

ORIGINAL ARTICLE

Does primary tumor localization has prognostic importance in seminoma patients?: Turkish Oncology Group Study

Birol Yildiz¹, Ahmet Kucukarda², Ali Gokyer², Atike Gokcen Demiray³, Semra Paydas⁴, Ipek Pinar Aral⁵, Ozge Gumusay⁶, Ahmet Bilici⁷, Nadiye Akdeniz⁸, Aykut Bahceci⁹, Hacer Demir¹⁰, Ece Esin¹¹, Ummugul Üyeturk¹², Ilker Nihat Okten¹³, Ismail Erturk¹, H. Mehmet Turk¹⁴, Ulas Serkan Topaloglu¹⁵, Tugba Basoglu¹⁶, Nazim Serdar Turhal¹⁷, Havva Yesil Cinkir¹⁸, Serkan Menekse¹⁹, Yagmur Cakmak²⁰, Yuksel Urun²¹, Ramazan Acar¹, Engin Kut¹⁹, Pinar Dal²², Teoman Sakalar²³, Oktay Halit Aktepe²⁴, Nuri Karadurmus¹

¹Health Sciences University, Gülhane Training and Research Hospital, Department of Medical Oncology, Ankara, Turkey. ²Trakya University Faculty of Medicine, Department of Medical Oncology, Edirne, Turkey. ³Pamukkale University Faculty of Medicine, Department of Medical Oncology, Denizli, Turkey. ⁴Çukurova University Faculty of Medicine, Department of Medical Oncology, Adana, Turkey. ⁵Nevşehir State Hospital, Department of Radiation Oncology, Nevşehir, Turkey. ⁶Gazi Osman Pasa University Faculty of Medicine, Department of Medical Oncology, Tokat, Turkey. ⁷Medipol University Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey. ⁸Dicle University Faculty of Medicine, Department of Medical Oncology, Diyarbakir, Turkey. ⁹Gaziantep Dr. Ersin ARSLAN Training and Research Hospital, Department of Medical Oncology, Gaziantep, Turkey. ¹⁰Afyon Kocatepe University Faculty of Medicine, Department of Medical Oncology, Afyon, Turkey. ¹¹Bayindir Hospital, Department of Medical Oncology, Ankara, Turkey. ¹²Abant Izzet Baysal University Faculty of Medicine, Department of Medical Oncology, Bolu, Turkey. ¹³Istanbul Medeniyet University, Goztepe Training and Research Hospital, Department of Medical Oncology, Istanbul, Turkey. ¹⁴BezmiAlem Vakif University, Department of Medical Oncology, Istanbul, Turkey. ¹⁵Kayseri City Hospital, Department of Internal Medicine, Kayseri, Turkey. ¹⁶Marmara University Faculty of Medicine, Department of Medical Oncology, Istanbul, Turkey. ¹⁷Anadolu Medical Center, Department of Medical Oncology, Kocaeli, Turkey. ¹⁸Gaziantep University Faculty of Medicine, Department of Medical Oncology, Gaziantep, Turkey. ¹⁹Manisa City Hospital, Department of Medical Oncology, Manisa, Turkey. ²⁰Kocaeli University Faculty of Medicine, Department of Medical Oncology, Kocaeli, Turkey. ²¹Ankara University, Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey. ²²Eskişehir City Hospital, Department of Medical Oncology, Eskişehir, Turkey. ²³Kahramanmaraş City Hospital, Department of Medical Oncology, Kahramanmaraş, Turkey. ²⁴Hacettepe University Faculty of Medicine, Department of Medical Oncology, Ankara, Turkey.

Summary

Purpose: The purpose of this study was to determine whether primary tumor localization may be a risk factor for relapse and survival in seminomatous germ cell tumors (GCT) patients.

Methods: In our study, 612 seminomatous GCT patients diagnosed in 22 centers between 01.01.1989 and 03.02.2019 were retrospectively evaluated. Patient interview information, patient files and electronic system data were used for the study.

Results: The primary tumor was localized in the right testis in 305 (49.9%) patients and in 307 (50.1%) in the left testis. Mean age of the patients was 36 years (range 16-85±10.4). The median follow-up period was 47 months (1-298). Recurrence was observed in 78 (12.7%) patients and 29 (4.7%) died during the follow-up period. Four-year overall survival (OS) was 95.4% and 4-year progression-free survival (PFS) was 84.5%. The relationship between localization and relapse was signifi-

cant in 197 patients with stage 2 and stage 3 ($p=0.003$). In this patient group, 41 (20.8%) relapses were observed. Thirty (73.2%) of the relapses were in the right testis and 11 (26.8%) in the left testis.

Four-year OS was 92.1% in patients with right tumor; and 98.7% in patients with left tumor ($p=0.007$). When 612 patients were evaluated with a mean follow-up of 4 years, there was a 6.6% survival advantage in patients with left testicular tumor and this difference was significant ($p=0.007$).

Conclusion: Survival rates of patients with primary right testicular localization were worse compared with left testicular localization, and relapse rates were higher in stage 2 and 3 patients with right testicular localization.

Key words: testicular cancer, germ cell tumor, seminoma, primary tumor localization, prognosis, survey

Corresponding author: Birol Yildiz, MD. Gulhane Training and Research Hospital, Department of Medical Oncology, Ankara, Turkey.

Tel: +90 312 304 40 31, Email: bfyildiz@gmail.com

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Introduction

Testicular cancer is the most common solid malignancy in men aged 15-35 years, although it appears to be only 1% among solid tumors. Of testicular cancer 95% are germ cell tumors (GCT). Testicular GCT are divided into two histopathological groups; seminoma and non-seminoma. The group called pure seminoma constitutes approximately 60% of the whole GCT [1,2].

Of stage 1 seminoma patients 85% can be followed without treatment for a long time with active surveillance after orchiectomy and in patients with retroperitoneal relapse during follow-up, treated as stage 2 at the time of diagnosis. Seminoma is very sensitive to radiotherapy and chemotherapy, and the cure rate is 90% with combined treatments. The majority of advanced stage and/or recurrent seminoma patients are treated with combinations of cisplatin-based chemotherapy. Advanced-stage seminoma patients are divided into good or moderate risk groups according to the prognostic scoring of International Germ Cell Cancer Collaborative Group (IGCCCG) [3]. According to IGCCCG scoring, 90% of advanced-stage seminoma patients have a good risk score and 5-year PFS and OS rates are 90 and 92%, respectively. The 5-year PFS and OS rates of patients in the middle-risk group of 10% were 67 and 72%, respectively [4,5]. In other words, the higher the risk score, the higher the proportion of patients who do not benefit from treatment. Additional risk scoring is then required.

Seminomatous GCT are spread by lymphovascular route similar to other solid cancers [6]. When the vascular anatomy of the testes is evaluated, it is clear that the vascular structure of the right and left testicles have different drainages. While the venous system of the left testis drains into the left renal vein, the venous system of the right testis drains directly into the inferior vena cava. Therefore, the right testis is exposed to less pressure and has relatively faster blood flow than the left testis. There is a hypothesis that due to the direct drainage to the heart and the low pressure in the vascular structure of the right testis the systemic spread will be higher in the right testicular cancer [7].

The purpose of this study was to determine whether primary tumor localization may be a risk factor for relapse and survival in seminomatous GCT patients.

Methods

612 seminoma patients diagnosed in 22 centers between 01.01.1989 and 03.02.2019 were retrospectively evaluated. Patient interview information, patient files and electronic system data were used for the study.

Patient demographic status, tumor localization, stage and pathological parameters of the disease, hormone values, treatment modality, treatment response and final status were recorded.

The primary endpoints were OS and PFS. The date of diagnosis was adopted as the starting date for the OS and PFS. The endpoint for OS was the last control date for living patients and the death date for deceased patients. The endpoint for PFS was the first event date for relapse and distant metastasis, and the last control date for non-recurrent patients. The study included patients with pathologic diagnosis of seminoma with fully available information, and being in stages 1-3C according to AJCC 8. Patients with bilateral mass, missing file and follow-up information were excluded from the study.

Table 1. Patient data and treatment details

	n (%)
Localisation	
Right	305 (49.9)
Left	307 (50.1)
Nodal involvement	
Negative	292 (54.7)
Positive	322 (47.3)
Stage	
1	414 (67.6)
2	108 (19.3)
3	80 (13.1)
RPLND	
Negative	574 (93.8)
Positive	38 (6.2)
RT	
Negative	531 (86.8)
Positive	81 (13.2)
First CT	
Carbo	146 (42.6)
BEP	192 (55.9)
EP	5 (1.5)
Salvage CT (after relaps)	
Negative	12 (15.4)
Positive	66 (84.6)
Salvage CT (after relapse) Protocols	
BEP	34 (50.7)
TIP	26 (38.8)
CE	1 (1.5)
EP	2 (3)
VIP	4 (6)
Second Salvage CT Protocols	
VIP	15 (71.4)
TIP	4 (19)
Gempox	2 (9.5)
Autologous Stem Cell Transplantation	
Negative	600 (98.0)
Positive	12 (2.0)

Statistics

SPSS Ver. 20 was used for statistical analyses. Descriptive statistics for continuous (quantitative) variables included mean, standard deviation, minimum and maximum values were expressed, while categorical variables are expressed as numbers (n) and ratios (%). The appropriateness of the data to normal distribution was examined statistically and visually, and it was determined that it was suitable for normal distribution and parametric tests to be applied. The characteristics and categorical data of the patients were evaluated by Chi-square (χ^2) test. Student's-t test was used for independent group analysis. In cases where there were more than two variables, one way ANOVA was performed. Pearson correlation test was used for correlation between numerical variables. Kaplan-Meier method was used for univariate analysis and log rank test was used to compare survival curves. In multivariate analyses, Cox regression model was used. Statistical significance was set at $p < 0.05$.

Results

The primary tumor was localized in the right testis in 305 (49.9%) patients and in 307 (50.1%) in the left testis. Mean patient age was 36 years (range 16-85).

Lymph node metastasis was observed in 322 (52.7%) patients, while 289 (47.3%) were metastasis-free. Of the patients 414 (67.6%) were diagnosed as stage 1 and 198 (32.4%) as stage 2 and stage 3. Patient data and treatment details are summarized in Table 1.

The median follow-up period was 47 months (1-298). Recurrence was observed in 78 patients (12.7%) and 29 (4.7%) died during the follow-up period. Four-year OS was 95.4% and 4-year PFS was 84.5% for all patients.

Detailed analysis of progression-free survival

4-year and 5-year PFS were 85.4 and 82.9%, respectively. Relapses were most commonly observed in the retroperitoneal region. Thirty-four patients (43.6%) had retroperitoneal metastasis, 21 (27%) mediastinal, 13 (16.7%) intrabdominal, 7 (9%) inguinal, and 2 (2.6%) had recurrence in the brain.

Of the relapses 45 (57.7%) were in right testicular tumors and 33 (42.3%) were observed in patients in left testicular tumor ($p = 0.14$). When all stages were evaluated together, there was no significant relationship between localization and relapse. When stage 1 patients were evaluated between themselves, there was no significant relationship between localization and relapse ($p = 0.19$). The relationship between localization and relapse was significant in stage 2 and 3 ($p = 0.003$).

A total of 197 patients were evaluated in stages 2-3. In this patient group, 41 (20.8%) relapses were observed. Thirty of the relapses were in tumors in the right testis (73.2%) and 11 (26.8%) of the tumors were in the left testis (Figure 1).

There was a significant relationship between PFS and nodal metastasis. Four-year PFS was 91.6% in node-negative patients and 77.6% in node-positive patients ($p < 0.001$), thus nodal metastasis was a risk factor for recurrence. The effect of nodal status on recurrence was also significant when evaluated by stage in multivariate analysis.

There was a significant relationship between stage and relapse. Four-year PFS was 90% in stage 1, 86% in stage 2, and 62.4% in stage 3 ($p < 0.001$), thus significantly higher relapses were observed in advanced-stage patients.

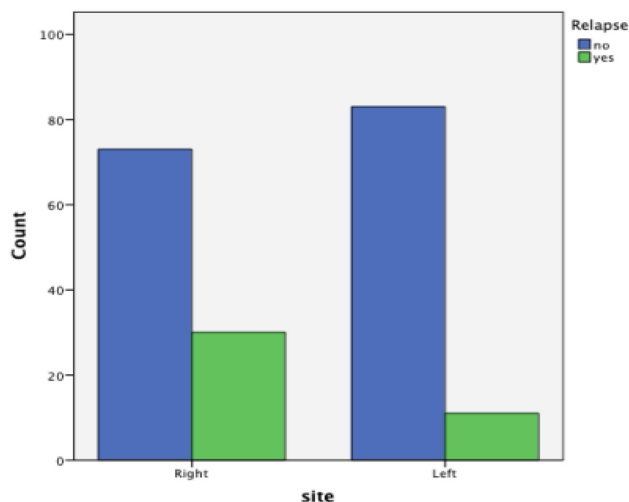


Figure 1. Relapse rate according to localization in stages 2-3 disease ($p = 0.003$).

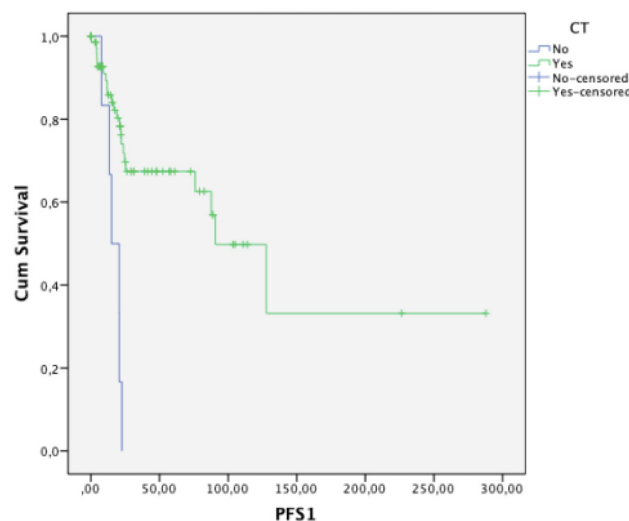


Figure 2. Effect of CT on PFS in right localized stage 3 tumors ($p < 0.001$).

The presence of metastasis at the time of diagnosis adversely affected PFS ($p < 0.001$). The 4-year PFS was 70.9% in patients with metastasis and 86% in patients without metastasis. Relapse after primary treatment was significantly higher in patients with metastasis at the time of initial diagnosis.

When the relationship between recurrences and the whole patient population was evaluated; no significant relationship between recurrence and chemotherapy (CT) was detected ($p = 0.33$). However, when multivariate analysis examined the effect of CT according to stage, the difference became significant ($p < 0.001$). In detailed analyses, the effect of CT on relapse was significant in stage 1 patients ($p < 0.018$); 4-year PFS in stage 1 patients receiving CT was 92.5% and 85.7% in those without CT. The contribution of CT in stage 2 patients was not

significant ($p < 0.81$). The positive effect of CT on PFS was especially significant in tumors located in the right testis. The positive effect of CT on PFS was also significant in stage 3 patients ($p < 0.001$) (Figure 2).

When CT was examined in detail, recurrence occurred in 43 (11.7%) of 343 patients who received CT in the first-line treatment [in 5 (3.4%) of 146 patients receiving carboplatin and in 34 (18.5%) of 184 patients receiving BEP]. Recurrence was observed in 1 (20%) of 5 patients who received EP ($p < 0.001$). Significantly higher recurrence rate was observed only in the arm receiving EP, and this significance persisted when corrected for stage in multivariate analysis.

Overall survival

In our study group, 4-year OS was 95.4% for all patients.

Four-year OS was 92.1% in patients with right tumor and 98.7% in patients with left tumor ($p = 0.007$), showing a 6.6% survival advantage in patients with left testicular ($p < 0.007$) (Figure 3).

No mortality was observed in the median 4-year follow-up period of patients receiving carboplatin, while 2 of the patients receiving BEP/EP died.

The relationship between lymphovascular invasion (LVI) and OS was significant ($p < 0.042$). Four-year OS was 93.8% in LVI positive patients and 98% in LVI negative patients (Figure 4).

When the relationship between stage and OS was evaluated, lower OS was seen in advanced stage as expected ($p < 0.001$). Four-year OS stage 1 patients was 98.5%, 95.5% for stage 2 patients and 79.8% for stage 3 patients.

When relapsed/refractory patients were evaluated, 4-year OS was 80.6% in salvage CT patients and 59.4% in non-salvage patients ($p = 0.028$). Although the difference was not significant, OS was higher in relapsed/refractory patients receiving salvage CT. No significant relationship was found between OS and different salvage CT protocols ($p > 0.05$).

Discussion

Seminomas are chemosensitive and radiosensitive tumors. Although their sensitivity is high, the long-term side effects of radiotherapy and chemotherapy and especially long-term survival data of stage 1 seminoma with only active surveillance are controversial in determining the optimal treatment of patients [8,9].

Although in non-seminoma GCT recurrences after 5 years follow-up are rare, recurrences of sem-

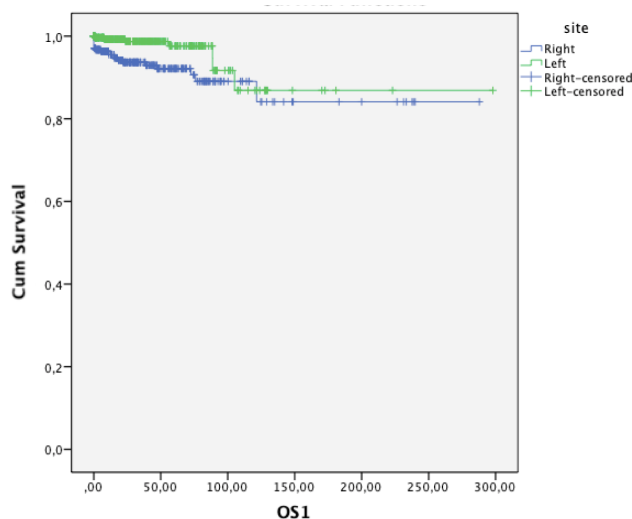


Figure 3. The relationship between localization and overall survival (OS) ($p < 0.007$).

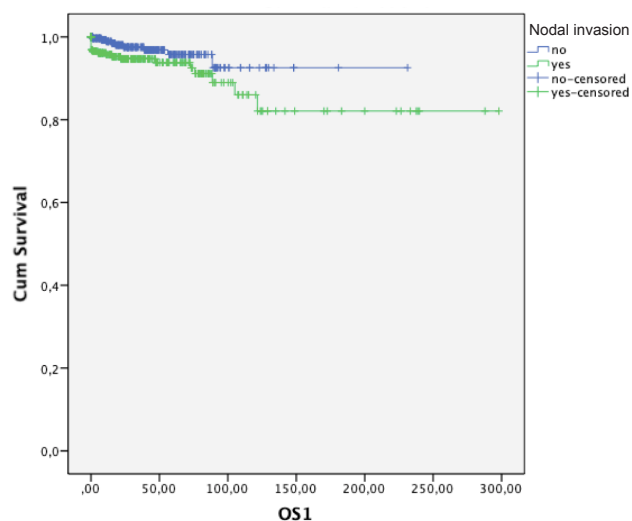


Figure 4. Relationship between nodal invasion and overall survival (OS) ($p < 0.042$).

inoma GCT patients can be quite high and therefore these patients need to be followed for at least 10 years [10].

In recent studies, designs have been planned to reveal risk factors for identifying high-risk patients in terms of recurrence in order to reduce side effects due to late recurrences and treatments [11,12]. In our study, we aimed to evaluate the effect of primary tumor location on recurrence and survival which have not been evaluated as a risk factor.

Evaluation of the human anatomy shows that the lymphovascular structures of the double organs are asymmetric and the disease incidence and prognosis of the right and left organs are also different due to the asymmetric structure [13]. To demonstrate the effect of primary tumor localization on survival a study designed by Roychoudhuri et al including breast, lung, kidney, testicular and ovarian cancer patients revealed that patients with left testicular cancer had better survival rates ($p=0.05$) [7]. When 612 patients were evaluated with a mean follow-up of 4 years, there was a 6.6% survival advantage in left localized tumors and this difference was significant ($p<0.007$).

The median follow-up period of our study was 47 months (1-298). Recurrence was observed in 78 (12.7%) patients and 29 (4.7%) patients died during the follow-up period. This study showed that 5-year PFS was 82.9%, relapses were most common in the retroperitoneal region (43.6%), and a significant relationship was found between stage and relapses. PFS was 90% for 4 years in stage 1, 86% for 4 years in stage 2, and 62.4% for stage 3 in 4 years ($p < 0.001$). According to IGCCC data, 5-year PFS is 90%, 67% in stage 1 and stage 3 patients [3], respectively, and shows that our data are consistent with the literature.

In a study planned by Haugnes et al which included seminoma patients, the 5-year relapse-free survival rate was 95% [14]. In this study, the rate of stage 1 patients with good PFS was 85% compared to 67.6% in our study. In another study involving seminoma patients by Torgrim Tandstad et al, relapse-free interval was 92.6% [12]. The present study has shown that advanced-stage seminoma cases are very rare (3%) but the rate of stage 3 patients was 13.1% and it was concluded that the decrease in the rate of PFS was due to these patients.

When all patients were evaluated in terms of relapse, no significant relationship was found between primary tumor localization and relapse. In stage 1 patients 30 (73.2%) patients with right primary testicular localization developed relapse, in contrast to 11 (26.8%) patients with left testicular localization. The reason for this difference is that

the right testis is connected directly to the vena cava inferior and can pass to more systemic circulation due to more blood supply and less pressure [7].

In a study involving 232 seminoma patients by Haugnes et al, 5-year OS was 95% [14]. In our study, the 4-year OS was 95.4% for all patients and was similar to the literature. In a study by Tandstad et al 5-year OS was 98.1% in 1384 seminoma patients [12]. This take was considered to be higher in our study and we think that the reason for this was that the rate of stage 3 patients with poorer survival time was 3% of all cases. In our study, the percentage of stage 3 patients was 13.1%. When the effect of tumor localization was evaluated in terms of survival, 4-year OS was 92.1% in patients whose primary mass was localized in the right testis and 98.7% in patients with left localization ($p<0.007$). In our study on non-seminomatous patients, when the factors affecting survival were evaluated, it was found that the localization of the primary mass in the right testicle was worse than the localization in the left testicle ($n=337.6$ months vs. not reached, $p=0.001$) [15].

When CT protocol was examined in detail, recurrence occurred in 43 (11.7%) of 343 patients who received CT in the first-line treatment: in 5 (3.4%) of 146 patients receiving carboplatin; in 34 (18.5%) of 184 patients receiving BEP; and in 1 (20%) of 5 patients receiving EP ($p<0.001$). In previous studies, the relapse rate in patients receiving adjuvant carboplatin was between 1.4% and 5.0% [12,16,17]. In our study, the rate of relapse was 3.4%, which is consistent with the literature, and in our study, as in other studies, relapse was most common in the retroperitoneal region [12,17].

Pathologically, nodal status was found to be a risk factor for recurrence. The effect of nodal metastasis on recurrence is also significant when evaluated according to stage by multivariate analysis. In their study, Horwich et al [18] and Von de Maase H et al [19], it was stated that primary tumor diameter and vascular invasion status were significant in terms of relapse. In the present study, 4-year OS was 93.8% in nodal-positive patients and 98% in nodal-negative patients. Nodal status had also a significant effect on OS ($p<0.042$). There was a significant relationship between PFS and lymph node status. Four-year PFS was 91.6% in node-negative patients and 77.6% in node-positive patients ($p<0.001$). Collectively, in our study it was observed that there was a significant correlation between nodal status and both OS and PFS, in accordance with the literature.

The weak points of this study were the short follow-up period and its retrospective nature. The study was performed in a heterogeneous group of

patients. The strengths of the study were its multicenter nature and research has been conducted on a large patient population. Its subject which has anatomical basis but has been underestimated has been studied in a large population.

In conclusion, the primary risk factor for relapse and survival caused by primary testicular localization, which has not been evaluated in the literature before, has been evaluated in detail in a large multicenter patient population. Survival rates of the patients with primary tumor with right

localization were worse than those with primary tumor with left localization, and the relapse rates were higher in stage 2 and stage 3 patients with right testicular localization. Evaluating the study in a prospective design will be more clear in determining the effectiveness of primary tumor localization as a risk factor for survival and relapse.

Conflict of interests

The authors declare no conflict of interests.

References

- Groll RJ, Warde P, Jewett MA. A comprehensive systematic review of testicular germ cell tumor surveillance. *Crit Rev Oncol Hematol* 2007;64:182.
- Warde P, Gospodarowicz M. Evolving concepts in stage I seminoma. *BJU Int* 2009;104:1357.
- International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. *J Clin Oncol* 1997;15:594.
- Ko JJ, Bernard B, Tran B et al. Conditional Survival of Patients With Metastatic Testicular Germ Cell Tumors Treated With First-Line Curative Therapy. *J Clin Oncol* 2016;34:714.
- Gilligan T. Testicular cancer survivorship. *Hematol Oncol Clin North Am* 2011;25:627.
- Weinstein MH. Lymphatic Drainage of the Testes. In: *Atlas of the Urologic Clinics of North America: Testis Cancer*, Rowland RG (Ed), W.B. Saunders Company, Philadelphia 1999, p.1.
- Roychoudhuri R, Putcha V, Moller H. Cancer and laterality: a study of the five major paired organs (UK). *Cancer Causes Control* 2006;17:655-62.
- Susanne Kregge, Jörg Beyer, Rainer Souchon et al. European Consensus Conference on Diagnosis and Treatment of Germ Cell Cancer: A Report of the Second Meeting of the European Germ Cell Cancer Consensus group (EGCCCG): Part I. *Eur Urol* 2008;53:478-96.
- Beyer J, Albers P, Altena R et al. Maintaining success, reducing treatment burden, focusing on survivorship: highlights from the third European consensus conference on diagnosis and treatment of germ-cell cancer. *Ann Oncol* 2013;24:878-88.
- Kollmannsberger C, Tandstad T, Bedard PL et al. Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. *J Clin Oncol* 2015;33:51-7.
- Tandstad T, Dahl O, Cohn-Cedermark G et al. Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. *J Clin Oncol* 2009;27:2122-8.
- Tandstad T, Smaaland R, Solberg A et al. Management of seminomatous testicular cancer: a binational prospective population-based study from the Swedish norwegian testicular cancer study group. *J Clin Oncol* 2011;29:719-25.
- Akbay E, Cayan S, Doruk E, Duce MN, Bozlu M. The prevalence of varicocele and varicocele-related testicular atrophy in Turkish children and adolescents. *BJU Int* 2000;86:490-3.
- Haugnes HS, Solhaug Ø, Stenberg J, Hjelle LV, Bremnes RM. Seminoma patients treated at a minor oncological department during 1986-2010: treatment and outcome. *Anticancer Res* 2014;34:4253-60.
- Yildiz B, Esin E, Basgoz BB, Erturk I, Acar R, Karadurmus N. The Effects Of Primary Testicular Tumor Localization On Prognosis In Patients With Nonseminomatous Testis Cancer. *Ann Oncol* 2019;30 (suppl_5): v356-v402. 10.1093/annonc/mdz249.
- Mead GM, Fossa SD, Oliver RTD et al. Randomized trials in 2466 patients with stage I seminoma: patterns of relapse and follow-up. *J Natl Cancer Inst* 2011;103:241-9.
- Aparicio J, Maroto P, del Muro XG et al. Risk-adapted treatment in clinical stage I testicular seminoma: the third Spanish Germ Cell Cancer Group study. *J Clin Oncol* 2011;29:4677-81.
- Horwich A, Alsanjari N, A'Hern R et al. Surveillance following orchidectomy for stage I testicular seminoma. *Br J Cancer* 1992;65:775-8.
- Von der Maase H, Specht L, Jacobsen GK et al. Surveillance following orchidectomy for stage I seminoma of the testis. *Eur J Cancer* 1993;29A:1931-4.