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ORIGINAL ARTICLE

The effect of diagnosis delay in testis cancer on tumor size, tumor stage and tumor markers

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Abstract
Introduction: In testicular cancer, the positive effect of early diagnosis on survival has been known for many years. In this study, we aimed to determine the diagnostic features of testicular cancer patients, to examine the effect of duration of diagnosis delay (DD) on tumor size, tumor stage, and serum tumor markers, and to reveal the possible benefits of early diagnosis.
Methods: A total of 71 patients who underwent inguinal orchiectomy due to suspicion of testicular cancer and whose pathology was found to be the germ cell tumor were included in the study. The relationship between the duration of diagnosis delay and tumor size, level of tumor markers, TNM stage, presence of LAP, and presence of metastasis were examined.
Results: Seminoma was detected in 39 (54.9%) patients and non-seminoma tumor was detected in 32 (45.1%) patients. In the correlation analysis between the markers, a significant and positive correlation was found between DD and radiological tumor size, pathological tumor size, retroperitoneal LAP detection rate, LDH and AFP levels, and N stage (respectively; $r = 0.345$ $p = 0.003$, $r = 0.324$ $p = 0.006$, $r = 0.244$ $p = 0.041$, $r = 0.286$ $p = 0.015$, $r = 0.244$ $p = 0.040$, $r = 0.238$ $p = 0.046$). It was determined that a 1-day increase in DD caused an increase of 0.431 mm in the pathological size of the tumor.
Conclusion: Duration of diagnosis delay is an issue that still keeps its importance for testicular tumors. Delay in diagnosis not only leads to an increase in tumor size but also negatively affects tumor stage and prognostic factors.

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PALABRAS CLAVE
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Malignidad;
Estadificación TNM

Efecto del retraso en el diagnóstico del cáncer testicular en el tamaño tumoral, estadio y marcadores tumorales

Resumen

Introducción: El impacto positivo del diagnóstico precoz sobre la supervivencia del cáncer testicular es bien conocido desde hace muchos años. El objetivo de este estudio fue determinar las características diagnósticas de los pacientes con cáncer testicular, examinar el impacto del retraso en el diagnóstico (RD) sobre el tamaño del tumor, el estadio tumoral y los marcadores tumorales séricos, e identificar los posibles beneficios del diagnóstico precoz.

Métodos: Se incluyeron en el estudio 71 pacientes sometidos a orquiectomía inguinal por sospecha de cáncer testicular, cuya patología se confirmó como tumor de células germinales. Se examinó la relación entre el tiempo de retraso en el diagnóstico y el tamaño del tumor, los niveles de los marcadores tumorales, el estadio TNM, la presencia de adenopatía (ADP) y de metástasis.

Resultados: Se detectó seminoma en 39 (54,9%) pacientes y tumor no seminomatoso en 32 (45,1%) pacientes. En el análisis de correlación entre marcadores, se encontró una correlación significativa y positiva entre el RD y el tamaño tumoral determinado por pruebas radiológicas (tamaño radiológico), el tamaño tumoral determinado por el estudio patológico (tamaño radiológico), la tasa de detección de ADP retroperitoneal, los niveles de LDH y AFP, y estadio N (respectivamente; r = 0,345 p = 0,003, r = 0,324 p = 0,006, r = 0,244 p = 0,041, r = 0,286 p = 0,015, r = 0,244 p = 0,040, r = 0,238 p = 0,046). Se determinó que un aumento de 1 día en el RD provocaba un aumento de 0,431 mm en el tamaño patológico del tumor.

Conclusión: El tiempo de retraso en el diagnóstico es un aspecto relevante en el contexto de los tumores testiculares. El retraso en el diagnóstico no sólo produce un aumento del tamaño tumoral, sino que también afecta negativamente el estadio tumoral y los factores pronósticos.

Introduction

Testicular cancer is the most commonly diagnosed solid tumor in young men aged 20–34 years, and its incidence is increasing with each passing decade, especially in industrialized societies.[1–3] In Western societies, approximately 3–10 new cases are detected per 100,000 men per year. While it constitutes about 1% of adult neoplasms, it is responsible for 5% of urological cancers. The most common histological type is germ cell tumors (GCT) with a rate of 90–95%.[4] GCTs are divided into two main groups as seminoma and non-seminoma. Non-seminomas are divided into four histological subtypes as embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma, but they usually appear as a mixture of these histological types.[5] While seminomas are most commonly seen in the 4th decade of life, non-seminoma tumors are more common in the 3rd decade.[4] Non-seminoma tumors have a more aggressive course than seminomas and they constitute the majority of high-stage testicular tumors.[6]

The risk factors known for testicular tumor development are cryptorchidism, Klinefelter syndrome, infertility, a history of testicular tumor in a first-degree relative, tumor in the contralateral testis, and the presence of testicular intraepithelial neoplasia (TIN).[7,8] It has been stated that microlithiasis alone does not increase the risk of testicular cancer in patients who do not have these risk factors compared to the general population.[9] The most common symptom for admission in testicular cancer cases is a painless unilateral scrotal palpable mass or testicular swelling. In 20% of patients, the first symptom is scrotal pain. In some patients, abdominal and back pain may be seen and may be a sign of metastatic disease.[10] The first imaging method to confirm the testicular tumor and check the other testicle is USG. Its sensitivity is close to 100% and it provides detailed information about the anatomical localization of the tumor.[11] Contrast-enhanced thorax and abdomen computed tomography (CT) is recommended for all patients for staging after pathological diagnosis or before orchiectomy.[12] Tumor markers are very valuable for diagnosis, staging, and prognosis in testicular cancer. Alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (B-hCG), and lactate dehydrogenase (LDH) are routinely used tumor markers in testicular tumors.[13] LDH is a less specific marker that can be elevated in seminoma and non-seminoma tumors but is associated with advanced disease.[14] There is an increase in B-hCG or AFP in 90% of non-seminoma tumors.[10] Approximately 30% of seminomas may have high β-hCG levels at the time of diagnosis.[15] A recent study reported that preoperative albumin/globulin ratio is an important marker in predicting lymph node involvement, distant metastasis and prognosis.[16] In every patient diagnosed with a testicular tumor, the gold standard treatment is inguinal orchiectomy at the level of the internal inguinal ring with all layers of the testis.[17]

The favorable effect of early diagnosis on survival in testicular cancer has been known for many years. When testicular cancer is diagnosed at high clinical stages, its prognosis worsens.[18] A 5-year survival rate was found to be 99% in localized testicular cancer, 97% in patients with regional lymph node involvement, and 73% in patients with distant metastasis.[19] The time from the onset of symptoms to the day of diagnosis has been defined as the diagnostic delay (DD). In 1981, Bosl et al. observed that the length of the DD was associated with a higher stage of cancer.[20] Patients who experience delay may also require more additional treatment and morbidity rates may increase.[21] As in other malignancies, early recognition of symptoms and rapid admission time play an important role in the early diagnosis of testicular cancer.[22] In studies investigating the causes of DD in testicular cancer, it has been stated that patients thinking of testicular swelling as a temporary problem and embarrassment due to the perception of private organs delays the admission period.[23,24]

In this study, we aimed to determine the diagnostic features of patients with testicular cancer, to examine the effect of DD on tumor size, tumor stage, and serum tumor markers, and to reveal the possible benefits of early diagnosis.

Material method

This study was conducted in the urology clinic of Hospital of Afyonkarahisar Health Sciences University and the urology clinic of Ankara Bilkent City Hospital between April 2023 and May 2023. The sample size was not calculated in the study, and an attempt was made to reach the entire population. After obtaining the ethical approval (Afyonkarahisar Health Sciences University Clinical Research Ethics Committee. 2011-KAEK-2, 2023/243) we recorded the data retrospectively. Our study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients who underwent inguinal orchiectomy due to suspected testicular cancer in the two hospitals during the study period were included in our study. Demographic and clinical data were reviewed retrospectively. Benign pathologies were detected in 3 of 78 patients who underwent inguinal orchiectomy. Lymphoma was detected in 2 patients and non-germ cell tumor was detected in 2 patients. A total of 7 patients were excluded for standardization of the study and the study was continued with 71 patients. All patients had the results of scrotal ultrasonography and tumor markers LDH (lactate dehydrogenase), AFP (alpha-fetoprotein), and B-hCG (Beta-human chorionic gonadotropin) tests at the time of diagnosis. All preoperative or postoperative patients had radiological examinations for metastasis screening. All patients were evaluated in terms of age, complaint of presentation, time from symptom onset to diagnosis (DD), radiological tumor size, pathological tumor size, tumor side, presence of retroperitoneal LAP (lymphadenopathy), LDH, AFP, B-hCG values, tumor being either seminoma or non-seminoma, histological type of the tumor and TNM (tumor-node-metastasis) stages. The relationship between the diagnosis delay time and tumor size, level of tumor markers, TNM stage, presence of LAP, and presence of metastasis were examined.

Statistical analysis

A statistical program (SPPS for Windows, v21.) was used for data analysis. The normal distribution of the data was evaluated with the Kolmogrov-Smirnov test, histograms, and skewness-Kurtosis coefficients. Nominal and ordinal variables were compared with the Pearson chi-square test. These data are given with numbers and percentages. The correlations between the diagnosis delay time and different parameters were analyzed using the Spearman correlation test, Pearson correlation test, Student's t-test, Mann-Whitney U, and ANOVA tests. The independent effects of diagnostic delay on pathological tumor size were examined using a univariate linear regression model. Model of fit was examined using the required residual and fit statistics. A value of $p < 0.05$ was accepted as statistically significant.

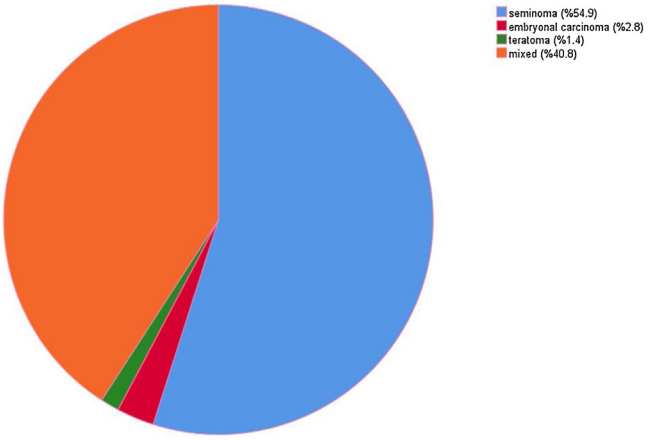

Figure 1 Classification of testis tumors regarding their histological types.

Results

The mean age of the 71 patients included in the study was 31.27 ± 8.87 years (min:16, max:53). No difference was observed between the seminoma and non-seminoma groups in terms of age ($p = 0.371$). The most common presenting symptom of the patients was painless swelling of the testis (38%) (Table 1). Seminoma tumors were detected in 39 (54.9%) patients and non-seminoma tumors were detected in 32 (45.1%) patients. The sub-classification of non-seminoma tumors is presented in Fig. 1. The mean diagnostic delay time was determined as 31.34 ± 26.87 days, and no statistically significant difference was found between the seminoma and non-seminoma groups ($p = 0.420$). No significant relationship was found between the patient's complaint at admission and the diagnostic delay time ($p = 0.464$). The mean radiological tumor size of all patients was 40.40 ± 22.55 mm, and the mean pathological tumor size was 40.63 ± 20.21 mm. A strongly positive correlation was found between radiological and pathological tumor sizes and was statistically significant ($r = 0.869$, $p < 0.001$) (Tables 1, 2).

There was no significant difference in terms of radiological and pathological tumor sizes between the seminoma and non-seminoma groups (respectively; $p = 0.461$, $p = 0.388$). The tumor was detected in the right testis in 37 (52.1%) patients. Retroperitoneal LAP was detected in 7 (17.9%) patients in the seminoma group and in 18 (56.3%) patients in the non-seminoma group. In the non-seminoma group, significantly higher rates of retroperitoneal LAP were detected ($p = 0.001$). While AFP and B-hCG values were found to be significantly higher in the non-seminomatous group, no statistically significant difference was observed between LDH levels ($p < 0.001$, $p = 0.010$, $p = 0.510$, respectively). When the two groups were compared in terms of T and N stages, significantly higher stages were found in the non-seminoma group (respectively; $p = 0.004$, $p = 0.001$). When M stages were compared, no significant difference was observed between the two groups ($p = 0.416$) (Table 1).

In the correlation analysis between the markers, a significant and positive correlation was found between the diagnostic delay time and radiological tumor size, pathological tumor size, retroperitoneal LAP detection rate, LDH and AFP levels, and N stage (respectively; $r = 0.345$ $p = 0.003$, $r = 0.324$ $p = 0.006$, $r = 0.244$ $p = 0.041$, $r = 0.286$ $p = 0.015$, $r = 0.244$ $p = 0.040$, $r = 0.238$ $p = 0.046$). Other markers that are thought to be correlated with each other are given in detail in Table 2.

Based on the hypothesis that the increase in the diagnostic delay time has a significant and positive effect on the pathological size of the tumor, the two data were evaluated by linear regression analysis (enter method). The model was statistically significant ($F = 8.113$, $p = 0.006$) and could explain 10.5% of the variance in

Table 1 Demographic and clinical data of the groups.

	Seminom group *N* = 39 *n* (%)	Non-seminom group *N* = 32 *n* (%)	*p*
Age	32.13 ± 8.23	30.22 ± 9.62	0.371
Complaint of admission			
Palpable mass	13 (33.3)	11 (34.4)	
Pain in testis	6 (15.4)	10 (31.3)	0.464
Painless swelling	19 (48.7)	8 (25)	
	0 (0)	1 (3.1)	
Incidental	1 (2.6)	2 (6.3)	
Diagnostic delay time	29.13 ± 25.34	34.03 ± 28.82	0.420
Radiological tumor size (mm)	38.87 ± 23.19	42.28 ± 31.97	0.461
Pathological tumor size	38.49 ± 19.38	43.25 ± 21.19	0.388
Side			
Right	21 (53.8)	16 (50)	0.747
Left	18 (46.2)	16 (50)	
Retroperitoneal LAP			
Present	7 (17.9)	18 (56.3)	0.001
Absent	32 (82.1)	14 (43.7)	
AFP	2.12*	115*	<0.001
B-hCG	1.64*	9.94*	0.010
LDH	275*	267.5*	0.510
T stage			
1	26 (66.7)	9 (28.1)	
2	13 (33.3)	18 (56.3)	0.004
3	0 (0)	4 (12.5)	
4	0 (0)	1 (3.1)	
N stage			
0	32 (82.1)	13 (40.6)	
1	5 (12.8)	7 (21.9)	0.001
2	2 (5.1)	7 (21.9)	
3	0 (0)	5 (15.6)	
M stage			
0	36 (92.3)	27 (84.4)	
1a	3 (7.7)	4 (12.5)	0.416
1b	0 (0)	1 (1.4)	

LAP: lymphadenopathy, AFP: alfa feto protein, B-hCG: beta-human chorionic gonadotropin, LDH: laktate dehydrogenase, *: median.

pathological tumor size without significant auto-correlation issues (Durbin-Watson = 1.659). In the linear regression analysis, diagnostic delay time was found to be a significant predictor of pathological tumor size. According to the standardized regression coefficients (β), a 1-day increase in the delay in diagnosis causes an increase of 0.431 mm in the pathological size of the tumor (Table 3).

Discussion

Testicular cancer presents as GHT with a frequency of over 90% and İT has been reported as the most common malignancy in young male papulation.[1–3] Although no significant difference was observed in terms of age between the groups in our study, the mean age was found to be 31.27 ± 8.87 years, consistent with the literature.

In an epidemiological study conducted at Ege University, 45.4% of GHT cases were observed as seminoma and 54.6% as non-seminoma tumors.[25] In a study of 439 patients conducted by Huyghe et al., 45% of the cases were found as seminoma and 55% as non-seminoma. In the same study, the mean age at diagnosis of non-seminoma cases was 27.7 years, and the mean age of diagnosis of seminoma was 37 years, and it was shown that non-seminoma cases were diagnosed significantly earlier.[26] In our study, 54.9% of the patients were in the seminoma group and 45.1% in the non-seminoma group, and no statistically significant difference was found between the mean age of the groups. Besides, the mean diagnostic delay time was found to be 31.34 days, and there was no significant difference in diagnostic delay times between the groups.

The most common presentation of testicular cancer has been reported as painless unilateral swelling. Also, Huyghe et al. reported painless swelling as the most common presenting symptom with a rate of 48% in their studies.[10,27] In our study, compatible with the literature, the most common presenting symptom was painless swelling with a rate of 38%. There was no significant relationship between the complaints at admission and the groups or on the diagnostic delay time.

As expected in accordance with the literature, AFP and B-hCG values were found to be significantly higher in the non-seminoma

Table 2 Correlation analysis of demographic and clinical data.

		Diagnostic delay (days	Age	USG tumor size	LAP	B-HCG	LDH	AFP	Pathological tumor size	T stage	N stage	M stage
Diagnostic delay (days)	*r*											
	p											
Age	*r*	−0.054										
	p	0.653										
Radiological tumor size (mm)	*r*	0.345	0.023									
	p	**0.003**	0.850									
Retroperitoneal LAP	*r*	0.244	−0.076	0.116								
	p	**0.041**	0.527	0.337								
B-HCG	*r*	0.118	−0.291	0.200	0.163							
	p	0.326	**0.014**	0.094	0.175							
LDH	*r*	0.286	−0.031	0.499	0.106	0.239						
	p	**0.015**	0.795	**<0.001**	0.377	**0.045**						
AFP	*r*	0.244	−0.138	0.054	0.237	0.378	0.080					
	p	**0.040**	0.252	0.652	**0.047**	**0.001**	0.507					
Pathological tumor size	*r*	0.324	0.069	0.869	0.208	0.234	0.450	0.055				
	p	**0.006**	0.569	<0.001	0.082	**0.049**	**<0.001**	0.650				
T stage	*r*	0.114	−0.107	0.278	0.430	0.387	0.304	0.494	0.269			
	p	0.345	0.376	**0.019**	<0.001	**0.001**	**0.010**	<0.001	0.023			
N stage	*r*	0.238	−0.077	0.122	0.936	0.208	0.147	0.322	0.0185	0.486		
	p	**0.046**	0.522	0.310	<0.001	0.081	0.221	**0.006**	0.123	<0.001		
M stage	*r*	0.181	−0.106	0.051	0.299	0.279	0.269	0.219	0.116	0.350	0.342	
	p	0.130	0.378	0.674	**0.011**	**0.018**	**0.023**	0.067	0.337	**0.003**	**0.004**	

r: correlstion coeficcient, LAP: lymphadenopathy, AFP:alfa feto protein, B-hCG: beta-human chorionic gonadotropin, LDH: laktate dehydrogenase.
The sections in bold are statistically significant.

Table 3 Linear regression analysis regarding the diagnostic delay time and pathological tumor size.

Variables	*B*	Standard error	β	*t*	*p*	95% confidence interval
Constant	13.813	6.862	–	2.013	**0.048**	0.123–27.503
Pathological tumor size	0.431	0.151	0.324	2.848	0.006	0.129–0.733

Dependent variable: pathological tumor size.
R: 0.324, $R^{2:}$ 0.105, F: 8.113, $p = 0.006$, Durbin-Watson: 1.659.
The sections in bold are statistically significant.

group in our study, but no statistically significant difference was observed between LDH levels. Conducted studies have shown that non-seminomatous testicular tumors show a higher rate of retroperitoneal LAP positivity than seminomas at the time of diagnosis and they present with higher stages. In our study, while retroperitoneal LAP was present in 56% of non-seminomas at the time of diagnosis, this rate was 17% in seminomas, and this difference was statistically significant. Also, in the comparison made in terms of T and N stages, patients in the non-seminoma group were observed to be in statistically significantly higher stages, while no significant difference was observed in terms of M stages.[10,27]

Tumor size has prognostic significance for testicular tumors, especially for seminomatous tumors.[28] In our study, the mean radiological tumor size of the patients was 40.40 ± 22.55 mm, and the mean pathological tumor size was 40.63 ± 20.21 mm. A strong level of positive correlation was observed between radiological and pathological tumor sizes.

The importance of early diagnosis in testicular tumors has been known and emphasized for many years. In the times when curative treatments were not yet applied, early diagnosis was perhaps the most important criterion for reducing mortality for testicular tumors. Today, although decreasing mortality rates are observed, early diagnosis maintains its importance as the main factor in reducing morbidity.[29] Therefore, many studies have been conducted to examine the factors that cause diagnostic delay. The main reasons are patients' education level, socioeconomic status, fear of cancer, fear of organ loss, active sexual life, and doctor-mediated delay.[30,31]

In the series of 542 patients examined by Huyghe et al., it was shown that diagnostic delay was significantly associated with increased stage of disease in the general population and in the non-seminoma group. Also, despite the modern chemotherapy protocols applied in this study, it was concluded that diagnostic delay still had a significant effect on survival.[25] In the studies by M.D. Anderson Cancer Center and Hernes et al., the negative effects of diagnostic delay on survival were also shown.[32,33] In another study in which diagnostic delay was associated with an increased need for adjuvant therapy, diagnostic delay and tumor size were found to be associated with high serum marker levels.[34] In our study, in parallel with this data, a significant and positive correlation was observed between diagnostic delay time and radiological tumor size, pathological tumor size, retroperitoneal LAP detection rate, LDH and AFP levels, and N stage.

Kobayashi et al. showed that the diagnostic delay time was correlated with the tumor size at the time of diagnosis, and this had negative effects on the survival of the patients, especially in the non-seminoma group.[35] In the linear regression analysis performed in our study, it was determined that the delay in diagnosis was a significant predictor of pathological tumor size. Accordingly, a 1-day increase in the diagnostic delay caused an increase of 0.431 mm in the pathological size of the tumor.

Mentioning the limitations of our study, it can be said that the number of patients is small and the diagnostic delay time is open to subjective interpretation by patients in some instances. The strengths of our study are that it was studied in a homogeneous patient group, careful patient records were used, tumor size and diagnostic delay time were evaluated by linear regression analysis

Conclusion

Diagnostic delay time is still an important issue for testicular tumors. Delay in diagnosis can be affected by many factors related to the disease and the person. Delay in diagnosis not only causes an increase in tumor size but also negatively affects the tumor stage and prognostic factors. We think that multicenter studies with a high number of patients in which these factors are also examined can contribute to the literature.

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Ethics approval and consent to participate

This study was approved by the local ethics committee (AFSU 2011-KAEK-2/2023/246) and was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Authors' contributions

O.G. K.T. and K.U designed the study; O.G, K.T and AK.Y recruited the participants and collected the data; O.G, K.T, AK.Y performed the statistical analysis; O.G, K.T, K.U and V.M.Y interpreted the data; O.G, K.U, AK.Y and V.M.Y drafted the first manuscript; and all authors critically reviewed the paper.

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