal cells of the myenteric plexus in the wall of any segment of the gastrointestinal tract; however, they can also arise from mesentery, omentum, and peritoneum.[1,2,4,5] GISTs affect males and females equally and are usually present at an older age.[6-10] The clinical presentation of GISTs differs depending on the location of the tumor. Especially GISTs arising from the upper gastrointestinal tract (e.g., stomach, duodenum) may present with minor or major gastrointestinal bleeding that could cause various clinical outcomes from mild anemia to hemorrhagic shock, whereas tumors involving distal gastrointestinal tumors may present with acute mechanical intestinal or colonic obstruction.[11,12] Histologically, the cellular appearance of GISTs usually is classified under three categories: spindle cell type (70%), epithelioid type (20%), and mixed type (10%).[2] GISTs typically harbor expression of the CD117 antigen (c-kit) that allows to distinguish them from other gastrointestinal spindle cell tumors.[13]

GISTs are usually diagnosed with suspicion via endoscopic or radiological appearance both in symptomatic or asymptomatic patients.[14-16] Pathological diagnosis can be obtained in patients with metastatic disease or larger tumor sizes who are eligible for neoadjuvant tyrosine kinase inhibitor treatment.[17] On the other hand, in patients with resectable tumors, complete surgical resection with negative margins is the first-line treatment with favorable survival outcomes.[17,18] Despite their variable biological behavior, all GISTs have the potential to develop recurrence or metastatic diseases according to the characteristics of the primary tumor.[2-10] The prognosis of GISTs originating from the stomach is better compared with tumors arising from the small intestine, colon, rectum, or mesentery.[2,3,6,9] As an independent prognostic predictor, tumor size and mitotic rate are the most relevant risk factor to estimate disease behavior.[19,20] According to these risk factors, there are several prognostic models to estimate recurrence risk or the need for neoadjuvant chemotherapy.[19-21]

In this study, we aimed to analyze the relationship between the clinicopathological features and recurrence of the patients with resected GISTs, as well as the factors associated with prognosis.

Materials and Methods

A single institutional retrospective data analysis from the medical record database was conducted between January

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2008 and December 2016 in Department of Pathology, Istanbul Medeniyet University, Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Istanbul, Turkey.

After receiving approval from Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee, the medical record database system was searched through pathology reports. Informed consent was not required since the study meets the criteria that the research involves no more than minimal risk to the subjects and involves no bridges of personal data protection law. 61 patients with a diagnosis of GIST were enrolled to study for inclusion. Patients who were diagnosed with GIST by only endoscopic or percutaneous biopsy without going under surgery were excluded. And also, patients who were lost to follow-up were excluded from the study. Pathological diagnoses were confirmed by re-evaluating the microscopic specimens. Demographic features, clinical presentations, and histopathological and immunohistochemistry features were evaluated. Patients were classified for risk groups by their mitotic rates and tumor sizes as no risk, low, intermediate, and high. Patients were followed up for five years with imaging every six months (three months if high risk).

Statistical Analyses

Descriptive statistics were presented as numbers (%) for categorical variables while mean ± standard deviation was used for continuous variables. Categorical variables were analyzed using a chi-square test or where appropriate, Fisher's exact test. Mann-Whitney U test was used for non-normally distributed variables. The difference between the two groups in survival curves was compared with a log-rank test. Univariate Cox proportional hazards regression models were estimated to evaluate factors affecting disease-free survival and mortality. Statistical analyses were performed using R (a language and environment for statistical computing, R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org). Double-sided *P* values less than 0.05 were considered statistically significant.

Results

Demographic, Clinical, and Operational Features

A total of 49 patients, who were operated on and diagnosed with GIST, were included in the study. Demographic, clinical, and operational features are revealed in Table 1. Patients were been divided into two groups; gastric and non-gastric. No significant differences were detected regarding age, sex, and common clinical symptoms among patients. 29 (59.1%) patients had gastric; 16 had small intestinal (32.6%); 3 (6.1%) had mesenteric; and 1 (2.2%) had rectal GIST. Anemia was the most common symptom among all patients but no significant difference was present between gastric and non-gastric tumors ($P=0.346$). There were nine incidental cases, among them, six tumors were detected by positron emission tomography during the follow-up of other malignancies. Three incidental tumors were detected in gastrectomy material performed for gastric adenocarcinoma and mean tumor sizes were 0.53 cm for those three lesions. Preoperative biopsy was performed on 20 patients. 12 were negative for any diagnosis (mostly normal hyperemic mucosal tissue) and 8 were suspicious for GIST (mesenchymal tumors with spindle-like cells). Six patients with gastric GIST received emergency surgery due to massive upper gastrointestinal bleeding and the other six patients who underwent emergency surgery presented with acute intestinal obstruction ($P=0.014$). Of 29 patients with gastric GIST, 25 received wedge resection, and 4 received gastrectomy. 13 small intestinal GIST had resection and anastomosis and 4 had wedge resection. Two mesenteric tumors received mass excision and one had resection and anastomosis of the related intestinal segment. One distal rectal tumor was resected with abdominoperineal resection.

Table 1. Demographic, clinical, and operational features of gastric and non-gastric GISTs

	Gastric (n=29)	Non-gastric (n=20)	*P* overall	N
Gender (%)			1.000	49
Male	17 (58.6%)	12 (60.0%)		
Female	12 (41.4%)	8 (40.0%)		
Age, mean	65.7±12.9	66.7±8.47	0.430	49
Symptoms				
Anemia	17 (58.6%)	9 (45.0%)	0.346	
Pain	9 (31.0%)	6 (30.0%)	1.000	
GI bleeding	9 (31.0%)	5 (25.0%)	0.890	
Obstruction	1 (3.44%)	6 (30.0%)	**0.014**	
Incidental	6 (20.6%)	3 (15.0%)	0.720	
Weight loss	2 (6.8%)	1 (5.0%)	1.000	
Preoperative biopsy, yes			0.111	20
Negative	10 (71.4%)	2 (33.3%)		
GIST suspicion	4 (28.6%)	4 (66.7%)		
Operation type			1.000	49
Open	28 (96.5%)	19 (95.0%)		
Laparoscopic	1 (3.5%)	1 (5.0%)		
Elective or emergency operation			0.512	49
Elective	23 (79.3%)	14 (70.0%)		
Emergency	6 (20.7%)	6 (30.0%)		

GI: Gastrointestinal, GIST: Gastrointestinal stromal tumor.

Risk Factors for Recurrence

During the follow-up period, eight patients developed recurrences. Comparison of tumor features, risk classification, and histopathological and immunohistochemistry evaluations between patients with and without recurrence are shown in Tables 2 and 3, and regression analysis in Table 4. Larger tumor sizes and tumors more than 5 cm were associated

with the recurrence of the disease (HR: 1.19, 95% CI: 1.06-1.34, $P=0.003$). Mitotic rates especially more than 5 per 5 mm^2 are related to recurrence development (HR: 1.08, 95% CI: 1.05-1.12, $P<0.001$). Microscopic tumor necrosis and tumor ulceration were also significant for disease recurrence (HR: 7.27, 95% CI: 1.45-36.4, $P=0.005$; HR: 3.85, 95% CI: 0.91-16.2, $P=0.049$). High-risk patients according to Miettinen's risk classification were more likely to develop a recurrence ($P<0.001$). Additionally, high-grade tumors were also a risk factor for recurrence ($P<0.001$). Ki-67 levels were available in 40 patients and the mean Ki-67 level was 16.8 in patients with recurrence, which was a significant risk factor in regression analysis (HR:1.24, 95%, CI:1.08-1-43).

Disease-Free Survival and Mortality

Of 49 patients, 13 deaths occurred during the follow-up period. Only six mortalities were GIST related and those who died of other reasons were excluded from mortality analyses (Table 4). Mean tumor size (12.7 cm) and mean mitotic rate (44.8 per 5 mm^2) were significant risk factors for mortality (HR: 1.07, 95% CI: 0.98-1.02, $P=0.004$; HR: 1.04, 95% CI: 1.01-1.06, $P=0.049$). Affected surgical margin was a significant risk factor for recurrence but no significant relation was observed for mortality ($P=0.002$, $P=0.06$, respectively). In patients with non-gastric and gastric GISTs, the 5-year disease-free survival rate was 62.3% and 90%, respectively ($P=0.044$) (Figure 1). The five-year survival rate of patients with tumor sizes less and more than 5 cm was 74.3% and 64.4%, respectively ($P=0.57$). Further, the 5-year overall survival rate of patients with non-gastric and gastric GISTs was 61% and 72.3%, respectively (0.63) (Figure 1).

Table 2. Tumor locations, tumor size, risk classification features, and differences between patients with and without recurrence

	No recurrence (n=41)	Recurrence (n=8)	*P* overall	N
Tumor location			0.050	49
Gastric	27 (65.8%)	2 (25.0%)		
Non-gastric	14 (34.2%)	6 (75.0%)		
Small intestine	11 (78.5%)	5 (83.4%)		
Mesentery	3 (21.5%)	0 (0.00%)		
Rectum	0 (0.00%)	1 (16.6%)		
Tumor size (mm), mean	6.91±5.35	13.9±4.95	**0.002**	49
Tumor size			**0.016**	49
<5	19 (46.3%)	0 (0.00%)		
≥5	22 (53.7%)	8 (100%)		
Tumor multifocality			0.120	49
Unifocal	39 (95.1%)	6 (75.0%)		
Multifocal	2 (4.9%)	2 (25.0%)		
Surgical resection margin			0.011	49
Negative	39 (95.1%)	5 (62.5%)		
Positive	2 (4.9%)	3 (37.5%)		
Metastatic disease	0 (0.00%)	8 (100%)	**<0.001**	49
Imatinib usage	7 (17.0%)	8 (100%)	**<0.001**	49
Miettinen risk classification			**0.001**	49
No risk	6 (14.6%)	0 (0.00%)		
Low	21 (51.2%)	0 (0.00%)		
Intermediate	7 (17.0%)	1 (12.5%)		
High	7 (17.0%)	7 (87.5%)		

Discussion

Even though GISTs have different biological features in terms of prognosis, they pose a risk for the development of metastatic disease, regardless of the primary tumor location.[1-12,19,20,22] In this context, considering the outcomes of tumors with these different characteristics, risk factors for recurrence and metastasis have been defined by multiple prognostic models.[19,22,23] In previous studies, the two most predictive independent risk factors for disease recurrence were identified as tumor size and mitotic rate regardless of primary tumor location.[5-10,21,24] Although lower disease-free survival is observed in tumors located in the colon, rectum, or outside of the gastrointestinal tract compared with tumors of the stomach and small intestine, it is difficult to make definite conclusions about the prognosis since these tumors are very rare.[21,24] In our study, larger tumor size and higher mitotic rates according to the Miettinen classification were related to decreased disease-free survival rates as compared with current literature.

Clinical symptoms may vary between GISTs according to location or tumor size.[18] In our series, anemia was the most common clinical symptom for all tumors, but it fails to indicate the location. Also, gastrointestinal bleeding for gastric and acute mechanical obstruction for small intestinal was the most frequent symptom among emergency surgeries. On the other hand, incidental cases are detected more frequently over the last decades with the more common use of imaging modalities and advanced pathological evaluation, especially after resections for upper gastrointestinal tract cancers.[25] Three of our patients with tumors less than 1 cm were diagnosed on the surgical specimen for gastric adenocarcinoma, and six patients were diagnosed on PET/CT scanning.

The most common subtype of GISTs according to cellular morphology was spindle cell type, however, recurrence-related clinical outcomes of morphological subtypes including epithelioid and mixed were insignificant both in our study and in previous reports.[1,2,10,11] Of the morphological features of GISTs, few studies have reported that tumor necrosis and tumor ulceration are related to shorter disease-free survival. Even more, tumor ulceration was linked to high mitotic rates.[26] In our study, tumor necrosis, tumor ulceration, and high-grade tumors were also more common in GISTs with recurrence.

On immunohistochemistry, approximately 95% of GISTs express KIT (CD117) due to various mutations, and genetic types are mostly used to determine the response

Table 3. Histopathological, immunohistochemistry features and differences between patients with and without recurrence

	No recurrence (n=41)	Recurrence (n=8)	*P* overall	N
Mitotic rate, *n*			**0.001**	49
<5	32 (78.0%)	1 (12.5 %)		
≥5	9 (22.0%)	7 (87.5%)		
Mitotic rate, mean	4.66±7.85	32.9±23.4	**<0.001**	49
Growth pattern			0.489	49
Expansive	35 (85.3%)	6 (75.0%)		
Infiltrative	4 (9.7%)	2 (25.0%)		
Mixt	2 (5.0%)	0 (0.00%)		
Tumor necrosis (yes/no)	11 (26.8%)/30 (73.2%)	6 (75.0%)/2 (25.0%)	**0.015**	49
Tumor ulceration, (yes/no)	8 (19.5%)/32 (80.5%)	3 (27.3%)/5 (72.7%)	0.361	48
Intratumoral hemorrhage (yes/no)	23 (56.0%)/18 (44.0%)	6 (75.0%)/2 (25.0%)	0.445	49
Tumor grade			**<0.001**	49
Low	33 (80.4%)	1 (12.5%)		
High	8 (19.6%)	7 (87.5%)		
Tumor cellularity			0.107	46
High	18 (47.3%)	7 (87.5%)		
Intermediate	11 (28.9%)	0 (0.00%)		
Low	9 (23.8%)	1 (12.5%)		
Nuclear Atypia			0.228	46
Not present	16 (42.1%)	1 (12.5%)		
Low	13 (34.2%)	3 (37.5%)		
Intermediate	4 (10.6%)	2 (25.0%)		
High	5 (13.1%)	2 (25.0%)		
CD117 (+/-)	38 (95.0%)/2 (5.0%)	7 (87.5%)/1 (12.5%)	0.429	48
DOG1* (+/-)	25 (96.1%)/1 (3.9%)	5 (83.3%)/1 (16.7%)	0.345	32
CD34 (+/-)	32 (86.7%)/5 (13.3%)	7 (12.5%)/1 (87.5%)	1.000	45
SMA** (+/-)	16 (55.1%)/13 (44.9%)	1 (12.5%)/7 (87.5%)	**0.048**	37
Ki-67, mean	7.39±14.8	16.8±6.99	**0.008**	40

*Discovered on GIST 1, ** Smooth muscle actin.

to the tyrosine kinase inhibitors.[27,28] Additionally, biomarkers, that are frequently used to distinguish GISTs from other tumors, are DOG-1 (~90%), CD34 (~70%), or smooth muscle actin (~40%).[4,22] Besides these biomarkers, recent studies have shown a correlation between high proliferation marker Ki67 expression and recurrence risk or overall survival of GIST.[18] In a multicenter study by the Turkish GIST Working Group with 1160 cases, it was suggested that Ki67 was also useful to predict disease course.[29] In our study, the mean Ki67 value of patients with recurrences was 16.8 (10-25%) ($P=0.003$). Zhao and colleagues have reported that patients who are receiving adjuvant therapy with more than 8% Ki67 levels may have a poorer prognosis.[30] Lopez Gordo et al also indicated a relevance between Ki67 levels and overall survival, however there it was not associated with recurrence.[18]

According to National Cancer Institute (Surveillance, Epidemiology and End Results: Localized, Regional a Distant), the 5-Year overall survival rate of all stages of GISTs including all primary tumor sites is 83% (28). Lopez Gordo et al reported that in patients with small intestine GISTs, 5-year disease-free survival was 65.7%, whereas it was 90.8% in patients with gastric GISTs. In our study, the 5-year overall survival rates of patients with non-gastric and gastric GISTs were 61% and 72.3%, respectively.[18]

Although absence of a consensus in the literature for the optimal negative resection margin length, surgical resections either as wedge, complete or simple excision with negative margins is still the first line of treatment for localized GIST.[18,25] In our series, of the five patients with positive surgical margins, two with macroscopic, and 1 with microscopic positive margins developed recurrence during the follow-up. Positive surgical margins were significantly associated with recurrence but no relation with mortality was observed.

In our study, larger tumor size, higher mean mitotic rate, and presence of microscopic tumor ulceration were associated with both higher recurrence and mortality rates; additionally, tumor location, tumor necrosis, tumor ulceration, and high Ki67 levels were associated with

Table 4. Univariant analyses of 5-year recurrences and mortality on Cox regression models

	Recurrence			Mortality		
	N (%) = 8 (100%)	**HR 95% CI**	***P***	**N (%) = 6 (100%)**	**HR 95% CI**	***P***
Gender			0.649			0.135
Male	4 (50%)	Ref.		4 (66.6%)	Ref.	
Female	4 (50%)	0.72 [0.18;2.91]		2 (33.3%)	2.59 [0.71;9.48]	
Age, mean	67.6 (8.12)	1.02 [0.96;1.08]	0.591	68.6 (8.78)	1.02 [0.97;1.07]	0.455
Tumor location			**0.044**			0.633
Gastric	2 (25.0%)	Ref.		1 (16.6%)	Ref.	
Non-gastric	6 (75.0%)	4.49 [0.90;22.3]		5 (83.4%)	1.30 [0.44;3.89]	
Small intestine	5 (83.3%)			4 (80.0%)		
Mesentery	0 (0.00%)			0 (0.00%)		
Rectum	1 (16.7%)			1 (20.0%)		
Tumor size (mm), mean	13.9 (4.95)	1.19 [1.06;1.34]	**0.003**	12.7 (6.76)	1.07 [0.98;1.02]	**0.004**
Tumor multifocality			0.105			0.856
Unifocal	6 (75.0%)	Ref.		4 (66.7%)	Ref.	
Multifocal	2 (25.0%)	3.49 [0.70;17.5]		2 (33.3%)	0.82 [0.11;6.34]	
Mitotic rate, n			**<0.001**			0.493
<5	1 (12.5%)	Ref.		1 (16.7%)	Ref.	
≥5	7 (87.5%)	18.8 [2.29;153]		5 (83.3%)	1.47 [0.48;4.52]	
Mitotic rate, mean	32.9 (23.4)	1.08 [1.05;1.12]	**<0.001**	44.8	1.04 [1.01;1.06]	**0.004**
Tumor necrosis (yes/no)	6 (75.0%)/2 (25.0%)	Ref.	**0.005**	5 (83.3%)/1 (16.7%)	Ref.	0.260
		7.27 [1.45;36.4]			1.86 [0.62;5.58]	
Tumor ulceration (yes/no)	3 (27.3%) / 5 (72.7%)	Ref.	**0.049**	4 (66.7%)/2 (33.3%)	Ref.	**0.005**
		3.85 [0.91;16.2]			4.24 [1.42;12.7]	
Intratumoral hemorrhage (yes/no)	6 (75.0%) / 2 (25.0%)	Ref.	0.404	4 (66.7%)/2 (33.3%)	Ref.	0.606
		1.95 [0.39;9.72]			0.75 [0.25;2.25]	
Surgical resection margin			**0.002**			0.060
Negative	5 (62.5%)	Ref.		3 (50.0%)	Ref.	
Positive	3 (37.5%)	7.33 [1.73;31.0]		3 (50.0%)	3.19 [0.87;11.6]	
		0.13 [0.02;1.10]			0.70 [0.20;2.47]	
Ki-67, mean	16.8 (6.99)	1.24 [1.08;1.43]	**0.003**	14	1.01 [0.95;1.08]	0.705

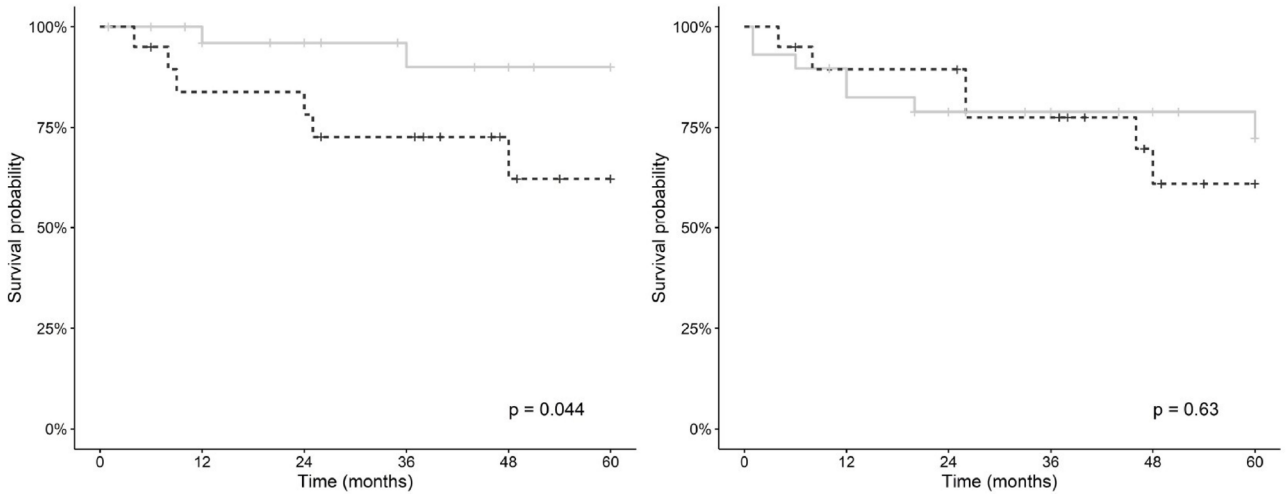

Figure 1. Kaplan-Meier curve of 5-year disease-free survival for gastric (upper/continuous line) and non-gastric (lower/dotted line) GISTs (left). Kaplan-Meier curve of 5-year overall mortality gastric (upper/continuous line) and non-gastric (lower/dotted line) GISTs (right)

recurrence. Treatment with tyrosine kinase inhibitors is recommended by National Comprehensive Cancer Network guidelines in high-risk patients; and even though the specific therapy depends on the mutation, imatinib is the most common type of treatment.[18] In our study, 15 patients received tyrosine kinase inhibitor therapy and 8 of them developed recurrences.

This study has some limitations. Firstly, retrospective analysis of low sample size with a heterogenous patient population resulted in widely varying outcomes at statistical calculations. Secondly, the small sample size may prevent the results from being generalizable.

In conclusion, non-gastric GISTs had lower disease-free survival compared with gastric GISTs. However, overall survival had no significant differences between the two groups. In this series, tumor size, location, and mean mitotic rates were associated with high recurrence rates as expected. Additional to these risk factors high Ki67 levels were also associated with recurrence.

Competing Interests

The authors declare no conflict of interest related to this work.

Ethical Approval

This study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee on 30.6.2021 with reference number 2021/0349.

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