RESEARCH ARTICLE

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Histopathological Analysis of Seminomatous and Non-Seminomatous Germ Cell Tumors of the Testis

Testisin Seminomatöz ve Seminomatöz Olmayan Germ Hücreli Tümörlerinde Histopatolojik Analiz

ABSTRACT

Objective

Approximately 90% of testicular tumors originate from germ cells. Tumor size, lymphovascular invasion, spermatic cord invasion, epididymal invasion, tunica vaginalis and hilar soft tissue invasion are important parameters for staging and prognosis in germ cell tumors of the testis and these parameters are related to prognosis. The aim of this study is to investigate the relationship between the subtype components of germ cell tumors and prognostic parameters.

Material and Methods

In this study, 80 cases diagnosed with testicular germ cell tumors were retrospectively analyzed. The patients' age, tumor size, invasion characteristics, tumor focus numbers, tumor subtypes and percentage amounts of the components were documented.

Results

Of the cases, 40 (50%) were seminoma, 32 (40%) were mixed germ cell tumors, 6 (7.5%) were embryonal carcinomas and 2 (2.5%) were postpubertal type teratomas. Of these 80 cases, 48.75% had rete testicular invasion, 5% had epididymal invasion, 18.75% had hilar soft tissue invasion, 10% had spermatic cord invasion, 52.5% had lymphovascular invasion, 3.75% had tunica vaginalis invasion and 2.5% had spermatic cord surgical margin invasion. A statistically significant correlation was found between tumor size and all invasion sites ($p < .05$). The correlation between yolk sac tumor component and epididymis, hilar soft tissue, spermatic cord and lymphovascular invasions was found to be significant ($p < .05$). There was also a statistically significant correlation between embryonal carcinoma component and epididymis and spermatic cord invasions ($p < .05$).

Conclusion

It is important to evaluate macroscopically and microscopically the tumor size and invasion sites which are determinants of prognosis in germ cell tumors of the testis. Additionally, it should be kept in mind that tumor subtypes may also be a factor determining the extent and site of invasion.

Key Words

Germ cell tumor, Seminoma, Pathological stage, Testicular tumor, Tumor size, Invasion

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ÖZ

Amaç

Testis tümörlerinin yaklaşık %90'ı germ hücrelerinden köken alır. Germ hücreli tümörlerde tümör boyutu, lenfovasküler invazyon, spermatik kord invazyonu, epididim invazyonu, tunika vajinalis ve hiler yumuşak doku invazyonu evreleme için önemli parametrelerdir ve bu parametreler prognozla ilişkilidir. Çalışmadaki amaç germ hücreli tümörlerin içerdiği alttip komponentler ile prognostik parametreler arasındaki ilişkiyi araştırmaktır.

Gereç ve Yöntemler

Testis germ hücreli tümör tanılı 80 olgu retrospektif olarak analiz edildi. Hastalar yaş, tümör boyutu, invazyon özellikleri, tümör odaklarının sayısı, tümör alttipleri ve komponentlerin oranları kayıt edildi.

Bulgular

Olguların, 40'ı (%50) seminom, 32'si (%40) mikst germ hücreli tümör, 6'sı (%7,5) embriyonal karsinom and 2'si (%2,5) postpubertal tip teratom. Seksen olgunun, %48,75'inde rete testis invazyonu, %5'inde epididim invazyonu, %18,75'inde hiler yumuşak doku invazyonu, %10'unda spermatik kord invazyonu, %52,5'inde lenfovasküler invazyon, %3,75'inde tunika vajinalis invazyonu ve %2,5'inde spermatik kord cerrahi sınır invazyonu vardı. Tümör boyutu ve bütün invazyonlar arasında istatistiksel olarak anlamlı bir ilişki saptandı ($p < .05$). Yolk sak tümör komponenti ile epididim, hiler yumuşak doku, spermatik kord ve lenfovasküler invazyon arasındaki ilişki de istatistiksel olarak anlamlı bulundu ($p < .05$). Ayrıca embriyonal karsinom komponenti ile epididim ve spermatik kord invazyonu arasındaki ilişki de istatistiksel olarak anlamlı bulundu ($p < .05$).

Sonuç

Testisin germ hücreli tümörlerinde makroskobik değerlendirme ve mikroskobik tümör boyutu ve invazyon alanları prognozu belirlemede önemlidir. Ek olarak, Tümör alttiplerinin de tümörün yayılımını belirlemek için bir faktör olabileceği akılda bulundurulmalıdır.

Anahtar Kelimeler

Germ hücreli tümör, Seminom, Patolojik evre, Testis tümörü, Tümör boyutu, İnvazyon

INTRODUCTION

Testicular tumors are cancers that occur in about 6 of every 100,000 men and an estimated 9,334 people worldwide died from testicular cancer in 2020 [[International Agency for Research on Cancer. Testis cancer fact sheet. Lyon (France): International Agency for Research on Cancer; 2020 Dec. Available from: https://gco.iarc.fr/today/fact-sheets-cancers.]]. Testicular tumors can occur at any age but have a higher incidence in adolescents and young adults. Testicular tumors are divided into different subtypes by the International Agency for Research in Cancer of the World Health Organization (WHO). Most of the testicular tumors are germ cell tumors. Approximately half of these tumors are seminoma, while the others are pure or mixed germ cell tumors (1).

Testicular germ cell tumors are usually associated with germ cell neoplasia in situ. Transformation into invasive germ cell tumors occurs with alterations in cancer pathways. No specific genes have been identified as responsible for the progression to germ cell tumor. The etiology of non- germ cell in situ-related tumors is less obvious (2).

Germ cell tumors may show biological behavior ranging from benign to more aggressive depending on their morphological and prognostic features. Histological features are undoubtedly the most important prognostic factors. Tumor size, lymphovascular invasion, spermatic cord invasion, epididymal invasion, tunica vaginalis and hilar soft tissue invasions are important parameters for staging and prognosis in germ cell tumors of the testis (3, 4).

According to the currently system used worldwide for the staging of testicular tumors, the pT1 stage, defined as confined to the testis, was divided into pT1a (<30mm) and pT1b (≥30mm) for seminomas depending on their size. In non-seminomatous germ cell tumors, tumor diameter has no role in staging. While lymphovascular, hilar soft tissue, epididymal or tunica vaginalis invasions upgrade to pT2, direct spermatic cord soft tissue invasion upgrades to pT3 (5).

Germ cell tumours include seminomas which account for approximately 50% of germ cell tumours and mixed germ cell tumours, referred to as 'non-seminomatous germ cell tumours'. Germ cell tumours may be show different behaviour depending on morphological differences. Their classification and staging have an important effect on patient care. The aim of this study is to compare tumor size and tumor morphology with histopathologic prognostic parameters in testicular germ cell tumors.

MATERIALS and METHODS

A total of 80 radical orchiectomy materials diagnosed with germ cell tumor of the testis between 2018 and 2023 were retrospectively retrieved from the archives. Demographic, clinical and histopathological data of the patients were obtained from hospital information system, patient records and pathology laboratory archive. The histopathological findings of all cases including tumor type, tumor size, invasion sites, laterality and tumor foci were recorded.
For mixed germ cell tumors, percentage of subtype components were noted. Evaluated invasion sites were rete testis, epididymis, hilar soft tissue, spermatic cord, lymphovascular and tunica vaginalis.

Statistical Analysis

The percentage of tumor subtypes, tumor size and invasion sites were statistically compared with the Chi-Square test and $p < .05$ value was considered statistically significant. Pearson coefficient test was used for correlation between percentage of subtypes and invasion sites.

RESULTS

Ages of the 80 patients ranged from 19 to 59 years and the average age was 35. Forty cases (50%) were diagnosed with seminoma, 32 cases (40%) with mixed germ cell tumor, 6 cases (7.5%) with embryonal carcinoma and 2 cases (2.5%) with postpubertal type teratoma. Three cases had bilateral tumor and all were seminoma. In five cases, two tumor focuses were observed in the same testis. Four of the five bifocal tumors were seminomas (Figure 1) and the other was mixed germ cell tumor consisting of yolk sac tumor, postpubertal type teratoma (Figure 2), embryonal carcinoma (Figure 3) and choriocarcinoma (Figure 4). Of these tumors, the stage of a seminoma case was pT2, while the stage of the others was pT1. In addition, in two cases, three tumor focuses were detected in the same testis. One of these tumors was a pT1b seminoma and the other was a pT2 mixed germ cell tumor consisting of yolk sac tumor and embryonal carcinoma (Table I).

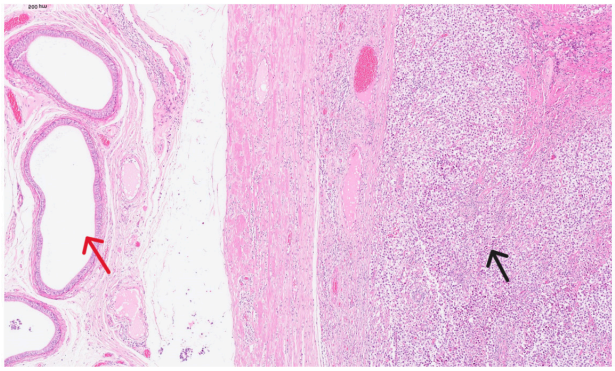

Figure 1. Microscopic image of seminoma (black arrow) next to epididymis (red arrow) in a hematoxilen-eosin stained slide.

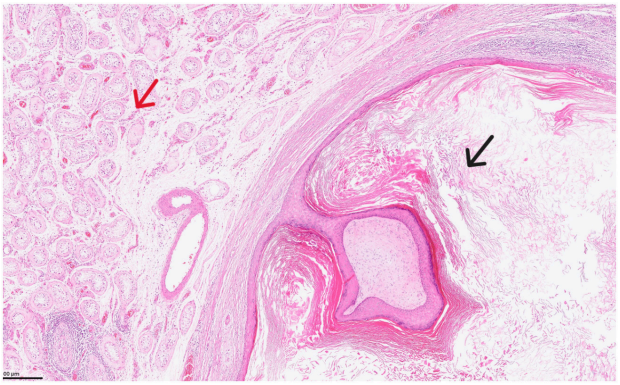

Figure 2. Microscopic image of teratoma (black arrow) next to testis (red arrow) in a hematoxilen-eosin stained slide.

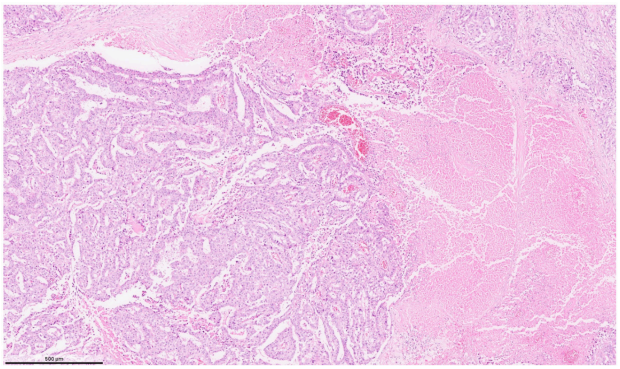

Figure 3. Microscopic image of embryonal carcinoma in a hematoxilen-eosin stained slide.

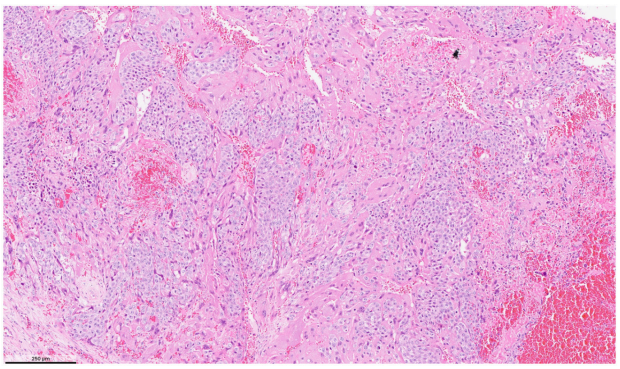

Figure 4. Microscopic image of choriocarcinoma in a hematoxilen-eosin stained slide.

Table I. Distribution of the number of cases according to their diagnosis and stage

	Number of pT1 tumors	Number of pT2 tumors	Number of pT3 tumors
Mixed germ cell tumors	13	14	5
Seminoma	6 (pT1a) 10 (pT1b)	23	1
Embryonal carcinoma	1	4	1
Postpubertal type teratoma	2	-	-

In cases diagnosed with mixed germ cell tumors, the largest tumor diameter was 27 cm, the smallest tumor diameter was 0.9 cm, and the mean diameter was 5.36 cm. In cases diagnosed with seminoma, the largest tumor diameter is 12 cm, the smallest tumor diameter is 0.7 cm, and the average diameter was 4.4 cm (Figure 5).

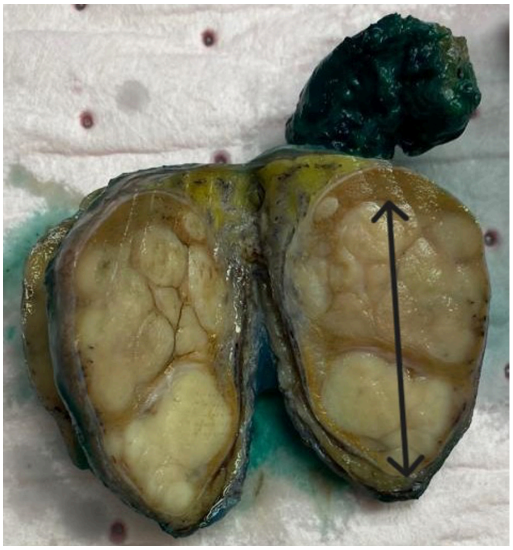

Figure 5. In macroscopic image of a seminoma case; there is a tumoral lesion with a diameter of about 4 cm.

The mean tumor diameter was 2.6 cm in embryonal carcinoma cases and 3.35 cm in teratoma cases (Table II).

Tumor subtypes included in mixed germ cell tumors were seminoma, postpubertal type teratoma, choriocarcinoma, embryonal carcinoma and yolk sac tumor. 20 cases had a yolk sac tumor component the percentages of yolk sac tumor ranged from 1 to 80, with a mean percentage of 22.6. There was embryonal carcinoma component in 24 cases and the percentages of it ranged from 7 to 99, with a mean percentage of 53. 18 cases with postpubertal type teratoma component the percentages of it ranged from 5 to 90, with a mean percentage of 40.3. There was seminoma component in 13 cases and the percentages of it ranged from 2 to 95, with a mean percentage of 39. There was choriocarcinoma component in 10 cases and the percentages of it ranged from 2 to 90, with a mean percentage of 23.4 (Table III).

Rete testis invasion was detected in 39 cases (48.75%), epididymal invasion in 4 cases (5%), hilar soft tissue invasion in 15 cases (18.75%), spermatic cord invasion in 8 cases (10%), lymphovascular invasion in 42 cases (52.5%) (Figure 6), tunica vaginalis invasion in 3 cases (3.75%) and spermatic cord surgical margin invasion in 2 cases (2.5%). A statistically significant correlation was found between tumor size and all invasion sites.

Table II. Mean tumor sizes of cases according to their diagnosis and stage

	Mean diameter (cm) of pT1 tumors	Mean diameter (cm) of pT2 tumors	Mean diameter (cm) of pT3 tumors
Mixed germ cell tumors	3.55	7.04	12.1
Seminoma	1.5	4.9	12
Embryonal carcinoma	4.18	2.75	4.5
Postpubertal type teratoma	3.35		

Table III. Distribution of the tumor subtypes in total 32 mixed germ cell tumor cases

Tumor subtype	Yolk sac tumor	Embryonal carcinoma	Postpubertal type teratoma	Seminoma	Choriocarcinoma
Number of cases containing	20	24	18	13	10
Mean percentage of subtype component	22.6	53	40.3	39	23.4

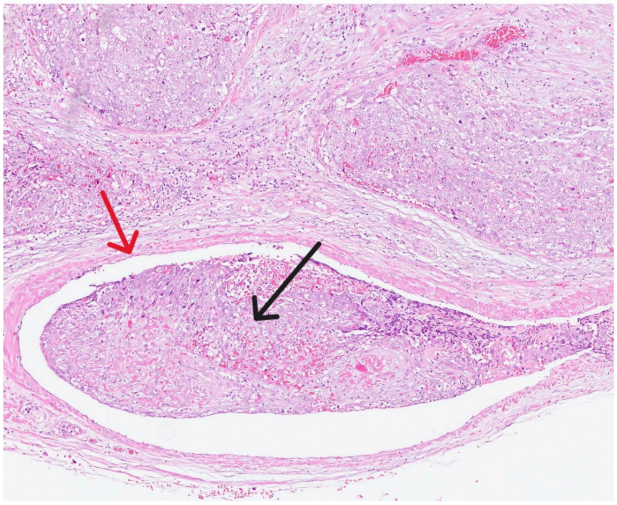

Figure 6. Lymphovascular invasion in a case of embryonal carcinoma; the red arrow shows the vessel wall and the black arrow shows the tumor within the vessel.

Mixed germ cell tumors were reevaluated according to the tumor components and the percentages of the components. A significant correlation was found between the yolk sac tumor component and epididymal, hilar soft tissue, spermatic cord and lymphovascular invasions. There was also a statistically significant correlation between embryonal carcinoma component and epididymal and spermatic cord invasion ($p< .05$).

A significant inverse correlation was found between spermatic cord invasion and the seminoma component (Table IV). In our series there were no pure seminoma cases with invasion of epididymis and tunica vaginalis. For the postpubertal type teratoma component, a significant correlation was found with lymphovascular invasion, while a negative correlation was found with rete testicular invasion ($p< .05$).

Table IV. Seminoma correlation with spermatic cord invasion

	Spermatic cord invasion (Yes)	Spermatic cord invasion (No)	Marginal Row Totals
Seminoma	1 (4.05) [2.3]	39 (35.95) [0.26]	40
Nonseminoma	7 (3.95) [2.36]	32 (35.05) [0.27]	39
Marginal column totals	8	71	79 (Grand total)
The chi-square statistic is 5,1783. The p-value is .022871. Significant at $p< .05$. The chi-square statistic with yates correction in 3,62. The p-value is .05709. Not significant at $p< .05$.			

DISCUSSION

Testicular germ cell tumors are relatively rare tumors but account for more than 90% of all testicular tumors. Seminomas also constitute approximately 50% of germ cell tumors (6). The remainder are either pure forms of other subtypes or non-seminomatous mixed germ cell tumors (7).

Most of the germ cell tumors occur between the ages of 15-45. The mean age of the patients was 35 years in this study. The distribution of testicular tumors between the ages of 19-40 was 46% mixed germ cell tumor, 43% seminoma, 10% embryonal carcinoma and 1% postpubertal type teratoma in this study. In addition, the frequency of the tumors seen older than 40 years were 74% seminoma, 21% mixed germ cell tumor and 5% postpubertal type teratoma.

Testicular germ cell tumors show different biological behaviors, ranging from benign to aggressive; their classification and staging have a strong impact on the clinical process. The rarity of testicular tumors limits the issues of classification and prognostic factors (8).

Tumor diameter has no role in staging for non-seminomatous germ cell tumors. The pT1 stage is defined as confined to testis. Lymphovascular, hilar soft tissue, epididymal or tunica vaginalis invasions upgrade to pT2 and direct spermatic cord soft tissue invasion upgrade to pT3. pT1 is divided into pT1a (<30mm) and pT1b (≥30mm) for seminomas depending on their size. In this study, a significant correlation was found between tumor size and all invasion sites for testis germ cell tumors. However, there are also studies that report tumor size insignificance in prognosis (9).

Mixed germ cell tumors in our study included various amount of seminoma, postpubertal type teratoma, choriocarcinoma, embryonal carcinoma and yolk sac tumor. In our series, there were no cases of placental site trophoblastic tumor, epithelioid trophoblastic tumor, cystic trophoblastic tumor and teratoma with somatic type malignancy which are other types of non-seminomatous germ cell tumors.

Non-seminomatous germ cell tumors are more aggressive than seminoma. Mixed germ cell tumors containing seminoma are treated as non-seminomas. In addition, the stage of tumor is the major determinant in the prognosis. Early-stage tumors have a markedly better prognosis than late-stage ones (10).

The presence of embryonal carcinoma, vascular invasion and rete testicular invasion is associated with an increased risk of metastasis in mixed germ cell tumors (7). However, there is no consensus on a cut-off value for the amount of embryonal carcinoma in mixed germ cell tumors. In this

study, there was embryonal carcinoma component in 24 cases and the percentages of it ranged from 7 to 99, with a mean percentage of 53 and 6 cases were pure embryonal carcinoma. Vascular invasion was present in 4 pure embryonal carcinoma cases and in 14 mixed tumors containing embryonal carcinoma. In addition, rete testicular invasion was also seen in 2 pure cases and 12 mixed germ cell tumors containing embryonal carcinoma.

On the other hand, the presence of yolk sac tumor component is associated with a low risk of metastasis (11). In this study, all 20 cases with yolk sac tumors components were mixed germ cell tumors. Of these cases, vascular invasion was detected in 14 cases, rete testicular invasion was detected in 11 cases, epididymal invasion was seen in 3 cases, hilar soft tissue invasion was seen in 7 cases, spermatic cord invasion was seen in 2 cases and there was tunica vaginalis invasion in 3 cases.

It is known that the presence of teratomas in germ cell tumors reduces the chance of metastasis but pure postpubertal teratoma is commonly seen in metastases after chemotherapy in non-seminomatous germ cell tumors which include teratoma component (12). In this study, lymphovascular invasion was positively correlated with the presence of teratoma as a component.

A high rate of choriocarcinoma in the tumor is associated with an aggressive clinical process (13, 14). In this study, no significant statistical results were obtained related choriocarcinoma due to the low number of choriocarcinoma cases.

Seminomas and non-seminomatous germ cell tumours can show different biological behaviour depending on morphological differences (15). In addition to the morphological types of tumors, prognostic parameters and stage are also effective in patient survival (16, 17).

The limitation of the study is that the sample size is not large enough. Another limitation is that tumor subtypes are observed interwined in some cases and it may not be possible to calculate the exact percentages of subtypes. More accurate results can be obtained with studies performed with a larger number of cases and calculation of tumor subtype with digital systems.

CONCLUSION

The macroscopic and microscopic features of the tumors are determinants in the classification and staging of germ cell tumors of the testis. Increased tumor size and lymphovascular invasion are also known to be strongly associated with advanced clinical stage. In this study, we observed that the larger the tumor, the greater the invasion, both of which are considered as prognostic risk factors. And also some tumor subtypes have been shown to be related to the extent and site of invasion.

Ethics Committee Approval

This research complies with all the relevant national regulations, institutional policies and is in accordance the tenets of the Helsinki Declaration, and has been approved by the Medical Faculty Ethical Committee, Istanbul Medipol University (approval number: E-10840098-722.02-7702).

Informed Consent

All the participants' rights were protected and written informed consents were obtained before the procedures according to the Helsinki Declaration.

Author Contributions

Concept – N.Y., A.Ç.; Design – N.Y., A.Ç., B.M.; Supervision – A.Ç., B.M.; Resources – N.Y., A.Ç., T.C.Ş., B.M.; Materials – N.Y., A.Ç., T.C.Ş.; Data Collection and/ or Processing – N.Y., T.C.Ş.; Analysis and/ or Interpretation – N.Y., A.Ç., B.M.; Literature Search – N.Y., A.Ç.; Writing Manuscript – N.Y., A.Ç.; Critical Review – N.Y., A.Ç., B.M.

Conflict of Interest

The authors have no conflict of interest to declare.

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