ORIGINAL ARTICLE

The effect of the COVID-19 pandemic on patients with testicular germ cell tumor

El efecto de la pandemia COVID-19 en pacientes con tumor de células germinales testicular

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Abstract

Purpose: *The aim of this study was to investigate the effects of the COVID-19 pandemic on the referral, diagnosis, treatment, and follow-up of germ cell tumor (GCT).* **Methods:** *A retrospective single-center analysis of all patients who underwent diagnostic and surgical procedures due to GCT was performed from September 2018 to September 2021.* **Results:** *65 patients were enrolled into the study by dividing them into two groups as before pandemic (Pre-CovGCT) and during the pandemic (CovGCT). 33 patients in the Pre-CovGCT group and 32 patients in the CovGCT group were evaluated and compared. A significant increase was observed for symptom duration (p = 0.018), the duration between diagnosis and surgical procedure (p = 0.028), and occult metastasis risk of stage 1 tumors (p = 0.05) during the pandemic period.* **Conclusions:** *The duration of symptoms and the duration between the diagnosis and surgical procedure were prolonged in GCT patients diagnosed during the pandemic. Furthermore, an increased risk of occult metastasis has been observed in stage 1 GCT patients. We underline the importance of raising the awareness of patients about admission to the hospital without delay in the presence of testicular cancer symptoms and recommend to be careful not to delay the treatment process.*

Keywords: *Testicular cancer. COVID-19. Pandemic. Tumor stage. Germ cell tumor. Orchiectomy.*

Resumen

Propósito: *El objetivo de este estudio fue investigar los efectos de la pandemia COVID-19 en la derivación, el diagnóstico, el tratamiento y el seguimiento de los TCG.* **Métodos:** *Se realizó un análisis retrospectivo unicéntrico de todos los pacientes que se sometieron a procedimientos diagnósticos y quirúrgicos debido a TCG entre septiembre de 2018 y septiembre de 2021.* **Resultados:** *Se inscribieron 65 pacientes en el estudio dividiéndolos en dos grupos como antes de la pandemia (Pre- CovGCT) y durante la pandemia (CovGCT). Se evaluaron y compararon 33 pacientes en el grupo Pre-CovGCT y 32 pacientes en el grupo CovGCT. Se observó un aumento significativo de la duración de los síntomas (p = 0.018), la duración entre el diagnóstico y el procedimiento quirúrgico (p = 0.028) y el riesgo de metástasis oculta de los tumores en estadio 1 (p = 0.05) durante el período pandémico.* **Conclusiones:** *Nuestro estudio mostró que la duración de los síntomas y la duración entre el diagnóstico y el procedimiento quirúrgico se prolongaron en los pacientes con TCG diagnosticados durante el período pandémico. Además, se ha observado un mayor riesgo de metástasis oculta en pacientes con TCG en estadio 1. Subrayamos la importancia de concienciar a los pacientes sobre el ingreso hospitalario sin demora en presencia de síntomas de cáncer de testículo y recomendamos tener cuidado de no retrasar el proceso de tratamiento.*

Palabras clave: *Cáncer testicular. COVID-19. Pandemia. Estadio tumoral. Tumor de células germinales. Orquiectomia.*

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Introduction

The rapid spread of the 2019 coronavirus disease (COVID-19) worldwide has had dramatic effects on healthcare systems. Hospitals have rapidly declined in capacity and reallocation of medical resources has been required to face the crisis[1]. The level of activity of medical disciplines that are not involved primarily in the treatment of patients with COVID-19 has declined and all "non-emergency" procedures have been postponed. A dramatic reduction in urooncological consultations and surgeries has also been reported, raising concerns about the risks of delayed diagnosis or adverse oncological outcomes associated with the treatment[2].

Testicular germ cell tumor (GCT) is a rare solid organ cancer that is most common in men between 15 and 44 years of age. Risks of delayed diagnosis and treatment also differ between different genitourinary tumors; therefore, some require more rapid intervention than others, including testicular cancer, high-grade bladder cancer, advanced renal cell carcinoma, and penile carcinoma[3]. The GCT guidelines of the American Urological Association, European Urology Association (EAU) and the National Comprehensive Cancer Network do not evaluate the early treatment of the disease or the effect of delayed treatment on the results. However, it is generally reported that delays in diagnosis affect the initial stage of the disease and therefore the prognosis of the disease, and that there is a significant relationship between survival and delay in diagnosis[4,5].

The effects of the pandemic on patients with GCT due to the decrease in emergency department and urology clinic admissions are not clear. The EAU Guidelines Office Rapid Reaction Group has published a guideline that assesses the disease priorities to adopt EAU guideline recommendations to COVID-19 period[6]. According to this guideline, four priority groups were created in the GCT and a certain period of delay in treatment was defined for patients in each group according to their priorities.

The aim of the study was to reveal how potential delays in diagnosis and treatment during the COVID-19 pandemic affect the tumor stage and the risk of occult metastasis in stage 1 GCT, as well as the duration of symptoms, the time between diagnosis and surgery, and the rate of post-operative follow-up.

Materials and methods

After the approval of the local ethics committee, patients who underwent inguinal orchiectomy due to GCT in the Urology Clinic of Ankara Training and Research Hospital from September 2018 to September 2021 were included in the study. The study was designed as a single center but our hospital is a reference center for COVID-19 patients and has been providing healthcare to a large patient population since the beginning of the pandemic. The study was conducted in accordance with the principles of the Declaration of Helsinki. GCT was identified as determination of testicular germ cell tumor in pathology specimen after the procedure. The exclusion criteria were existence of a prior history of a testicular cancer, chronic liver disease and hepatocellular cancer; furthermore, those who have rejected to participate were excluded from the study.

The patients were included in one of two groups: CovGCT or Pre-CovGCT. Patients who were prospectively followed up until September 2021 after the first cases of COVID-19 in our country in March 2020 were included in the CovGCT group, and patients who were retrospectively investigated between September 2018 and March 2020 were included in the Pre-CovGCT group.

After the pre-operative diagnosis of GCT, all patients were prepared for surgery regardless of risk. No patient was referred to another center due to the competence to manage all GCT cases in our center during the pandemic period. Spinal anesthesia was performed before all inguinal orchiectomy procedures and all procedures were performed by the same surgeon.

Demographic data and pre-operative characteristics include age, body mass index, tumor side, tumor size, presence of pathology in the contralateral testes, type and duration of symptoms, and pre-operative tumor markers. Alpha-fetoprotein (AFP), beta human choriogonadotropic hormone (Beta-hCG), and lactate dehydrogenase (LDH) were used as tumor markers.

GCT therapies and follow-ups were planned according to the recommendations of the EAU Guidelines Office Rapid Reaction Group during the COVID period[6]. All patients in the Pre-CovGCT group were treated and followed according to the EAU testicular cancer guidelines[7]. Analysis of postoperative tumor markers is planned for day 7 and thoracoabdominal computed tomography was planned within the first 2 weeks. Patients who did not receive these planned treatments were considered as those who did not apply to the hospital for follow-up. AFP level above 40 ug/l, Beta-hCG level above 5 IU/l and LDH level above × 1.5 were accepted as higher than upper limits.

Primary tumor (T), regional lymph nodes (N), distant metastasis (M), and serum tumor markers (S) were evaluated in patients with GCT, and tumor stages were determined and the two groups were compared through 2016 TNM classification with the recommendations of the International Union Against Cancer. The risk for occult metastasis was evaluated for patients with stage 1 GCT. The risk of occult metastasis for seminoma was defined as the presence of a tumor larger than 4 cm or invasion of the rete testis, or both. It was also determined as lymphovascular invasion (LVI) for non-seminomatous germ cell tumor (NS-GCT). The duration between diagnosis and operation was defined as the number of days between physical examination and scrotal ultrasonography performed on the same day, and inguinal orchiectomy operation. Admission to the hospital for follow-up, duration of symptoms, post-operative tumor markers, histology, post-operative hospital stay, complications were discussed and compared between the two groups. Furthermore, the risk of occult metastasis was evaluated for stage 1 tumor and two groups were compared.

Data analysis was performed with PASW 23 (SPSS, IBM, Chicago IL) software program. Compliance of continuous variables to the normal distribution was evaluated with Kolmogorov-Smirnov and P-P plot tests. Data were shown with mean ± standard deviation (SD), and median and interquartile range (IQR). Categoric variables were shown as n (%). Pearson's Chi-square and Fischer's Exact test were used to compare categorical data between groups, and an independent sample t-test and Mann–Whitney U test were used to compare continuous data. Results have been interpreted in light of the effect estimates with 95% confidence intervals. Any p-value below 0.05 was considered statistically significant.

Results

A total of 65 patients with GCT were compared in our institution from September 2018 to September 2021, 33 of whom were before the Covid-19 pandemic and 32 during the COVID-19 pandemic. Demographic and pre-operative clinical data are listed in table 1. The duration of the symptoms of the patients is shown in figure 1.

In the current study, only one patient (4%) decrease was found in newly diagnosed GCT cases in the 20-month COVID-19 period compared to the 20-month pre-COVID-19 period. Tumor characteristics, histology, stage 1 GCT results, complications, and follow-up rates are presented in table 2. Rates of tumor stages are shown in figure 2. The risk rates for occult metastasis in stage 1 GCT are shown in figure 3. Post-operative complications were observed as post-operative fever (>38.2%) and hematocele; no major complication was detected. The pre-operative and post-operative evaluation of serum tumor markers is presented in table 3. All patients in the Pre-CovGCT group had post-operative tumor markers tested; however, three patients in the CovGCT group did not have post-operative tumor markers tested.

Discussion

In our study, patients with a diagnosis of GCT who applied during the COVID-19 pandemic and before the pandemic were divided into groups and compared. The duration of symptoms and the time between diagnosis and operation was longer in the group admitted during the COVID-19 period, and the risk of occult metastasis increased in patients with stage 1 GCT compared to the group presenting before the pandemic.

GCTs are the most common solid malignancies in young men aged 15-35 years and have a high incidence among whites. Testicular cancer represents 1% of adult neoplasms and 5% of urological tumors with three to ten new cases per 100,000 men per year in western societies[7,8]. The incidence has significantly increased in industrialized countries in particular[9]. Furthermore, GCT remains one of the best treatable solid cancers, even if metastatic, and 5-year survival in metastatic GCT is approximately 95% due to the excellent sensitivity of these cancers to cisplatin-based chemotherapy[10]. In stage 1 GCT, cancer-specific survival is > 99% with high cure rates[11].

The COVID-19 pandemic has increased the burden on the health system, especially in emergency and intensive care units, and this has caused delays in many diagnostic and treatment procedures in noncritical patients. Diagnostic pathways have been particularly disrupted in cancers with screening programs such as prostate, colorectal, or cervical cancers. A decrease of 77% in newly diagnosed prostate cancers when compared to the period before the COVID-19 pandemic, 62% in colorectal cancers and 26% in breast cancers were observed during the pandemic. A significant decrease of 66% was observed in newly diagnosed bladder cancers during the COVID-19 pandemic period compared to the previous period[12]. This study, only one patient (4%) decrease was found in newly diagnosed GCTs in the 20-month period compared to the

Table 1. Baseline patient characteristics

	Pre-CovGCT (n = 33)	CovGCT (n = 32)	p-value
Age (year)	30.3 ± 8.0/31 (23-37)	33.2 ± 9.2/31 (25-40)	0.1
BMI (kg/m^2)	24.9 ± 3.3/26.1 (22.3-27.5)	26.2 ± 4.6/25.5 (22.4-29.3)	0.2
Prior scrotal surgery	1 (3.0)	3 (9.4)	0.3
Symptoms			
Mass	26 (78.8)	22 (68.8)	0.6
Pain	7 (21.2)	8 (25.0)	
Abscess	0 (0.0)	1 (3.1)	
Infertility	0 (0.0)	1 (3.1)	
Symptom duration (day)	26.2 ± 23.5/20 (10-35)	42.9 ± 31.3/37 (16-60)	0.018*
Time from diagnosis to treatment (day)	2.0 ± 1.7/1 (1-3)	3.2 ± 2.5/3 (1-5)	0.028*

(*) A statistically significant difference. Data are shown as mean ± SD/median (IQR), and n (%). Pearson's Chi-square and Fischer's Exact test were used to compare categorical data between groups, and an independent sample t-test and Mann–Whitney U test were used to compare continuous data.

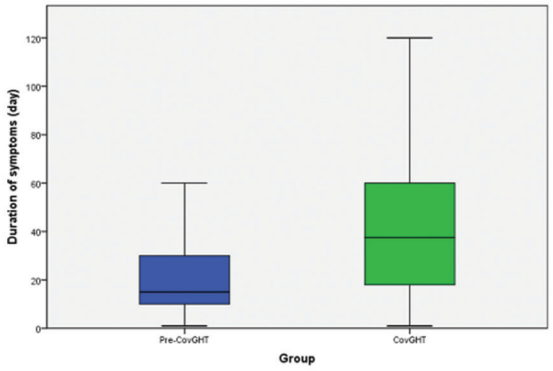

Figure 1. *The duration of symptoms before admission was 26.2 ± 23.5 days and 42.9 ± 31.3 days in the Pre-CovGCT and CovGCT groups, respectively (p = 0.018).*

same period before the pandemic. The public's concern about avoiding exposure to the disease may have resulted in a decrease in the number of hospital admissions, resulting in a high reduction in the new diagnosis of some cancers, but we did not detect a significant decrease in the rate of newly diagnosed GCT in our study.

The literature has shown that delay in diagnosis and treatment is significantly associated with survival in GCT. A significant correlation was found between delay in diagnosis and metastasis in a previous study[4]; in other studies, a significant correlation was found between delay in diagnosis and 3-year cancer-specific survival, metastasis, and overall survival[5,13]. The duration of the symptoms of the patients at the time of the first admission was 26.2 ± 23.5 and 42.9 ± 31.3 days (p = 0.018) in the Pre-CovGCT and CovGCT groups, respectively, in our study, and this duration was found to be longer during the COVID-19 pandemic period. Furthermore, the duration between diagnosis and operation in our study was 2.0 ± 1.7 and 3.2 ± 2.5 days (p = 0.028) in the Pre-CovGCT and CovGCT groups, respectively, and the time between diagnosis and operation was prolonged during the COVID pandemic period. Mortality rate increases with prolonged symptom duration in GCT patients, while cancer-specific survival and cure rates decrease; this shows us that delay in admission or treatment may cause worsening in the oncological results of the disease due to the delay in hospital admissions due to the concerns of the patients during the pandemic process that has been going on for 20 months.

For patients with seminoma in stage 1 GCT, the standard of care following inguinal orchiectomy is close follow-up. Most relapses occur within 2 years after diagnosis, but approximately 5% occur after 5 years[14]. However, identifying stage 1 seminoma patients at high risk of recurrence is largely based on two prognostic factors: primary testicular tumor size and rete testis invasion (RTI). Patients with one or two risk factors were shown to have higher risk factors compared to those without such risk factors[15]. Therefore, in patients with one or both of the risk factors, adjuvant treatments such as a course of carboplatin have been recommended to reduce the risk of relapse[16,17]. Occult metastasis is present in the lymph nodes in 30% of stage 1 patients with NSGCT[18]. For stage 1 NSGCT, invasion of the primary tumor into the blood or lymphatic vessels (LVI) is the single most reliable predictor of occult metastatic disease. These patients will relapse if treated with active surveillance,

Table 2. Surgical and tumor characteristics, and stage 1 GCT results

	Pre-CovGCT (n = 33)	CovGCT (n = 32)	p-value
Tumor size (cm)	3.1 ± 1.1/3 (2.2-4.1)	3.7 ± 1.4/4 (2.1-4.8)	0.1
Tumor side			
Right	15 (45.5)	15 (46.9)	0.9
Left	18 (54.5)	17 (53.1)	
Pathology on other testicle	5 (15.2)	5 (15.6)	0.9
GCT			
Seminoma	17 (51.5)	16 (50.0)	0.9
NSGCT	16 (48.5)	16 (50.0)	
Primary Tumor (T)			
T1	21 (63.6)	13 (40.6)	0.2
T2	10 (30.3)	16 (50.0)	
T3	1 (3.0)	2 (6.3)	
T4	1 (3.0)	1 (3.1)	
Regional lymph nodes (N)			
N0	23 (69.7)	19 (59.4)	0.2
N1	3 (9.1)	5 (15.6)	
N2	7 (21.2)	5 (15.6)	
N3	0 (0.0)	3 (9.4)	
Metastasis (M)			
M0	30 (90.9)	28 (87.5)	0.8
M1a	3 (9.1)	3 (9.4)	
M1b	0 (0.0)	1 (3.1)	
Serum tumor marker (S)			
S0	28 (84.8)	25 (78.1)	0.7
S1	4 (12.1)	5 (15.6)	
S2	1 (3.0)	1 (3.1)	
S3	0 (0.0)	1 (3.1)	
Tumor stage			
Stage 1	22 (66.7)	17 (53.1)	0.6
Stage 2	8 (24.2)	11 (34.4)	
Stage 3	3 (9.1)	4 (12.5)	
Stage 1 GCT			
Seminoma	12/22 (54.5)	12/17 (70.6)	0.3
NSGCT	10/22 (45.5)	5/17 (29.4)	
Risk of occult metastasis	10/22 (45.5)	13/17 (76.5)	0.05*
Metastasis			
No Metastasis (Stage 1)	22 (66.7)	17 (53.1)	0.2
Metastasis (Stage 2 and 3)	11 (33.3)	15 (46.9)	
Complication			
Post-op. fever	0 (0.0)	1 (3.1)	0.9
Hematocele	1 (3.0)	0 (0.0)	
Not present	32 (97.0)	31 (96.9)	
Hospitalization time (day)	1.0 ± 0.3/1 (1-1)	1.0 ± 0.1/1 (1-1)	0.4
Follow-up	33 (100.0)	29 (90.6)	0.1

(*) A statistically significant difference. Data are shown as mean ± SD/median (IQR), and n (%). Pearson's Chi-square and Fischer's Exact test were used to compare categorical data between groups, and an independent sample t-test and Mann–Whitney U test were used to compare continuous data.

therefore a course of adjuvant treatments such as bleomycin-etoposide-cisplatin (BEP) is recommended for patients at high risk for occult metastasis[7]. Among 39 stage 1 patients, 22 were detected in the Pre-CovGCT group and 17 were detected in the CovGCT group. The number of patients at risk of occult

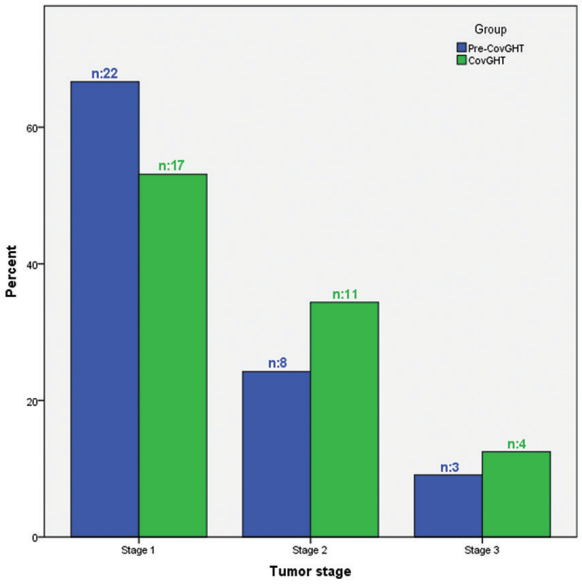

Figure 2. *In terms of tumor stage, 22 (66.7%) of 33 patients in the Pre-CovGCT group were stage 1, 8 (24.2%) were stage 2 and 3 (9.1%) were stage 3; in the CovGCT group, 17 (53.1%) of 32 patients were identified as stage 1, 11 (34.4%) as stage 2, and 4 (12.5%) as stage 3 (p = 0.6).*

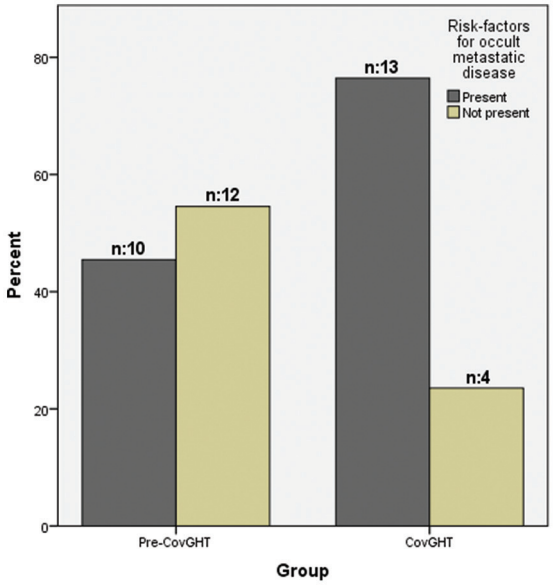

Figure 3. *The risk of occult metastasis in stage 1 GCT was determined as 45.5% and 76.5% for Pre-CovGCT and CovGCT groups, respectively, (95% CI: 0.27-0.59, p = 0.05).*

Table 3. Serum tumor markers

	Pre-CovGCT (n = 33)	CovGCT (n = 32)	p-value
Pre-op. high AFP level	11 (33.3)	12 (37.5)	0.7
Pre-op. high Beta-hCG level	13 (39.4)	12 (37.5)	0.8
Pre-op. high LDH level	20 (60.6)	22 (68.8)	0.4
Postop. high AFP level	4 (12.1)	9/29 (31.0)	0.06
Postop. high Beta-hCG level	5 (15.2)	5/29 (17.2)	0.8
Post-op. high LDH level	9 (27.3)	13/29 (44.8)	0.1

Data are shown in n (%). Pearson's Chi-square and Fischer's Exact test were used to compare categorical data between groups.

metastasis was 10 (45.5%) in the Pre-CovGCT group and 13 (76.5%) in the CovGCT group (p = 0.05). Along with these results, the occult metastasis risk and the risk of relapse may increase in patients diagnosed during the COVID-19 pandemic.

The most important limitation of our study is the shorter follow-up period to observe the oncological outcomes caused by tumor recurrence and progression. A larger population with longer follow-up is required to prove whether the pandemic has an additional adverse effect on survival outcomes, especially in patients at risk for metastatic GCT or occult metastasis risk of stage 1 tumor. Multicentric studies are needed to increase the number of cases. However, our study is important to be more careful in terms of testicular cancer in both patients and health-care providers in the pandemic. It is critical in this process for patients to admit to the hospital without delay in case of testicular cancer symptoms and for healthcare providers to be more careful while evaluating them. To the best of our knowledge, this study is the first and unique testicular cancer research during the COVID-19 pandemic.

Conclusions

The duration of symptoms and the duration between the diagnosis and surgical procedure were prolonged in GCT patients diagnosed during the pandemic. We underline the importance of raising the awareness of patients about admission to the hospital without delay in the presence of testicular cancer symptoms and recommend being careful not to delay the treatment process. Furthermore, due to the increased risk of occult metastatic disease in stage 1 GCT, the risk of recurrence may increase in patients admitted during the pandemic.

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Conflicts of interest

The authors declared no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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