Ahead of Print

Turk J Urol 2018 • DOI: 10.5152/tud.2018.48855

TURKISH JOURNAL OF UROLOGY

UROONCOLOGY

Original Article

Evaluation of germ-cell neoplasia in situ entity in testicular tumors

Mehmet Akyüz, Ramazan Topaktaş, Ahmet Ürkmez, Orhan Koca, Metin İshak Öztürk

Cite this article as: Akyüz M, Topaktaş R, Ürkmez A, Koca O, Öztürk Mİ. Evaluation of germ-cell neoplasia in situ entity in testicular tumors. Turk J Urol 2017; 44:DOI: 10.5152/tud.2018.48855.

ABSTRACT

Objective: Germ-cell neoplasia in situ (GCNIS) is accepted as the precursor of the testicular tumors. The aim in our study is to compare the lymphadenopathy and metastasis parameters in patients diagnosed with testicular tumor with or without GCNIS based on pathological evaluation.

Material and methods: Data from 108 patients who underwent orchiectomy for testicular tumor between January 2007 and December 2014 in our clinic were retrospectively analyzed and included in the study. Patients were divided into two groups based on the pathology reports as GCNIS or not. Groups were compared regarding lymphadenopathy, metastasis, tumor marker levels, tumor size, lymphovascular invasion, rete testis invasion. Mann-Whitney U test was used for statistical evaluation.

Results: Mean age of the patients included in the study were calculated as 34.6±9.3 years. Eighty-five (78.7%) patients had GCNIS, while 23 (21.3%) of them had not. In terms of metastasis, lymphadenopathy, marker levels, tumor size, lymphovascular invasion and rete testis invasion, no statistical significant difference were observed between two groups (p>0.05).

Conclusion: In our study, no statistical significant difference was observed on the prognostic factors concerning the GCNIS entity, which is reported frequently in testicular tumor pathologies. For presently these findings show us that GCNIS cannot be used as a prognostic factor.

Keywords: Germ- cell neoplasia in situ; prognostic factors; testicular cancer.

ORCID IDs of the authors:
M.A. 0000-0002-5394-9741;
R.T. 0000-0003-3729-3284;
A.Ü. 0000-0001-8357-7734;
O.K. 0000-0002-6184-8801;
M.İ.Ö. 0000-0001-9369-8206.

Department of Urology, Health Sciences University Haydarpaşa Numune Training and Research Hospital, İstanbul, Turkey

Submitted:
13.11.2017

Accepted:
22.01.2018

Available Online Date:
16.03.2018

Correspondence:
Mehmet Akyüz
E-mail:
drmehmetakyuz67@gmail.com

Available online at
www.turkishjournalofurology.com

Introduction

Though rarely seen, testicular tumors constitute the most frequently seen malignant tumors of young men. Testicular cancers comprise 5% of all urological cancers, and 1-1.5% of all male cancers. Besides every year 3-10 new cases are seen in 100.000 men.[1]

Germ-cell neoplasia in situ (GCNIS) known as precursor of testicular tumor, was firstly reported by Niels Skakkebaek[2] in the year 1972 as carcinoma in situ. Skakkebaek[2], described this entity as carcinoma in situ in two of his biopsized patients, and reported this entity as precursor of testicular invasive tumors excluding prepubertal testicular tumors, and spermatocytic seminoma seen in advanced ages, because of its concomitancy with invasive germ cell tumors.[2] Various terminologies which describe the same histological structure including testicular intraepithelial neoplasia, carcinoma in situ or intratubular germ cell neoplasia, intratubular germ cell neoplasia of unclassified type are abandoned, and nowadays the term germ-cell GCNIS has been used.[2-4] GCNIS is a noninvasive, and asymptomatic neoplasia which has been identified in 4-8% of the patients who had undergone radical orchiectomy together with contralateral testicular biopsies. Development of germ-cell carcinoma in 50% of GCNIS patients within 5 years, its frequent detection in patients with a patient group carrying a high risk for testicular cancer, and its location in seminiferous tubuli adjacent to testicular germ cell tumor in 80-90 % of the cases indicate its characteristics as a precursor lesion.[5-7] All through this article only the term GCNIS will be used instead of other terminologies.

In this study, we aimed to evaluate the effect of GCNIS on the parametres of metastasis, and lymphadenopathy in patients diagnosed as germ-cell testicular tumor , and histopathological examination of the post-radical orchiectomyperformed in our clinic revealed concomitant absence or presence of GCNIS.

Material and methods

Medical files of 108 patients histopathologically diagnosed as testicular germ-cell neoplasia, and underwent inguinal radical orchiectomy in our clinic with the initial diagnosis of testicular tumor between January 2007, and December 2014 were retrospectively screened after retrieval of patients' approvals from electronic database of the hospital. Physical examination findings, scrotal ultrasound reports, and tumor markers of the patients were examined. All histopathological examinations were performed by a single pathologist. For the detection of GCNIS, highly sensitive placental alkaline phosphatase (PLAP), periodic acid-Schiff (PAS) staining methods had been used. For staging, and grouping of testicular tumors TNM (tumor-node-metastasis) classification system published by International Union Against Cancer (UICC) in the year 2009 was used. the patients were divided into two groups based on the presence or absence of GCNIS in addition to testicular germ cell malignancy indicated in histopathology reports. Both groups were compared as for the presence of lymphadenopathy, organ metastasis, tumor marker positivity, tumor size, lympho-vascular invasion, and invasion of rete testis. Staging computed tomography and/or magnetic resonance imaging had been performed immediately before or within the first two days after surgery, and the presence of lymphadenopathy, and metastasis were recorded. The patients whose histopathology reports did not contain any evidence of malignant testicular tumor, or any evaluation of organ metastasis or lymphadenopathy were excluded from the study.

Table 1. The association between GCNIS, and presence of metastasis, and lymphadenopathy

	Metastasis (+)	Metastasis (-)	LAP (+)	LAP (-)
GCNIS (+), n	8	54	28	34
GCNIS (-), n	6	19	11	14
		p>0.05		p>0.05

LAP: lymphadenopathy; GCNIS: germ-cell neoplasia in situ

Statistical analysis

Mann-Whitney U test was used for statistical analysis For analysis of data Statistical Package of Social Sciences version 13.5 (SPSS Inc.; Chicago, IL, USA) was employed. P<0.05 was accepted as statistically significant.

Results

Mean age of 108 study participants was 34.6±9.3 (range, 15-58 yrs) years. The patients were diagnosed as seminoma (n=44; 40:7%), and non-seminomatous germ-cell tumor (n=64; 59.3%). GCNIS was detected in a total of 78.7% (n=85) of the patients. GCNIS accompanied 32 out of 44 (72.7%) seminoma, and 53 out of 64 (82%) non-seminomatous germ-cell patients. At the time of diagnosis of the seminoma patients, lymphadenopathy

Table 2. Association between GCNIS, and histopathological, and biochemical findings

	GCNIS (+) (n=75)	GCNIS (-) (n=33)	p
AFP, ng/mL	468.2±1845.6	941.6±2887.9	>0.05
LDH, IU/L	385.9±246.6	928.9±1309.8	>0.05
βhCG, mIU/mL	881.7±2299.7	2368.2±6523.2	>0.05
Tumor size	5.4±2.6 cm	7.6±3.7 cm	>0.05
Lymphovascular invasion	28/75 (37.3%)	10/33 (30.3%)	>0.05
Seminoma	6/28	3/10	
NSGCT	22/28	7/10	
Rete testis invasion	32/75 (42.6%)	21/33 (63.6%)	>0.05
Seminoma	3/32	11/21	
NSGCT	29/32	10/21	

AFP: alpha- fetoprotein; LDH: lactate dehydrogenase; βhCG: beta-human chorionic gonadotropin; GCNIS: Germ-cell neoplasia in situ; NSGCT: non-seminomatous germ cell tumor

(n=13), and lung and/or other organ metastases (n=4) were detected. Testicular germ-cell patients with or without GCNIS were divided into two groups. The association between GCNIS, and the presence of metastasis, and lymphadenopathy is shown in Table 1. Lymphadenopathy was detected in 36.1% (n=39) of these patients, while organ metastasis was found in 14 (12.9%) patients. The association between histopathological findings, tumors markers with GCIS is summarized in Table 2. Any intergroup statistically significant difference was not detected as for the presence of GCIS, and organ metastasis, lymphadenopathy, increased tumor markers, tumor size, lymphovascular invasion, and rete testis invasion ($p>0.05$). In any one of cancer patients, clinical and radiological assessments revealed any evidence of bilateral testicular involvement.

Discussion

Though germ-cell tumors are rarely seen among male cancers, and they are most frequently seen malignancies especially among young men aged between 20, and 40 years. Besides in recent years, global incidence of testicular tumors is increasing day by day. Based on US data, it is the second most frequently seen type of cancer among adolescents, and youngsters aged 15-20 years after leukemia. Although it manifests itself as painless unilateral testicular mass, in 20% of the cases, scrotal pain may accompany clinical symptoms.[8,9] Ninety-95% of testicular tumors are germ-cell tumors which constitute of seminomas (40%), and non-seminomatous tumors (60%).[10] Confirmed risk factors involving in the pathogenesis of testicular tumor are history of undescended testis, Klinefelter syndrome, infertility, history of testicular cancer in a first degree relative, contralateral testicular tumor, and presence of GCNIS.[11] Not precisely confirmed risk factors which may cause testicular tumors including scrotal trauma, atrophic testic, inguinal hernia, previous testicular infections, mumps orchitis, testicular torsion, increased scrotal temperature, and varicocele. These risk factors are also effective in the pathogenesis of GCNIS which is the presursor of testicular germ-cell tumors.

GCNIS which is accepted as the presursor of germ-cell tumors is localized in the basal layer of neighbouring seminiferous tubuli, and resembles primitive gonocytes, and germ-cell activity is not observed. GCNIS which is accepted to be a precursor of germ-cell tumors has been encountered in the vicinity of seminomatous, and non-seminomatous germ-cell tumors in nearly 80-100%, in the contralateral testis of germ-cell tumors in 5%, in undescended testis in 4, in testicular biopsies performed in infertility in 1% of the cases, and only 0.43% of healthy men.[10,12,13] In our study in compliance with the literature in nearly 79% of our cases GCNIS was detected in testicular tissue adjacent to germ-cell tumors. This finding supports the opinion which asserts that GCNIS is the precursor of testicular germ-cell tumors. GCNIS cells stain positively with PAS, and PLAP dyes, while normal cells do not. Besides, these cells with conspicuous nuclei, and abundant cytoplasms are typically larger, and bigger than normal spermatogonia cells. In our study, our pathologist used these staining methods during examination of testicular pathologies to detect this entity.

Since GCNIS is entrapped in seminiferous tubuli, it is an asymptomatic, and noninvasive neoplasm. When left untreated, nearly half of them transform into invasive germ-cell tumor, and during long-term follow-up invasive germ-cell tumor develops in almost all patients.[14] On the contrary, patients who had not demonstrated disease progression for 15 years have been reported. But generally spontaneous regression is not observed.[15] When literature is evaluated, though it has been stressed that GCNIS may have higher malignancy potential in a small percentage of patients disease progression might not be observed. When all these factors are taken into consideration, most authors have agreed that GCNIS should be diagnosed, and treated at an early stage in order to decrease the incidence of testicular cancer.

GCNIS has been considered as an precursor lesion of testicular tumor for some reasons. Firstly, an average of 5 years after testicular biopsy invasive germ- cell testicular tumor develops in 50% of the patients, secondly it is seen very frequently in groups of patients carrying higher risk for testicular cancer, and thirdly it is localized in seminiferous tubuli in the close vicinity of testicular germ-cell tumors excluding spermatocytic seminoma, and prepubertal germ-cell tumors.[10] In adults, GCNIS is found in 80-90% of tissues adjacent to seminomatous, and non-seminomatous invasive germ-cell tumors excluding spermatocytic seminoma.[10] Skakkebaek[2] firstly described GCNIS in two patients who had undergone testicular biopsy with the indication of infertility. The author detected development of embryonal carcinoma in one of these two patients, and performed prophylactic orchiectomy in the other patient. Definitive post-orchiectomy pathology of the second patient was reported as persistent GCNIS.[2] When we contemplate that pediatric testicular tumors have a relatively benign course, and GCNIS is not encountered in this age group, one may consider GCNIS as an precursor lesion of testicular tumor.

Treatment options of GCNIS with higher potential of malignant transformation include, surveillance, local testicular radiotherapy or orchiectomy.[16] Among them the most frequently used alternative with highest success rate is radiotherapy because of radiosensitivity GCNIS. Since radiotherapy will lead to infertility, before initiation of radiotherapy, the patient should be attentively enlightened.

The presence of GCNIS used in the staging of testicular tumors is not currently used in histopathological staging

which determines prognosis, and in the prediction of occult metastases. In stage 1 seminoma patients, size of the tumor (>4 cm) and presence of rete testis invasion are parameters used in the prediction of occult metastases, and increased risk of recurrence.[17] In stage I non-seminomatous tumors some parameters as lymphovascular invasion, the ratio of embryonal carcinoma more than 50%, proliferation index higher than 70%, and presence of yolk sac component.[17] When these current literature parameters are taken into consideration, GCNIS has no place in the prediction of occult metastases, and risk of recurrence Besides GCNIS has no role in the determination of prognosis of the tumor, and prediction of germ-cell testicular tumor. In addition, the place of GCNIS in the prediction of recurrences, and especially rete testis invasion is still debatable.[18] In a current study, it has been reported that incidence of GCNIS increases in parallel with the grade of the tumor, and in cases with non-seminomatous germ-cell tumors, increased alpha-fetoprotein levels before orchiectomy are in close relationship with GCNIS. Besides GCNIS was also associated with more aggressive tumors.[19] In our study we also retrospectively investigated the impact of histopathologically detected GCNIS in germ-cell testicular cancers on metastasis, and lymphadenopathy. In compliance with current literature, we could not detect any statistically significant correlation between the presence of GCNIS, and metastasis, and lymphadenopathy. Contrary to expectations, lower incidence of metastasis, and lymphadenopathy was observed in patients with GCNIS. Still in our study a significant correlation was not detected between levels of alpha-fetoprotein, other tumor markers, and the presence of GCNIS. Limitations of our study include its single-centered retrospective design and relatively small number of patient population.

In conclusion, in our study any statistically significant correlation was not detected between GCNIS which is frequently reported in testicular tumor pathologies, and metastasis, and lymphadenopathy which are important prognostic factors in patients with testicular tumors. We think that detection of any association between these prognostic factors and GCNIS, and arrival at more robust conclusions require conduction of larger-scale, prospective, and multicenter studies.

Ethics Committee Approval: Due to the retrospective nature of the study, ethics committee approval was not required.

InformedConsent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.A., R.T.; Design - R.T.; Supervision - M.İ.Ö., O.K.; Funding - R.T., A.Ü.; Materials - R.T., M.A.; Data Collection and/or Processing - M.A., R.T., A.Ü.; Analysis and/or Interpretation - M.İ.Ö., R.T.; Literature Review - R.T., M.A., A.Ü.; Writer - R.T., M.A.; Critical Review - O.K., M.İ.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer Worldwide: a review. J Urol 2003;170:5-11. [CrossRef]
2. Skakkebaek NE. Possible carcinoma in situ of the testis. Lancet 1972;2:516-7.v
3. Montironi R. Intra tubuler germ cell neoplasia of the testis. Eur Urol 2002;41:651-4. [CrossRef]
4. In Brierley JD, Gospodarowicz MK, Wittekind C. The TNM classification of malignant tumours, 8th ed. Oxford: Wiley Blackwell, 2017.
5. Hargreaves TB. Carcinoma in situ of the testis. Br Med J 1986;293:1389-90. [CrossRef]
6. Coffin CM, Ewing S, Dehner LP. Frequency of intra tubuler germ cell neoplasia with invasive testicular germ cell tumors. Arch Patol Lab Med 1985;109:555-9.
7. Dieckmann KP, Kulejewski M, Pichlmeier U, Loy V. Diagnosis of contralateral testicular intraepithelial neoplasia (TIN) in patients with testicular germ cell cancer: systematic two-site biopsies are more sensitive than a single random biopsy. Eur Urol 2007;51:175-83. [CrossRef]
8. Shaw J. Diagnosis and treatment of testicular cancer. Am Fam Physician 2008;77:469-74.
9. Shanmugalingam T, Soultati A, Chowdhury S, Rudman S, Van Hemelrijck M. Global incidence and outcome of testicular cancer. Clin Epidemiol 2013;17:417-27.
10. Andrew JS, Timothy DG. Neoplasms of the Testis Campell-Walsh Urology. 10th ed. Philadelphia: Saunders Elsevier; 2012.pp.837-70.
11. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K, et al. EAU guidelines on testicular cancer: 2016 update. Eur Urol 2011;60:304-19. [CrossRef]
12. Bilir G, Çakır E, Benzer E, Pak I, Kebat T, Ardıç F. Intratubular germ cell neoplasia accompanying germ cell tumors. Ege J Med 2007;46:73-7.
13. Linke J, Loy V, Dieckmann KP. Prevalence of testicular intraepithelial neoplasia in healthy males. J Urol 2005;173:1577-9. [CrossRef]
14. Bahrami A, Ro JY, Ayala AG. An overview of testicular germ cell tumors. Arch Pathol Lab Med 2007;131:1267-80.
15. Dieckmann KP, Pichlmeier U. Clinical epidemiology of testicular germ cell tumors. World J Urol 2004;22:2-14. [CrossRef]
16. Dieckmann KP, Wilken S, Loy V, Matthies C, Kleinschmidt K, Bedke J, et al. Treatment of testicular intraepithelial neoplasia (intratubular germ cell neoplasia unspecified) with local

radiotherapy or with platinum-based chemotherapy: a survey of the German Testicular Cancer Study Group. Ann Oncol 2013;24:1332-7. [CrossRef]
17. Vogt AP, Chen Z, Osunkoya AO. Rete testis invasion by malignant germ cell tumor and/or intratubular germ cell neoplasia: what is the significance of this finding? Hum Pathol 2010;41:1339-44.
18. Valdevenito JP, Gallegos I, Fernández C, Acevedo C, Palma R. Correlation between primary tumor pathologic features and presence of clinical metastasis at diagnosis of testicular seminoma. Urology 2007;70:777-80. [CrossRef]
19. Basiri A, Movahhed S, Parvin M, Salimi M, Rezaeetalab GH. The histologic features of intratubular germ cell neoplasia and its correlation with tumor behavior. Investig Clin Urol 2016;57:191-5. [CrossRef]