Survival patients with pulmonary metastases in testicular cancer

MAN MILENA*, ANTIGONA TROFOR**, DANA ALEXANDRESCU***, OVIDIU BALANESCU****, IOANA NEAGOE*, MONICA POP*, RUXANDRA RAJNOVEANU*,
Pneumology, Medical Informatics Department
*University of Medicine and Pharmacy "Iuliu Haţieganu" Cluj-Napoca, ** University of Medicine and Pharmacy "Gr.T.Popa" Iaşi, *** University "Transilvania" Braşov, **** Oncologic Institute Cluj
Caraiman 3 Street, Cluj-Napoca
ROMANIA
manmilenaadina@yahoo.com

Abstract:

Testicular cancer is a rare disease reaching only 1% of all cancer types characteristic to men with ages between 15 and 34 years and has shown an increasing worldwide incidence over the past 30 years. In contrast, the mortality rate has decreased. Hematogen metastases are responsible for the apparition of pulmonary nodules. Determining the pulmonary relapse model, studying prognosis factors for defining risk groups and applying different therapeutic strategies with the evaluation of survival represent the study's main objectives.

We conducted a survey from January 2000 to December 2005 on 17 patients admitted in Cluj-Napoca Oncology Institute. We introduced in the study patients diagnosed with testicular carcinoma and pulmonary metastases, we analyzed risk factor and evolution of the diseases with survival function calculated since cancer diagnosis, and the other calculated since pulmonary metastases. We evaluated the risk factors correlated with survival: the average age ,place of origin, histology tumor markers for our batch: Beta HCG, AFP (alpha-fetoprotein), LDH ,types of pulmonary metastases, the presence of other metastases, the number of metastatic locations, the time span between the apparition of symptoms and diagnosis, the free interval the diagnosis of the primary tumor and metastasis, and value of tumor markers at the time of diagnosis. Based on these prognosis factors, the patients were divided into a good prognosis category (good) and unfavorable (poor) . Because the risk factors usually available are not sufficient to identify the subgroups of patients with an unfavorable prognosis, we tried to evaluate new genetic markers which could prove their prognosis value. We also sought to evaluate the involvement of the hTERT gene in testicular pathology.

Patients with metastases will have a different prognosis depending on the relapse model and will require individual strategies selected based on the risk factors by combining available therapeutic modalities. Early diagnosis and treatment of metastasis may lead to an improvement in the survival rate of cancer patients

.*Key-Words:* prognostic factor, survival, pulmonary metastases hTERT Gene, testicular carcinomas, risk factor

Introduction

Testicular cancer is a rare disease reaching only 1% of all cancer types characteristic to men with ages between 15 and 34 years (1,2) The incidence of testicular cancer in Europe is rising with doubling every 20 years. The current incidence is 63/100 000/year, with the highest rate in Northern European countries (68/100 000/year) The death rate is very low (3.8 cases/100 000/year) (3) Therapeutic improvements emerged at the same time with the introduction of chemotherapy in the 70's make it so that 95% of patients with testicular cancer (1) and 70-80% of patients with metastases become treatable (1).

The etiology of germinal tumors is not known. An increase in the frequency among patients with development anomalies and testicle descent was described (4) and this signaled the existence of genetic components(5).

The histology of testicular tumors divides these cancers into seminomas (50%), teratomas or non-seminomas and mixed tumors (6). Tumor markers [AFP, β-HCG and lactate dehydrogenase (LDH)] are needed for risk assessment according to UICC/IGCCCG stage and prognostic index. Markers are determined before orchiectomy and repeated a minimum of 7 days after orchiectomy (for differentiation of stage and IGCCCG prognostic group). HCG must be followed until normalization.

The metastasis pattern is predictable.(3) The first metastases to appear are retroperitoneal adenopathies (regional metastases). Hematogen metastases are responsible for the apparition of pulmonary nodules and left side over-clavicle ganglion metastases. Hepatic bony metastases are rare and represent an unfavorable prognosis factor. The presence of pulmonary metastases does not necessarily imply an unfavorable risk group if the patients have not presented a previous therapeutic failure and if they are not accompanied by other visceral metastases (liver, brain, bone).

The identification of prognostic factors is valuable due to the following three reasons:

1. Optimum treatment may be selected for each patient
2. Various therapeutic strategies could be compared among groups of patients with similar recurrence risks and treatments
3. The knowledge that allows the identification of recurrence patterns may be improved and new treatment strategies established. Why spend money on inefficient therapies that are sub-optimally dosed in high-risk patients or excessive in low risk patients? The selection of the optimum therapy is a challenge for each team involved in the treatment of cancer patients with lung metastases (7)

2 Problem Formulation

THE WORK HYPOTHESIS

Pulmonary metastases are frequently met among cases of testicular cancers. Determining the pulmonary relapse model, studying prognosis factors for defining risk groups and applying different therapeutic strategies with the evaluation of survival represent the study's main objectives. Knowing these prognosis factors and evaluating them allows us to identify metastasizing risk factors (vascular invasion, histology of the primary tumor, precocious relapse) Patient division into high or low risk categories according to prognostic factors may allow differential approaches, individualized follow-up for the early detection of recurrences and efficient treatments aimed at increasing the patients' quality of life and survival chances.

MATERIAL

Between 2000 and 2006 we studied 17 patients diagnosed with testicular cancer who presented pulmonary, pleural and mediastinal metastases. The patients were admitted at the "Leon Daniello" Clinical Pneumonology Hospital, the Oncology Institute from Cluj or the Oncology Department of the County Clinical Hospital. **Inclusion criteria**: patients with testicular cancer (tumors with germinal cells diagnosed from a histological point of view and/or serological one) which presented pulmonary metastases on the chest – pleural pulmonary x-ray and/or CT as well as the presence of Beta HCG and AFP markers. The histopathology exam of pulmonary metastases was not necessary for the inclusion in the study. **Exclusion criteria:** patients without follow up

METHOD

Evaluation of the patients was made: trough anamnesis, clinical exam, biological samples and imagistic explorations. The histopathology exam of the testicular tumor was made before acceptance into the study as it was established as an inclusion criterion. We analyzed the main prognosis factors: age, histology, position of the primary tumor, localization of metastases (regional or remote), the number of metastatic localizations, the type of pulmonary metastasis, the time span between the apparition of symptoms and diagnosis, the free interval the diagnosis of the primary tumor and metastasis, and value of tumor markers at the time of diagnosis. Based on these prognosis factors, the patients were divided into a good prognosis category (good) and unfavorable (poor)(1) :

-Good risk: HCG and ATP increase, metastasized cervical ganglions, minimal pulmonary metastases (less than 5 on the pulmonary field and under 3 cm), mediastinal masses under 50% of the intra-thoracic diameter, solitary over 2 cm metastases with no abdominal masses;

-Poor risk: extended pulmonary metastases (more than 10 on the pulmonary field), pulmonary metastases bigger than 3 cm with/without abdominal masses, mediastinal masses greater than 50% of the intra/thoracic diameter, abdominal masses, non/pulmonary visceral metastases (hepatic, bone, cerebral).

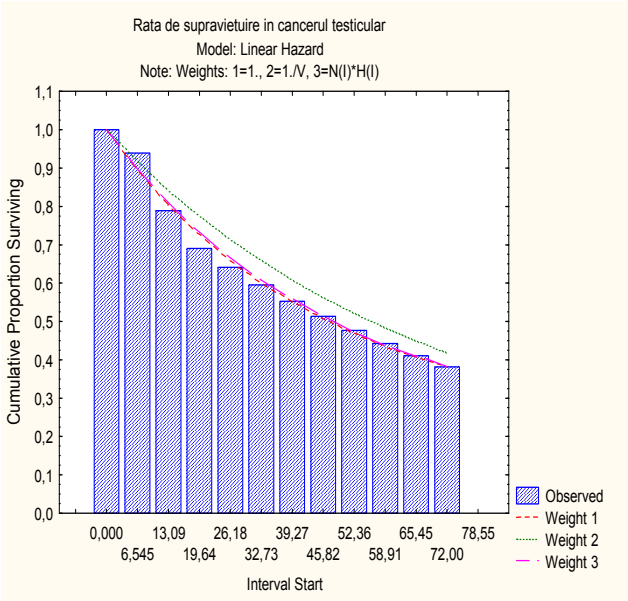
The Multidisciplinary Board (oncologist, radiotherapist, surgeon, thoracic surgeon) decided the best therapy adapted to every case in part. The type of treatment applied was orchiectomy (before start of chemotherapy) associated with chemotherapy. The initial chemotherapy used Cisplatin in various combinations (bleomycin, vinblastin, etoposid, ifosfamid) with curative intent. Evaluation of treatment was made at 28 days after the first cycle and the last chemotherapeutic cycle. In case of remission we performed radiotherapy (20 Gy with 2.0 Gy for each session, 5 days a week).

3 Results

The diagnosis of testicular cancer was made before entering the study due to the apparition of symptoms on a local level in 15 from the 17 patients included in the batch. The pulmonary metastasis diagnosis was initially made only for two patients and we tried to find the starting point. In the hereditary collateral antecedents of 2 patients we emphasized first degree relatives with neoplasia (mother and grand mother with cancer without finding any men with testicular cancer). We only emphasized the presence of an ectopic testicle as risk factor in one patient.

From the survival table for testicular cancer one can notice the 6 months survival rate was 0.93 (93%), the 13 months survival rate was 0.78 (78%), at 26 months it was 0.64 (64%), that at 39 months was 0.55 (55%) and the survival rate at 72 months equaled 0.38 (38%). These survival rates can also be seen in the diagram below:

Figure 1.Survival rate



The clinical pathological characteristics of patients with testicular tumors and evaluation of risk factors associated to the host.

The average **age** of the patients included in the study was 29.76 years (between 16 and 45 years of age). We cannot state if age is a prognosis factor for patients with testicular cancer (p=0.613). The average survival rates for patients younger than 30 years, respectively patients older than 30 are: 22.29 months, respectively 10.89 months

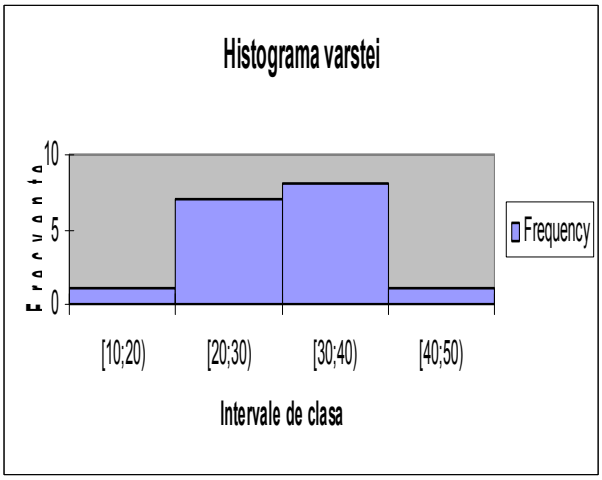


Figure 2.Age repartition

The life environment: 65% of the patients included in the batch come from urban environments. Likewise, we could not state if the life environment is a prognosis factor for patients with testicular cancer in the case of the patients under study (p=0.895). The average survival rates for patients from an urban environment compared to those of patients from a rural environment are: 21.83 respectively 11.18 months.

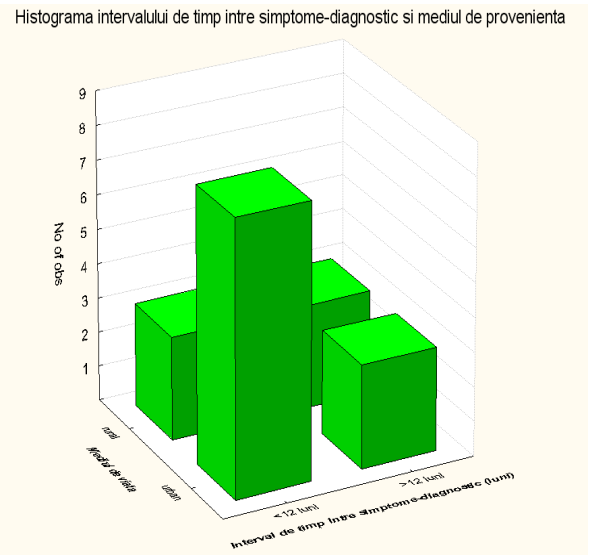


Figure 3.Time interval between the apparition of symptoms -diagnosis and life environment

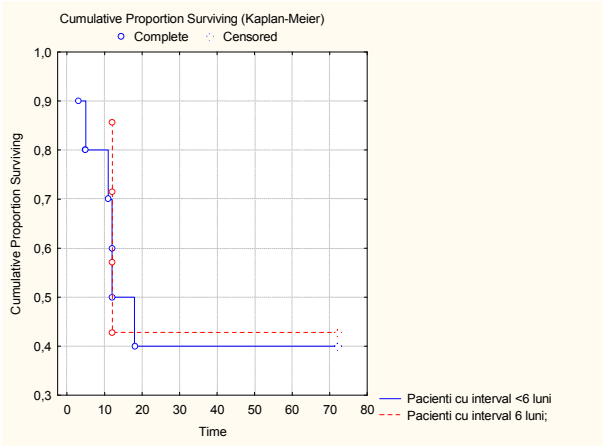


Figure 4.Survival curve for patients who had time interval between the apparition of symptoms and diagnosis more or less6 month

If the **time interval between the apparition of symptoms and diagnosis** is shorter (respectively longer) than 6 months does not influence survival (p=0.622 >>0, 05) and this also applies if the reference time interval is 12 months (p=0.275).

Prognosis factors associated with the primary tumor (testicular tumor).

The histology of primary testicular tumors was established before admission into the study using orchiectomy. In the case of 4 patients (26%) it could not be confirmed (administrative reasons). In one case we could only emphasize an extended necrosis without being able to establish it into the type of testicular tumor (seminoma, non-seminoma, or mixed).

Histology

Tipe of tumors	Frecvențe absolute	Frecvențe relative (%)
carcinoma+seminoma+ teratom	1	5,88
carcinoembrionar+tu. sinus endodermal	1	5,88
carcinoembrionar+coriocarcinom	1	5,88
carcinom embrionar	2	11,76
cc embrionar+teratom	1	5,88
necrosis	1	5,88
unprecised	4	23,53
nonseminoma	1	5,88
semin+teratom+carcinoembrionar	1	5,88
semin+teratom+coriocarcinom	1	5,88
seminom+Yolk+carcinoembrionar	1	5,88
Teratom, cc embrionar. Yolk	1	5,88
Yolk	1	5,88

Figure 5. Histology

Our batch comprises cases of mixed tumors (65%) and non-seminomas (6%) but lacks cases of pure seminomas. This can explain the favorable evolution at a reduced number of patients (compared to data from literature). The histology of our batch does not influence survival, p= 0.078 >>0, 05.

The tumor markers for our batch: Beta HCG, AFP (alpha-fetoprotein), LDH does not influence survival (p= 0.786), (p= 0.345) respectively (p= 0.153).

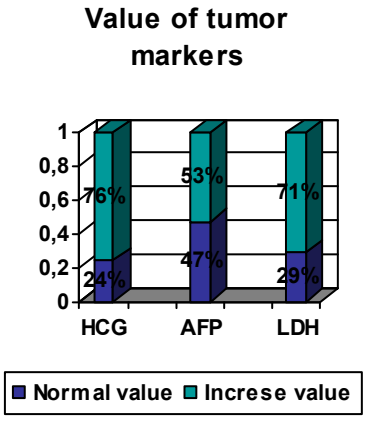


Figure 6. Value of tumor markers

Prognosis factors associated with the degree of tumor progression

All the patients in our study presented pulmonary metastases (2 unilateral, 15 bilateral, 5 other types of metastases). **The types of pulmonary metastases**: (unique 6%, micro-opacities 6%, multiple 7%, multiple + mediastinal adenopathies 6%, mediastinal adenopathies + pleuresy 6%) do not influence survival (p=0.08 >0.05). The micro and macro opacities do not influence survival (p= 0.171 >>0.05). The unilateral, respectively bilateral pulmonary metastases: statistically from out batch (2 patients could benefit from metastasistectomy) the types of pulmonary metastases (unique 12% or multiple 88%) do not influence survival: (p=0.149 >>0. 05).

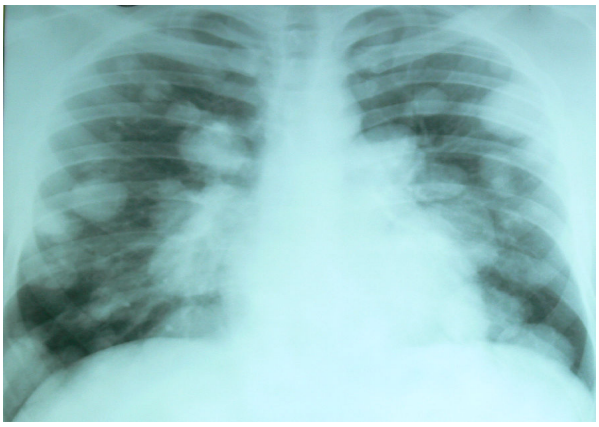
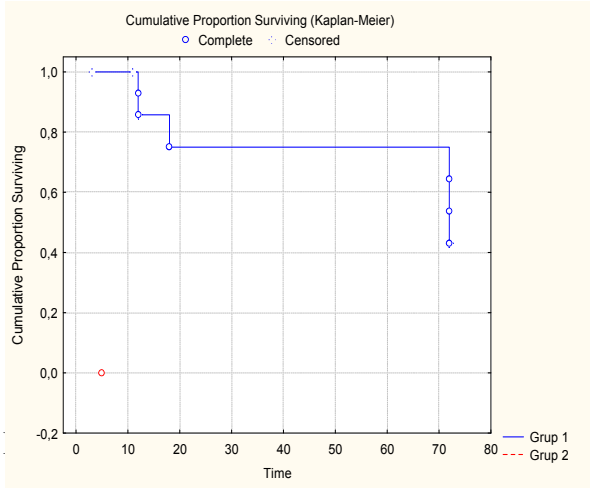


Figure 8. Pulmonary metastases

The presence of **other metastases**: within our batch we encountered retroperitoneal metastases in 60% of cases, hepatic + retroperitoneal in 10% of cases, hepatic + peritoneal carcinomatosis 105, cerebral 105, and pelvic 10%. The presence or lack of ganglion retroperitoneal metastases or of other metastases does not influence survival (p=0.439, respectively p=0.115). The number of metastasis localizations does not influence survival in testicular cancer (p= 0.465 >>0.05).

Risk groups: if we divide patients into two groups as follows: the first group will contain patients with increased HCG and ACG and with multiple pulmonary metastases and the second group will consist of patients with unique metastasis and with retroperitoneal metastases and we found out that patients belonging to the first category have "high risk" marking whereas the second group has a "poor risk" marking" (p=0.0254).



Treatment and response to treatment

Response to treatment influences survival: p =0.0064 < 0.05. It is noted that there is a favorable survival rate only in the case of 35% of patients. 24% only had a partial remission under treatment followed subsequently by evolution and death. Only 6 patients are still alive and have registered complete remission. Of the patients with an

unfavorable evolution, the longest survival period was 18 months and the shortest was 3 months.

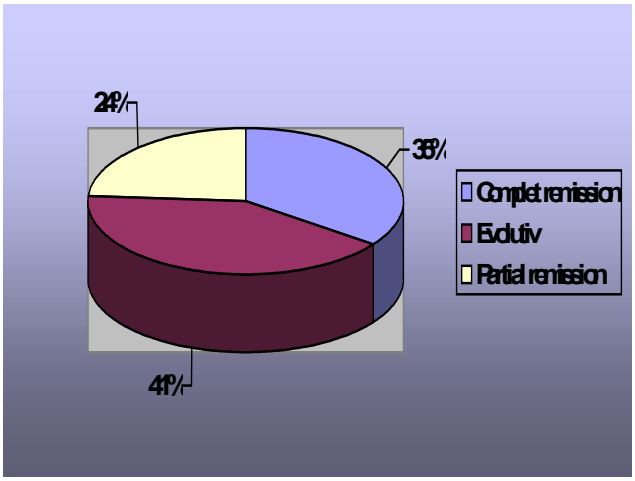


Figure 10.Response to treatment

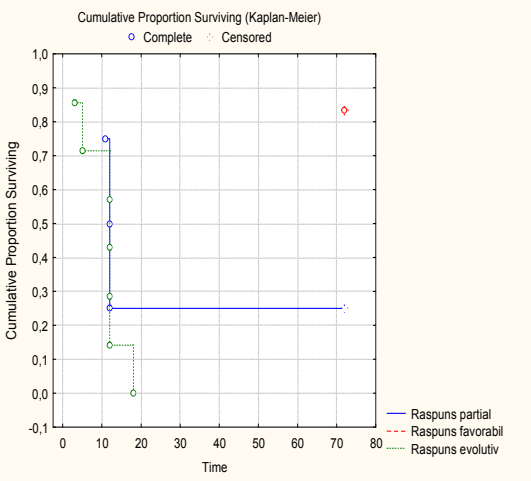


Figure 11.Survival curve for patients who had good response to treatment, partial and evolution of disease

For the patient who survives 3 months we tried to evaluate a genetic factor trough the presence of the hTERT gene We evaluated **the HTERT gene** on 2 patients who had testicles with tumors that presented pulmonary metastases, on 2 patients who had testicular cancer without metastases and one patient with a normal testicle. To this end we accomplished a quantitative determination (evaluation of the messenger RNA transcript) by the reaction of quantitative PCR (real time PCR) of the hTERT gene. Extracting, purifying and making a quantitative evaluation of total RNAs from biological samples. From the qualitative analysis we noted the existence of a sample with degraded RNA (sample 2404) which did not correspond to quality requirements (heterogeneous base line and species ratio 28S/18S below the value of 1.5). From the data obtained so far we ascertained a grouping of samples into two subgroups specific to the type of pathology: a group of two samples were we noted an expression of the hTERT gene increased at the level of testicular seminomas respectively a group of two carcinomas compared to the adult teratoma considered as a reference.

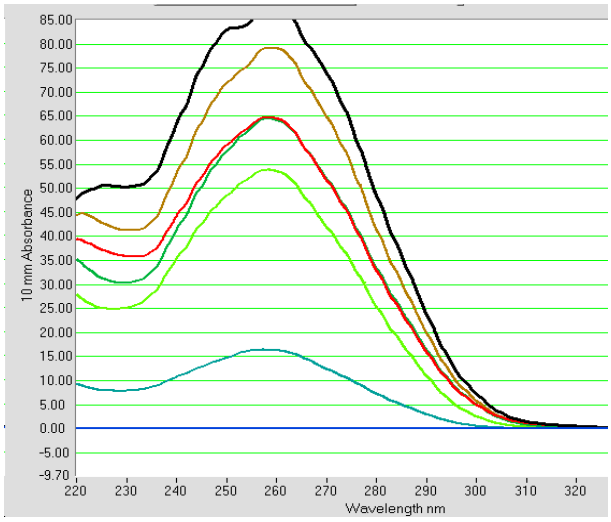


Figure 12. Extracting RNA– spectre de absorbție (nanodrop ND-1000) TriReagent.

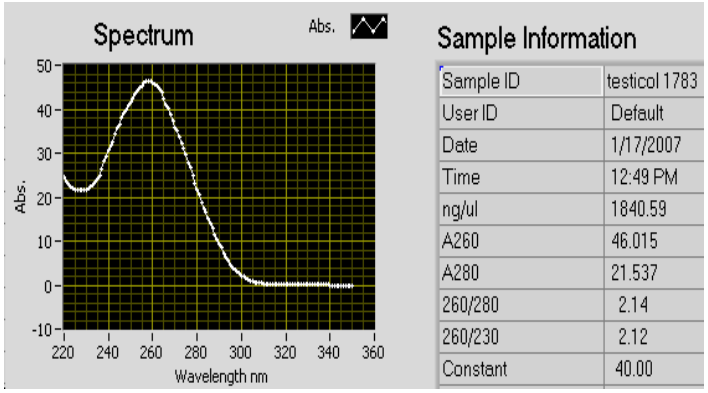


Figure 13.Purifying - Spectul de absorbție N purificat (Qiagen) proba 178

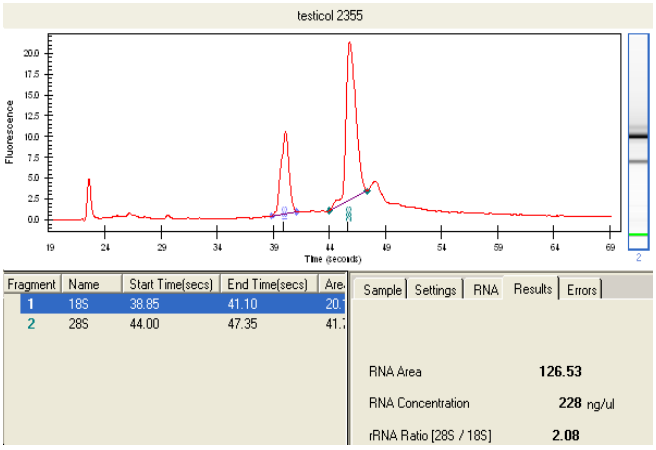


Figure 14.Quantitative evaluation of total RNAs

Relative Value of gene expression (no of transcript copy) hTERT gene

Nr crt	probe	patologie	Nivel expresie genică (nr copii transcript)
1	1783	seminom	1,215 E3
2	1779	seminom	1,45 E2
3	2812	carcinom embrionar	2,39 E3
4	2355	carcinom epidermoid	2,41 E3
5	1933	teratom adult	1

Generale data Quality and Quantitative evaluation of RNA

Nr crt	probe	Bioanalizor 2100		Nanaodrop ND-1000		
		calitate	Raport ARN 28S/18S	Conc. ARN Qiagen (ng/ul)	Raport 260/280	Raport 260/230
1	1783	ok	2,15	1840,59	2,14	2,12
2	1779	ok	2	1586,61	2,16	2,10
3	2404	degradat	1,92	1315,96	2,19	2,22
4	2812	ok	2,18	1270,64	1,89	1,91
5	2355	ok	2,08	1693,45	1,99	2,03
6	1933	ok	1,74	650,95	2,26	2,06

Figure 15. Evaluation of RNA

Standard curves for hTERT gene

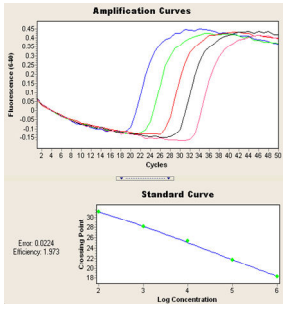


Figure 16.Standard curves for hTERT gene

Figure 17. Standard curves for hTERT

From the qualitative analysis we noted the existence of a sample with degraded RNA (sample 2404) which did not correspond to quality requirements (heterogeneous base line and species ratio 28S/18S below the value of 1.5). From the data obtained so far we ascertained a grouping of samples into two subgroups specific to the type of pathology: a group of two samples were we noted an expression of the hTERT gene increased at the level of testicular seminomas respectively a group of two carcinomas compared to the adult teratoma considered as a reference. According to the data obtained we note that in the case of seminomas there is an increase in the level o gene expression equaling 1.215 E3 respectively 1.45E2 compared to the reference value taken into consideration for the adult teratoma. In the case of carcinomas, the level of expression is 2.93E3 for the embryonic one respectively 2.41E3 in the case of the epidermoide one compared to reference 1 for the adult teratoma. As we noted before in the evaluation of the hTERT gene, its level in aggressive testicular tumors with pulmonary metastases is way bigger than in the case of testicular tumors without dissemination.

4 Discussion

The incidence of testicular cancer is reduced and although the number of patients with testicular

cancer is small, more than half of these cases present metastases. In Japan, for a population of 120 million inhabitants there are less than 50 new patients diagnosed every year compared to the USA where there are 7200. The evaluation of their evolution and identification of the prognosis factors made the object of several studies because the rate of survival of patients with a metastatic disease is very variable even with the new cytostatic treatments. There are descriptions of survival rates of only 45-55% among patients with metastasized testicular tumors compared to an 80-90% survival rate among patients without the disseminated disease. Identifying the subgroups of patients with a less favorable prognosis is the purpose of numerous prognostic models.

Bower and collaborators reported an average age between 27.3 (between 14-72%) (8). Kenneth Kester reported (in a study of 421 patients) an average age of 26.8 years. Stuart Kinton described in his study an average age of 32 years with ages between 19 and 52 years (9). Schmoll reported at the "European Congress for the Diagnosis and treatment of Germinal Tumors from 2004" an age of 34 years which he considered irrelevant as a prognosis factor in the evolution of patients(10). Aass reported an age over 35 years as an unfavorable prognosis factor. Within our batch we noticed an average age of 29.63 years (between 16 and 45) with a predominance in the 30 to 40 years age group (7 patients) without considering age a statistically significant prognosis factor (p=0.613).

The life environment and social economic level can influence the act of appearing before a doctor. In our study tough, this has not been a significant prognosis factor (p=0.895).

The time between the apparition of symptoms and the establishment of a diagnosis can represent a factor that may influence survival due to the increased stage of presentation. In our study, the average was 6.1 months and this ensues form the high stage of presentation of all patients from the batch (stage III and IV). Considering the delay is establishing a diagnosis, this did not influence survival (p=0.622). Other studies reported much smaller time intervals. In his study, Collette reported an average of 10 days from the date the disease made its appearance and the date diagnosis was established (1).Early metastasis did not always giverise in the lymph nodes (11).Serum tumor markers play an important role, vital even, in the evolution of patients with testicular cancer (5). The 5 years survival rate for patients with testicular cancer is 96%. Tumor markers contribute to this favorable evolution due to the completion of the diagnosis on one hand and the monitoring of follow-ups after orchiectomy on the other hand. They are important prognosis factors and their values, before the start of therapy help identification into various risk groups and indirectly help establish the therapeutic conduct. Also, their monitoring allows early identification of relapse cases after the start of treatment. Tumor markers are considered to be independent prognosis factors on one hand by participating in establishing the diagnosis as well as for their role in the early discovery of reappearance. Aass reported in a multivariate analysis that AFP greater than 1000 μg/l and HCG higher than 10.000units/l are unfavorable prognosis factors. Generally, the level of tumor markers after the 10^{th} day of the first chemotherapy cycle reflects the evolution under treatment without being highly selective (12). In our study (as in many other analyses) we have not assessed the discriminative value of these markers' decline. How quickly they decrease, in what percentage and how sensitive the modification of their value is. We haven't calculated the markers' standardization interval which in some studies from literature was defined as an independent prognosis factor (12). In our study the value of LDH, beta HGC and AFP did not represent a significant statistic prognosis factor (0.153; 0.786 and 0.345).

The performance status of patients influences survival in numerous neoplasias.

This was not a significant prognosis factor for the testicular tumor cases with metastases from our studies. Collette reports the influence of the performance status on survival (1). Patients with pulmonary metastases were included into different risk groups and depending on the other prognosis factors (number of metastasis localizations, position of the primary tumor, values of tumor markers). Although all patients had pulmonary metastases, in our study not all were included in the "poor risk" category. The chemotherapy treatment was made with various combinations of Cisplatin followed by the surgical resection of the residual tumor. The response to treatment was 35% complete response, 24% partial response and 41% progressive response.

Motzer(13) reported a ratio of complete response among "good risk" patients (treated with four cycles of Etoposid + Cisplatin or three cycles of BEP) of 90%.

20 to 30% of patients with advanced testicular cancer suffered either from relapse or had an incomplete response to chemotherapy. These patients can be identified however during the initial presentation into "poor risk" groups (histology non-seminoma, pre-therapeutic high levels of markers, hepatic, bone, cerebral metastases, mediastinal localizations of primary tumors). Half of all "poor risk" patients will die. Patients who obtained only a partial response with the first BEP line and who were progressive were considered to be refractory and a second line of treatment was administered. Few of these patients will have a complete response with the rescue therapy (vinblastine, ifosfamide, cisplatin). These patients have a low chance of survival despite the high performance treatments (13).

The survival rate of patients with testicular cancer is generally very good as this is considered a type of curable cancer with a 5 year survival rate of approximately 90%. In the US and Europe this survival rate can reach even 95%. In Japan, although the survival rate has improved it could not be reported statistically due to the rarity of the disease (12,14). Bower reported in a study conducted on 339 a rate of survival at 5 years of 82%. For patients with an unfavorable prognosis, the 3 year survival period was 75% (8). Schmoll and Kollmannsberger (Eupean Consensus) reported a 90% survival rate for patients with a favorable prognosis (56% of them with a favorable prognosis), 80% for patients with intermediary risk (28% of them) and a 50% survival rate at 5 years for patients with an unfavorable prognosis (16% of them) (5). Kenneth Kesler noted in a study of mediastinal metastases a survival rate at 5 years of 86% +/- 2% and a 74% +/- 4% survival rate at 10 years. De Vita reported survival within localized stages at 95.1% in cases with regional invasion 69.4% and with remote invasion 33.1 %(1,9). Stuart Kinton published in his study (trial of the Eastern cooperative oncology group) the favorable response of 80% of cases and a lasting response among 73% of patients with tumors of the germinal cells(15). In his study, Motzer published a complete response at 77%, incomplete response at 20%, partial response but with a standardization of tumor markers at 3% and relapse at 6%. He also reported a complete response based on prognosis factors 86%, 50% and 25%. Of the patients who had an unfavorable response and received rescue therapy with increased doses of chemotherapy medicines associated with autolog Stem cell transplant, 57% had a complete response and 35% a durable response for more than 18 months. We observe the significant differences of evolution and survival between various reported studies(4,9 ,16,17). This is explained on one hand by the different experience that various oncology centers have, by the diagnosis conducts and non-standardized therapeutic conducts, varied access to last generation medicines, application of chemotherapies with large dosages followed by autolog bone marrow transplant only in few centers and on a reduced number of patients.

Generally, patients with metastases will have a different prognosis depending on the relapse model and will require individual strategies selected based on the risk factors by combining available therapeutic modalities (irradiation, chemotherapy, surgery of residual tumor masses). This entire arsenal can lead to a very high healing rate. Nevertheless, testicular cancer cases without a complete remission are some of the most disseminative cancers. Early diagnosis and treatment of metastasis may lead to an improvement in the survival rate of cancer patients. The diagnosis of metastasis using molecular biological techniques has been attempted with various tissues including blood, pancreatic juice, ascites, lymph nodes, but the methods is still controversial. Micrometastasis, which is not detectable by routine histological examinations, can now be identified by genetic methods(18). Long term survival (over 5 years) and the curability rate of patients with testicular cancer, although in literature is above 90%, our study revealed only a 35.29% survival rate. (19)

5.CONCLUSIONS

Germ cell tumors are characterized by the acquisition of extra copies of chromosome 12p, most commonly through an isochromosome (i12p). Several candidate genes have been localized to 12p and may be important to the pathogenesis of GCT. In addition, 10% to 20% of seminomas may harbor

activating mutations in the *c-KIT* gene. Germ cell tumors are also frequently triploid or hypotetraploid in DNA content, suggesting that other genetic aberrations play a role in their pathogenesis (20)

The evaluation of other prognosis factors at an immune-histological, genetic or molecular level allows the redefinition of the prognosis and improvement of the germinal tumors' management.. Presently, survival among patients is low although improved compared to the last few years before the discovery of chemotherapy with Cisplatin. This justifies the increase of investigations regarding patients with unfavorable risk factors.

Detection of recurrent disease relies on careful follow-up with a combination of clinical assessment, serum marker analysis, chest radiography, and abdominal CT. Follow-up protocols vary depending on the type of tumor, stage, treatments given, and individual institutions. They are based on the known patterns of disease relapse in testicular GCT(21)

Follow up should be extended from the usual 2 years to 5 years before cure can be stated. Until a broad international consensus is reached Oldenburd and col. Recommend follow up of all patients for at least 10 years (22)
Huddard recommend for patients on surveillance: clinical review, chest X-ray and tumor markers monthly for 1 years, 2 monthly for second years , 4 monthly third year, then 6 monthly to 5 years. Ct abdominal after 3 and 12 month. Post chemotherapy patients ;Clinical review, chest X-ray and tumor markers 2 monthly for 1 years, 3 monthly for second years than 6 monthly to 5 years than annually; Ct scan only as clinically indicated (3) Understanding the biology and tumor cell genetic can become research therapeutic targets. Until the identification of new prognosis factors (for example hTERT), validated by future studies, treatment and conduct will be based on the predictive value of other classical prognosis factors. (19).

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