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# Testicular Tumors – Occurrence of Retroperitoneal Lymphadenomegaly at the Time of Diagnosis

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## ABSTRACT

**Introduction:** Testicular tumors account for approximately 1% of all malignancies in men, but the age of patients and its increasing incidence make this malignancy one of the leading oncological problems. In spite of the fact that the testicles are organs accessible for self-examination and the accessibility of ultrasound examination as the method of choice in diagnostics, these tumors are often detected in an advanced stage of the disease.

**Aim of the Study:** The aim of this study is to evaluate the occurrence of advanced disease at the time of diagnosis of testicular germ cell tumors, through retrospective analysis.

**Patients and Methods:** Our study examines patients with testicular germ cell tumor (seminomatous and non-seminomatous) according to numerous parameters – anamnesis with special emphasis on risk factors, clinical examination, laboratory analyses with tumor markers, and diagnostic imaging examinations (thorax, abdomen and pelvis CT scan). Before the specific treatment, spermiogram and semen cryopreservation were done for most patients, while in some cases additional diagnostics (MRI of the endocranium, skeletal scintigraphy) was indicated as well.

**Results:** During the observation period, 132 patients with testicular germ cell tumor were treated and observed, of which 58 patients (44%) with seminomatous tumor type and 74 patients (56%) with non-seminomatous tumors. Of the total number of patients, at the time of disease diagnosis, there were 41 patients (31%) with N1-N3 status of retroperitoneal lymph nodes and 17 patients (12.8%) with M1a-M1b metastatic status.

**Conclusion:** A large number of newly detected testicular tumors are diagnosed in an advanced stage of the disease. It is necessary to raise awareness of the general population about this malignancy, emphasise the importance of self-examination in younger men, and promote the possibility of routine ultrasound examinations with the aim of early detection of the disease.

**Key words:** testicular germ cell tumor, advanced disease

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## Introduction

Testicular tumors represent the most common solid tumors in male population aged between 18 and 35 years. They account for 1% of malignancies in men, that is, for 5% of all urological malignancies.[1] In the last decades, there has been a continuous increase in the number of patients, with significant geographical variations. In Denmark, the incidence is 13.4/100,000 men per year, in Switzerland 12.7/100,000, in Norway 12.7/100,000, while in Egypt the incidence is 0.5/100,000.[2] Since 2001, when Registry of Malignant Diseases was founded in the Republic of Srpska, 422 patients with malignant testicular tumors have been registered, and 61 have died.[3] Approximately 95% of all malignant testicular tumors are germinal epithelium tumors, which are classified into seminoma and non-seminomatous tumors. Non-seminomatous tumors include choriocarcinoma, embryonal carcinoma, yolk sac tumor and teratoma (mature and immature). Seminoma has better prognosis than non-seminomatous tumors.[4] Most often, seminomatous tumors occur between the ages of 30 and 40, while non-seminomatous tumors in most cases occur between 20 and 30 years of age.

Cryptochidism is considered the most important risk factor, along with Klinefelter syndrome and a positive family history. Gynecomastia in young males requires additional diagnostic treatment.

Data from family cancer databases have shown that sons whose fathers have testicular cancer have four times the risk of testicular cancer, and brothers of patients with testicular cancer have eight times the risk of having testicular cancer.[5] Genetic changes have been described in patients with testicular cancer. A specific genetic marker (an isochromosome of the short arm of chromosome 12 - i(12p) - has been described in all histological types of germ cell tumors and in testicular intraepithelial neoplasia (TIN). Alterations in the p53 locus have been identified in 66% of cases of testicular TIN. A deregulation in the pluripotent programme of foetal germ cells (identified by specific markers, M2A, C-KIT and OCT4/NANOG) is likely responsible for the development of TIN and germ cell neoplasia. There is an overlap in the development to seminoma and embryonal carcinoma as shown by genome-wide expression analysis and detection of alpha-fetoprotein (AFP) mRNA in some atypical seminoma.[6]

A history of testicular germ cell tumor represents a significant risk factor for contralateral testicular cancer, which has to be taken into account in the restaging and follow up of the patient once the specific oncological treatment is completed. Infertility and gonadal dysgenesis, with pathological spermiogram findings, are often associated with the onset of testicular cancer. The role of previous testicular trauma and the association with microlithiasis are being examined.[7]

Pathological prognostic factors in metastatic disease:

- seminoma
  - Tumor larger than 4 cm,
  - *rete testis* invasion,
- non-seminomatous tumors
  - vascular/lymphatic or peritumoral invasion,
  - *proliferation rate* (MIB-1) higher than 70%,
  - percentage of embryonal carcinoma higher than 50%.

Clinical prognostic factors in metastatic disease:

- primary location,
- elevated tumor marker levels,
- presence of non-pulmonary visceral metastases.

International Germ Cell Cancer Collaborative Group (IGCCCG) has defined prognostic factors for the staging system for metastasis germ cell tumors (mGCT), including a good and intermediate prognosis for seminoma, and a good, moderate and poor prognosis for NSGCT (non-seminomatous germ cell tumors). Depending on the clinical stage of the disease and prognostic factors, expected five-year survival is different.[8]

Testicular germ cell tumors are highly curable - 100% in stage 1 and up to 80% for metastatic disease.

## Aim of the Study

The aim of this study is to evaluate the occurrence of advanced disease at the time of diagnosis of testicular germ cell tumors, through retrospective analysis.

## Patients and Methods

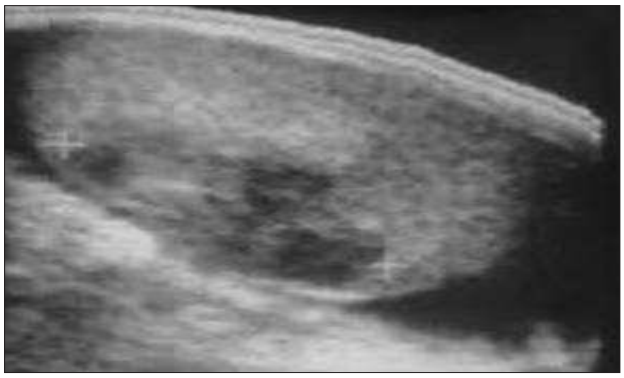
The study examines 132 patients with testicular germ cell tumor (seminomatous and non-seminomatous), who were treated at the Oncology Clinic of the University Clinical Centre in Banja Luka and the Healthcare Institution Hospital for Surgical and Internal Medicine “S.tetik”, in the period between 2009 and 2014. After a radical orchiectomy and an examination of the pathohistological (PH) finding, at the first oncologist examination, a detailed

anamnesis was taken from all the patients and they all underwent an oncological clinical examination. Further treatment in accordance with ESMO (European Society for Medical Oncology), EAU (European Association of Urology) and NCCN (National Comprehensive Cancer Network) recommendations was indicated - laboratory analyses, including postoperative tumor markers - category S (alpha-fetoprotein – AFP, human chorionic gonadotropin – HCG and lactate dehydrogenase – LDH), as well as a thorax, abdomen and pelvis CT scan, which represents standard diagnostic treatment for this histological type of tumor. Before the specific treatment, spermiogram and semen cryopreservation were done for most patients, while in some cases additional diagnostics (MRI of the endocranium, skeletal scintigraphy) was indicated as well. The research represents a retrospective study.

## Results

During the observation period encompassing six years, 132 patients (22 patients per year on the average) were treated and observed. There were 58 patients (44%) with seminomatous tumor type, of which 52 (90%) with classical seminoma, and 74 patients (56%) with non-seminomatous tumors. In all of patients, it was gonadal primary tumor localization. Primary tumor was in most cases diagnosed by ultrasound imaging (Figure 1).

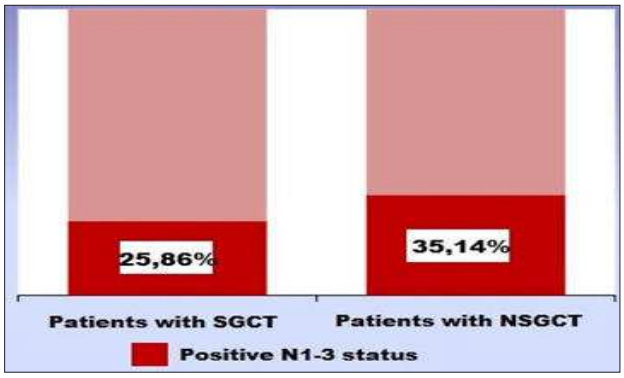
**Figure 1.** Testicular Ultrasound – Non-Homogenous Hypoechoic Change Corresponds to a Testicular Tumor



The average age of patients with seminoma was 38 years, while the average age of patients with non-seminomatous tumor was 30 years. Of the total number of patients, at the time of disease diagnosis, there were 41 patients (31%) with N1-N3 status of retroperitoneal lymph nodes and 17 patients (12.8%) with M1a-M1b metastatic status. M1a status indicates the presence of metastases in nonregional lymph nodes and lungs, and M1b refers to metastases in other organs.

Of 41 patients with a positive N status, there were 15 patients with seminoma (25.8% of the total number of patients with seminoma) and 26 patients with non-seminomatous tumor (35.1% of the total number of patients with NSGCT). These results are shown in Figure 2. Difference in representation of patients with positive N status and patients with seminomatous tumor and patients with non-seminomatous tumor was not statistically significant . (Pearson's $\chi 2$ test of contingency: $p=0.253$).

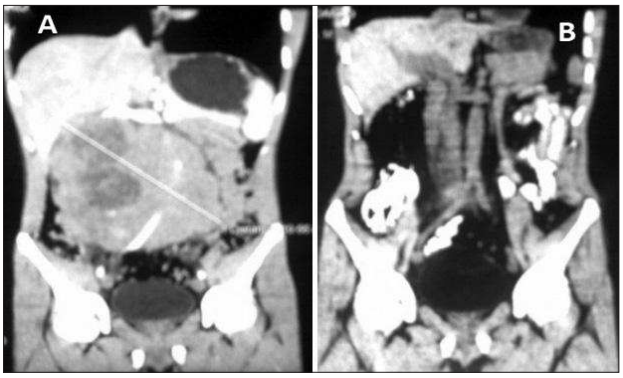
**Figure 2.** Percentage Representation of Patients with Positive N Status by Type of Germinative Tumor




At the time of disease diagnosis, when it comes to patients with seminoma, N1 status was found in 6 patients (metastasis in the lymph node 2 cm or smaller in the largest diameter, or multiple metastases in the lymph nodes, none exceeding 2 cm), N2 status (metastasis in the lymph nodes 2-5 cm, or multiple metastases, none exceeding 5 cm) in 7 patients, and N3 status (lymph node larger than 5 cm) in 3 patients. Non-seminomatous tumors were mainly combined (mixed) tumors, consisting of varying percentages of embryonal carcinoma, choriocarcinoma, seminoma, teratoma and yolk sac tumor. The study also included 2 cases with pure embryonal carcinoma, 1 case with pure choriocarcinoma and 1 case with pure yolk sac tumor with initial hematogenous hepatic metastasis. At the time of disease diagnosis, when it comes to patients with non-seminomatous tumor, N1 status of lymph nodes was found in 10 patients, N2 status in 9 patients and N3 status in 7 patients. Conglomerate retroperitoneal lymph nodes were found in a patient with NSGCT, with the largest diameter of 20 cm at the time of disease diagnosis (Figure 3a). The patient consulted a doctor due to pain in the lumbar region. After systemic chemotherapy, there was a great regression of lymphadenomegaly in a large number of patients, which once again demonstrated the efficacy of cisplatin-based chemotherapy in the treatment of metastatic germ cell tumors (the same patient – Figure 3b). The status of tumor marker values – category S, which is required along with the TNM classification for

determining the clinical stage of the disease), was not the subject of our analysis in this study.

**Figure 3. a) - Abdomen CT Scan – 20 cm Conglomerate Retroperitoneal Lymph Nodes in a Patient Aged 24 (NSCGT) ) b) - Abdomen CT Scan – Full Regression of Retroperitoneal Lymphadenomegaly after Chemotherapy**

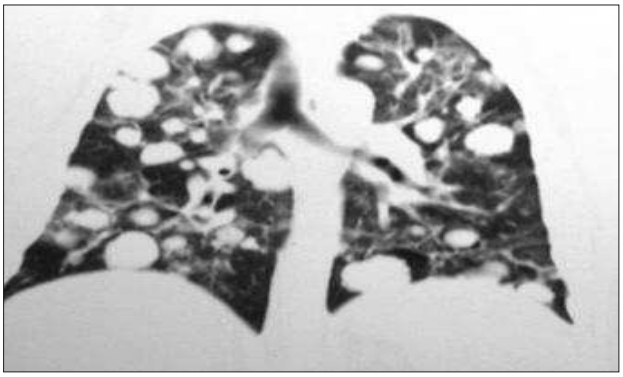



Of 15 patients with seminoma with N1-N3 status, there were 3 patients with M1a distant disease category. Of 14 patients with non-seminomatous tumor, M1a was indicated in 4 patients (nonregional lymph nodes or lungs) (Figure 3) and M1b was indicated in 10 patients (bone, brain, liver).

Of the total number of patients with seminoma (58), M1a was indicated in 3 patients (5.1%).

Of the total number of patients with non-seminomatous testicular tumor (74), M1 was indicated in 8 patients (10.8%) and M1b was indicated in 10 patients (13.5%) (8 patients with associated secondary deposits in lungs and 2 patients with extrapulmonal metastasis).

**Figure 4. Thorax CT Scan – Multiple Meta-Changes in the Lungs in a patient with Non-Seminomatous Testicular Tumor**



An analysis of the anamnestic data has shown that 72% of the patients have never performed self-examination, 32% of them provided information about previous testicular trauma during sport activities, 3.7% reported cryptochism, and 3% reported ginaecomastia. In addition, 15% of the patients reported positive family history. The first symptom in 15% of the patients was retroperitoneal pain. In 39% of the patients, numerous anomalies were found in spermiogram findings, ranging from reduced mobility of spermatozoa and reduced sperm count, to total absence of spermatozoa (azoospermia) in 9 patients (6.8%). No significant incidence of the pathological spermiogram findings was observed for the histological type of tumor.

## Discussion

According to world literature data, around 11% of testicular cancers are diagnosed in N+ stadium.[9]

Albers and al. published that 10% out of all patients suffered with metastatic disease in the moment of diagnosing it. The most common hematogenic place of tumor expansion were lungs. Impressive surviving has been proved in treating patients with combined specific oncological therapy (Surgical intervention led by chemotherapy based on cisplatina). [10]

In research which analized patients with bad performance status - ECOG 3, Gillesen and al. proved that NSGCT with bad prognosis was in 90% of patients, of which 80% had N1-N3 status and 75% M1 status. According to frequency other viscelar organs were liver, bones and brain (M1b).[11]

In our examination, the middle age of patients with seminoma was 38 years, and the ones with nonseminoma 30 years. According to data, seminomatous tumors occur between the ages of 30 and 40, while non-seminomatous tumors in most cases occur between 20 and 30 years of age.[12]

Seminoma tends to be less aggressive, to be diagnosed at an earlier stage, and to spread predictably along lymphatic channels to the retroperitoneum before spreading hematogenously to the lung or other organs. Seminoma is also associated with a lower incidence of occult metastasis and a lower risk of systemic relapse. According to some research the retroperitoneal lymph node size is the most important factor for predicted recurrence.[13]

Our research showed that 15 patients (25.8% of all patients with seminom) had N1-N3 status and 26 nonseminous tumours (35.1% of all patients with NSGCT). In patients with seminoma (58), M1a status was proved in 3 patients (5.1%). In the ones with nonseminous tumour(74), 8 had

M1a status (10,8%) and 10 had M1b status (13,5%).

In comparison with other literature data, our patients had more frequently advanced disease in case of retroperitoneal lymfadenomegaly and hematogenic spread in distant organs.

## Conclusion

Regardless of the fact that the testicles are accessible for self-examination and expert clinical examination and the fact that ultrasound diagnostics of the testicles is simple, harmless, painless and available, a large number of patients consult a doctor once the disease has advanced, when the treatment is very complex and the outcome is uncertain. It is necessary to increase the level of education in this regard, in order to raise awareness and improve knowledge of the general population about this problem. In addition, organised programmes and activities of experts and volunteers should serve to work towards the early detection of this malignant disease.

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# Tumori testisa – učestalost retroperitonealne limfadenomegalije u trenutku dijagnostikovanja bolesti

**SAŽETAK**

**Uvod:** Tumori testisa ukupno čine oko 1% svih maligniteta kod muškaraca, ali životna dob oboljelih i sve veća učestalost, čine ovaj malignitet jednim od vodećih onkoloških problema. Bez obzira na činjenicu da testisi spadaju u organe dostupne samopregledu, te pristupačnost ultrazvučnog pregleda koji predstavlja metodu izbora u dijagnostici, ovi tumori se često otkrivaju u uznapredovalom stadijumu bolesti.

**Cilj rada:** Cilj rada je retrospektivnom analizom zaključiti kolika je učestalost uznapredovale bolesti u trenutku dijagnostikovanja germinativnih tumora testisa.

**Ispitanici i metode:** U našem radu obradili smo pacijente sa germinativnim tumorom testisa (seminomskim i neseminomskim) po brojnim parametrima - anamneza sa posebnim osvrtom na faktore rizika, klinički pregled, laboratorijske analize sa tumorskim markerima, te slikovne dijagnotičke pretrage (CT toraksa, abdomena i karlice). Većini pacijenata je prije specifičnog tretmana urađen spermiogram i krioprezervacija sperme, a u nekim slučajevima je indikovana i dodatna dijagnostika (MR endokranijuma, scintigrafija skeleta).

**Rezultati:** U analiziranom periodu liječena su i praćena 132 pacijenta sa germinativnim tumorima testisa, od čega je bilo 58 pacijenata (44 %) sa seminomskim tipom tumora i 74 pacijenta (56%) sa neseminomskim tumorom. Od ukupnog broja pacijenata u trenutku dijagnostikovanja bolesti, 41 pacijent (31%) je bio sa statusom retroperitonealnih limfnih čvorova N1 – N3, te 17 (12,8%) pacijenata sa statusom metastatske bolesti M1a –M1b.

**Zaključak:** Veliki broj novootkrivenih tumora testisa se dijagnostikuje u uznapredovaloj fazi bolesti. Neophodno je povećati informisanost opšte populacije o ovom malignitetu, naglasiti značaj samopregleda kod mlađih muškaraca, te mogućnosti rutinskih UZV pregleda u ranom otkrivanju bolesti.

**Ključne riječi:** germinativni tumor testisa, uznapredovala bolest