doi:10.4149/neo_2009_06_473

Damage of hormonal function and bone metabolism in long-term survivors of testicular cancer

M. ONDRUSOVA[1,2*], D. ONDRUS[3,4], L. DUSEK[2], B. SPANIKOVA[5]

[1]Department of Cancer Epidemiology, Cancer Research Institute, Slovak Academy of Sciences, Bratislava, Slovak Republic; e-mail: martinacuninkova@hotmail.com, [2] Institute of Biostatistics and Analyses, Masaryk University, Brno, Czech Republic; [3]1st Department of Oncology, Comenius University, Faculty of Medicine, St. Elisabeth Cancer Institute, Bratislava, Slovak Republic; [4]National Cancer Registry of the Slovak Republic, National Health Information Center; Bratislava, Slovak Republic; [5]Out Patient`s Department of Osteology, St. Elisabeth Cancer Institute, Bratislava, Slovak Republic

Received March 3, 2009

Improved survival of testicular cancer (TC) patients leads to rising of interest on the disease consequences for the whole organism (impact on hormonal status, bone metabolism). The aim of the study was to present three years experience with hormonal and osteologic examination in long-term survivors of TC. During the period of 11/2005-1/2009 879 patients who were previously treated for TC (823 with unilateral, 56 with bilateral disease) were examined. Each patient underwent hormonal and osteologic examination, results of which were associated with therapy following orchiectomy and with the time interval since the primary therapy. The median follow-up time in patients with unilateral TC was 96 months since the therapy. Mean age at the time of examination was 32 years. Testosterone deficiency was observed in 171 patients (19.5%), increased LH in 168 patients (19.1%), increased S-CTx in 388 patients (44.1%). Bone damage (osteopenia and/or osteoporosis) was observed in 445 patients (50.6%). The median follow-up time in patients with bilateral TC was 175 months. Mean age at the time of examination was 27 years. Testosterone deficiency was observed in 47 patients (83.9%), increased LH in 45 patients (80.4%), increased S-CTx in 31 patients (55.4%). Bone damage was observed in 41 patients (73.2%). Hormonal examination and testosterone substitution may be recommended as an important aspect of patient´s follow-up in bilateral TC, moreover in unilateral disease. The important part of standard examination algorithm should be also osteological examination to prevent osteopenia or even osteoporosis development.

Key words: bone densitometry, post-treatment hypogonadism, testicular cancer

Testicular cancer is quite a rare malignancy, but their medical and social importance has come out from a rapid growth of the incidence in the last decades and decrease or stabilisation of mortality rates in the last years. Improved survival of testicular cancer patients during the last decades with last published age-adjusted 5-year survival – 94.2% (95 CI 93.4-04.0) [1] leads to rising interest on the disease consequences for the whole metabolism. Testicular cancer belong to ethiologic factors leading to male hypogonadism [2, 3]. Decreased testosterone level may lead to the symptoms of androgen deficiency with subsequent negative impact on to the patients quality of life.

Not only the tumor alone, but also its treatment (mainly radiotherapy or chemotherapy) may have impact on patients´ hormonal status and bone metabolism [4]. Hypertension, dyslipidemia, obesity and insulin resistance are components of the metabolic syndrome many times described in patients after systemic chemotherapy, which may increase risk of cardiovascular disease development [5]. Gonadal dysfunction is supposed to be a long-term complication of antitumor therapy. Patients, who were treated for testicular cancer, have higher risk of hypogonadism development than the healthy male population [6]. Hypogonadism may be associated with osteoporosis [2, 7].

The aim of this study is to assign the claim of hormonal profile examination and complete osteological examination into algorithm of follow-up not only in patients with bilateral disease, but also in patients with unilateral testicular tumor. It is to propose, that prolonged testosterone substitution and osteologic treatment can lead to improvement of the bone metabolism parameters in patients with hormonal deficiency and concomitant decrease of bone density.

* Corresponding author

Patients and methods.

This is a single-center retro-prospective study, where osteological examination was performed in 879 male patients who were previously treated for testicular cancer, examined during the period of 11/2005-1/2009. Out the whole group of 823 patients were with unilateral (group A) and 56 patients with bilateral (group B) disease. Patients with bilateral TC received no androgen replacement therapy or inadequate/insufficient replacement therapy before beginning of this study.

BMD measurements were made by dual-energy x-ray absorptiometry (DEXA) using a Hologic Explorer imaging bone densitometer (QDR Explorer, Hologic, Inc., Bedford, MA, USA) at the lumbal spine (L1-L4), hips and forearms. The results of DEXA scans were discussed with patients and advice was given about lifestyle issue and, where appropriate, bone-specific treatments.

DEXA measures BMD in grams per centimeter squared (g/cm^3) and is considered the gold standard. The DXA g/cm^3 result is compared to „young adult" normals of the same sex (T-score). The difference between the patients´s score and the norm is expressed in standard deviation (SD) above or below the mean. The WHO defines a normal BMD as a T-score equal to, or greater than, - 1, osteopenia or low bone mass as a T-score less than – 1 SD but greater than – 2.5, and osteoporosis as a T-score less than or equal to – 2.5 [8].

Blood samples for biochemical and hormone measurements were taken from each patients at the time of the DEXA scan as part of the study. Each patient was examined for luteinising hormone (LH) (normal value 1.8-8.2 mU/ml) and serum testosterone (normal value 12.0-28.0 nmol/l) using chemiluminescent microparticle immunoassay by Architect-2000 SR (fy Abbot Lab., Diagnostic Division, Abbot Park, IL, USA), marker of bone resorption – S-CTx (serum C-terminal cross-linking telopeptides of type I collagen) (normal value 0.130-0.480 ng/ml) by enzyme immunoassay with serum Crosslaps ELISA (fy IDS Immunodiagnostic system, Boldon, UK) and serum calcium (normal value 2.20-2.80 mmol/l) by indirect potenciometry with Synchron LX system (fy Beckman Coulter, Fullerton, CA, USA).

Results of the osteologic examination and hormonal profile examination were associated with therapy following orchiectomy (orchiectomy alone, chemotherapy, radiotherapy, chemotherapy and radiotherapy) and with the time interval since the primary therapy.

All key analyses were carried out separately for unilateral and bilateral tumors. Log-normally distributed follow-up time was summarized using rank statistics, median and 5^{th}-95^{th} percentile range. Other quantitative variables were summarized using mean estimate supplied with standard error (SE). Standard univariate statistical techniques were used to test the differences between groups of patients (ML chi-square test, one-way ANOVA). Unconditional logistic regression was used to relate potential risk factors to osteopenia and/or osteoporosis. All odds ratio estimates were adjusted for patient's age at the time of osteologic examination and supported with estimate of 95% confidence interval (95% CI).

Results

During the period of 11/2005-1/2009, we examined 879 patients with testicular cancer after a median follow-up of 96 months (5-95 % percentile 18-255, range 3-462).

Group A: 823 patients with unilateral testicular cancer were followed-up for a median period of 89 months (5^{th}-95^{th} percentile range 18-248, range 3-353) since the primary therapy – orchiectomy (OE). Time to examination was 6.1 (0.3-20.0) years since primary diagnosis. Mean age at the time of examination was 32 years, SD 9.0 (range 14-68). (Table 1). Testosterone deficiency (<12.0 nmol/l) was observed in 124 patients (15.1%). Normal LH levels by mean were 5.1 mU/ml (SD 3.0). Increased LH (>8.2 mU/ml) was observed in 123 patients (15.0%). Increased S-CTx (>0.480 ng/ml) was observed in 357 patients (43.4%). Primary distribution of LH and TST levels is documented in Figure 1. DEXA shows osteopenia and/or osteoporosis in 404 patients (49.1%). Serum calcium levels were in all cases in normal value.

Group B: 56 patients with bilateral testicular cancer were followed-up for a median period of 175 months (5^{th}-95^{th} percentile range 37-347, range 13-462) since the beginning of the therapy (Table 2). Time to examination was 12.5 (1.3-26.2) years since primary diagnosis. Testosterone deficiency was observed in 47 patients (83.9%). Increased level of serum LH was observed in 45 patients (83.9%). Increased S-CTx was observed in 31 patients (55.4%). Primary distribution of LH and TST levels is documented in Figure 1. DEXA shows osteopenia and/or osteoporosis in 41 patients (73.2%). Serum calcium levels were in all cases in normal value. Bilateral cancer is associated with significantly increased incidence of both osteopenia and osteoporosis.

Influence of age at examination and time to examination: Age at the time of examination was significantly higher in patients with osteoporosis (on average by 7 years) both in unilateral ($p<0.001$) and bilateral ($p = 0.039$) tumors. The risk of osteopenia and/or osteoporosis increased with continuously increasing time since primary therapy in unilateral tumors (OR = 1.02, 95% CI: 1.01–1.04, $p<0.05$). Furthermore, significant risk cut-off time points were found both for unilateral tumors (> 8 years, OR = 1.10, 95% CI: 1.03–1.54, $p < 0.05$) and bilateral tumors (> 10 years, OR = 1.96, 95%CI: 1.02–7.92, $p < 0.05$). In bilateral tumors, time > 10 years since 2^{nd} testicular cancer diagnosis was proved as additional component contributing significantly to the risk of osteoporosis (OR =3.38, 95% CI: 1.07-1.77). Age at time of examination is closely associated with osteoporosis as it is documented in Table 1 both for unilateral and bilateral cancer. Therefore, all ORs estimated for potential risk factors (Table 2) are calculated as age-adjusted in order to minimize the risk of bias.

Influence of primary therapy: In unilateral disease, applied chemotherapy (CHT) and/or radiotherapy (RT) increased

Table 1. Osteopenia and osteoporosis in relation to age and time to examination [1]

1A Unilateral tumors (N = 823)

Categories	Age at examination (years)		Time to examination (years since diagnosis)	
Overall coding				
Normal (N = 419)	38.6	(10.6)a	7.2	(6.4) a
Osteopenia (N = 301)	39.1	(9.5) a	7.8	(6.4) a
Osteoporosis (N = 103)	43.2	(9.7) b	8.0	(6.5) a
	p < 0.001		p = 0.352	
Osteoporosis or osteopenia: specific impairment				
Impairment of cord (N = 217)	40.4	(9.4)*	7.6	(6.2)
Overall impairment (N = 150)	39.4	(9.8)	8.1	(6.8)
Other local impairment (N = 37)	41.9	(11.0)	8.0	(6.3)

1B Bilateral tumors (N = 56)

Categories	Age at examination (years)		Time to examination (years)			
			Since 1st dg		Since 2nd dg	
Overall coding						
Normal (N = 15)	36.1	(6.8) a	11.2	(7.3) a	4.2	(5.4) a
Osteopenia (N = 28)	43.9	(10.4) b	15.1	(7.5) a	5.5	(6.1) a
Osteoporosis (N = 13)	41.7	(9.9) b	13.1	(8.9) a	7.9	(7.5) a
	p=0.039		p=0.289		p=0.301	
Osteoporosis or osteopenia: specific impairment						
Impairment of cord (N = 19)	40.4	(7.7)	12.2	(6.7)	4.4	6.0)
Overall impairment (N = 20)	44.5	(12.4)*	15.8	(8.5)	7.8	(6.7)
Other local impairment (N = 2)	44.1	NA	22.3	NA	8.5	NA

[1] Age and time to examination expressed as arithmetic mean and standard deviation (in parentheses); p value: significance level of one-way ANOVA model on log-transformed data

[a-b] mark of statistical difference among three variants (normal, osteopenia, osteoporosis) as tested in one-way ANOVA on log-transformed data: variants marked by the same letter are not significantly different

* mark of statistical significance of a given category of specific impairment against normal variant (p< 0.05; one-way ANOVA model)

NA: not assessed due to limited sample size

significantly LH level, and applied CHT+RT significantly decreased TST and CTX level; no such influence was found in bilateral disease (Figure 2). Increased LH and decreased TST levels (as compared with overall average values) were observed namely in case of seminoma treated by RT. In unilateral disease, applied RT increased significantly age-adjusted risk of osteopenia and/or osteoporosis (OR=1.23, 95% CI: 1.02-1.89, p<0.05). Application of radiotherapy specifically increased age-adjusted risk of lumbar spine BMD impairment (OR = 1.26; 95% CI: 1.01-2.03, p<0.05). Radiotherapy was also significantly associated with increased TST and decreased LH levels at the time of examination in unilateral disease. In bilateral tumors, no significant association between therapy and risk of osteoporosis was found. It can be explained by very significant risk potential of cancer bilaterality itself. Bilaterality reached highly significant odds ratio for osteoporosis (OR = 3.34, 95% CI: 1.44-7.31, p<0.001) as well as for osteoporosis + osteopenia (OR = 2.57; 95% CI: 1.42-5.02, p<0.001).

Discussion.

Cancer therapies, including hormone therapy, chemotherapy, radiation therapy, and surgical castration, can directly or indirectly damage bone, resulting in loss of bone mass (i.e. osteopenia and osteoporosis) [9]. In our patients applied therapy increased significantly age-adjusted risk of osteopenia and/or osteoporosis as aggregated endpoint. It can dramatically reduce bone density and increase the rate of bone alteration and the risk of fragility fractures [10]. There are several etiologies of bone metabolism disorders, including low serum sex hormone levels. Male hypogonadism is an important and treatable cause of osteopenia and/or osteoporosis [11]. Patients with testicular cancer receiving therapies known to

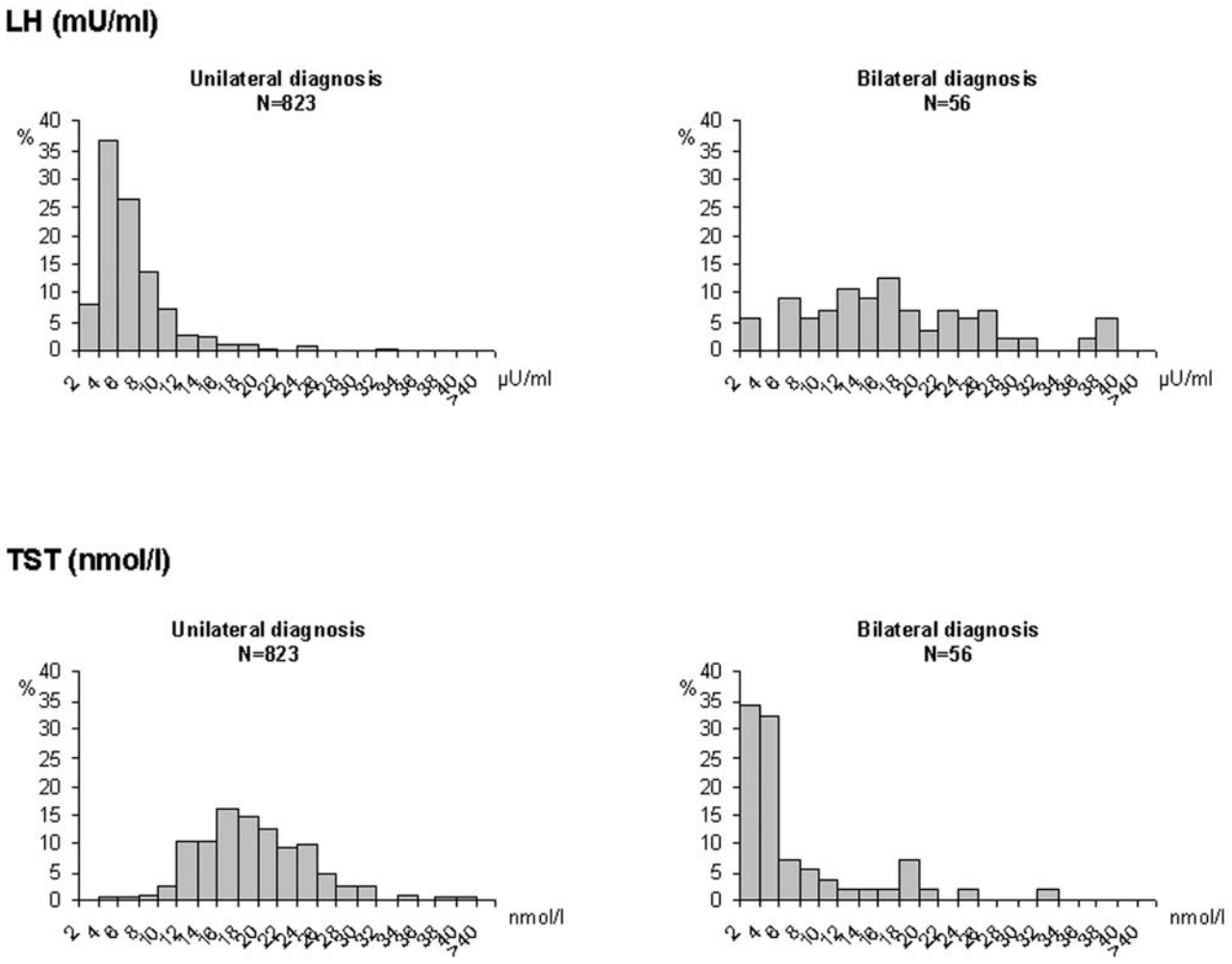

Figure 1. Sample distribution of LH and TST values in unilateral and bilateral tumors

cause hypogonadism are also at risk for developing cancer-treatment-induced bone loss [9].

Testicular germ-cell cancer patients are at risk of developing Leydig cell insufficiency. Different treatment modalities, such as orchiectomy, chemotherapy and radiotherapy may also affect the Leydig cell function [12]. A Leydig cell impairment with subnormal/normal serum testosterone values, and/or increased luteinizing hormone (LH) was found in patients who underwent chemotherapy [13]. In our patients LH abnormality increased significantly both due to chemotherapy and radiotherapy (from 5% in patients treated only with orchiectomy to nearly 20% under CHT/RT therapy). However, in other studies, no difference in testosterone or LH after chemotherapy was found [14]. These discrepancies might be due to differences in the chemotherapy regimen used, doses and also the lenght of follow-up [12]. Analysis of Murugaesu et al showed no evidence in association between cases of osteopenia and lenght of follow-up [15].

Effect of different therapeutic approaches in testicular cancer on testicular function is well described in the literature [16]. Damage of gonadal function and subnormal levels of TST were described not only in patients, following chemotherapy or radiotherapy, but also in subjects who are long-term survivors following orchiectomy alone. No significant differences were found in hormonal levels of TST and LH between the chemotherapy and surveillance (orchiectomy alone) groups [15]. Lackner et al [16] detected hypogonadism and androgen deficiency symptoms in 26.5% of patients after testicular cancer treatment, irrespective of the treatment strategy. In our patients bilateral tumors are associated with highly decreased levels of TST and increased levels of LH, but there is only limited space for occurrence of abnormal value among unilateral tumors. Several authors describe that bone density in hypogonadal men of all ages improves under TST replacement [17, 18].

In conclusion, based on the analysis of the laboratory tests of patients with testicular tumors, it has been shown

Table 2.
Potential risk factors and their relation to osteopenia and/or osteoporosis evaluated by logistic regression models

2A. Unilateral tumors (N = 823)

Risk factor and its incidence (N)	I. Osteopenia or Osteoporosis		II. Osteoporosis		III. Impairment of cord	
	– Age-adjusted OR [1] –					
Time since 1st diagnosis						
Continuous in years	1.02	(1.01 – 1.04)*	0.98	(0.94 – 1.01)	0.99	(0.97 – 1.02)
> 8 years	1.10	(1.03 – 1.54)*	0.86	(0.54 – 1.36)	0.95	(0.67 – 1.35)
Primary therapy /referent: only OE/						
OE +CHT	1.19	(0.85 – 1.66)	1.12	(0.66 – 1.91)	1.01	(0.69 – 1.48)
OE +RT	1.16	(1.01 – 1.80) *	1.27	(0.67 – 2.43)	1.33	(1.06 – 2.16)*
OE +CHT+RT	2.38	(0.69 – 8.17)	1.52	(0.30 – 7.69)	0.58	(0.12 – 2.74)
RT in total	1.23	(1.02 – 1.89) *	1.30	(0.69 – 2.44)	1.26	(1.01 – 2.03)*
CHT in total	1.21	(0.87 – 1.69)	1.13	(0.67 – 1.92)	1.00	(0.68 – 1.46)

[1] ORs supported by 95% CI (in parentheses); adjusted for age at time of examination (entered as continuous variable in years)
* Statistically significant OR ($p < 0.05$)

2B. Bilateral tumors (N = 56)

Risk factor and its incidence (N)	I. Osteopenia or Osteoporosis		II. Osteoporosis		III. Impairment of cord	
	– Age-adjusted OR [2] –					
Time since 1st diagnosis						
Continuous (in years)	1.01	(0.91 – 1.11)	1.00	(0.91 – 1.10)	0.96	(0.88 – 1.05)
> 10 years	1.96	(1.02 – 7.92) *	1.26	(0.30 – 5.31)	1.31	(0.37 – 4.67)
Time since 2nd diagnosis						
Continuous (in years)	1.00	(0.88 – 1.14)	1.13	(0.99 – 1.29)	0.94	(0.85 – 1.05)
> 10 years	0.66	(0.12 – 3.55)	3.38	(1.07 – 10.77)*	0.42	(0.09 – 1.90)
Primary therapy [2] /referent: only OE in primary therapy/						
OE +CHT	1.82	(0.39 – 8.48)	1.23	(0.27 – 5.65)	1.52	(0.39 – 5.90)
OE +RT	0.76	(0.14 – 4.16)	0.86	(0.13 – 5.63)	0.49	(0.08 – 2.84)
Therapy of 2nd tumor [2] /referent: only OE in 2nd therapy/						
OE +CHT	0.75	(0.17 – 3.26)	1.38	(0.31 – 6.25)	0.72	(0.17 – 2.94)
OE +RT	0.72	(0.12 – 4.24)	1.25	(0.22 – 7.00)	1.54	(0.34 – 6.89)

[1] ORs supported by 95% CI (in parentheses); adjusted for age at time of examination (entered as continuous variable in years)
[2] Regimen OE+RT+CHT could not be evaluated due to low sample size (N = 2)

* Statistically significant OR ($p < 0.05$)

that the decreased testosterone level may appear also in patients after unilateral orchiectomy. Further evidence has been accumulated and indicates that the majority of patients with bilateral testicular cancer treated by hormonal substitution therapy, are in fact cured inadequately. This is why the proposed hormonal profile examination should be performed before hormonal treatment initiation as an indispensable part of the examination algorithm, indicated not only in cases with bilateral tumor occurrence, but also in patients with unilateral testicular tumor. Examination of hormonal status along with the comprehensive osteologic examination should be implemented into the standard examination of followed-up patients, since the testosterone replacement therapy may block the early development of osteopenia and osteoporosis in testicular tumor long-term survivors.

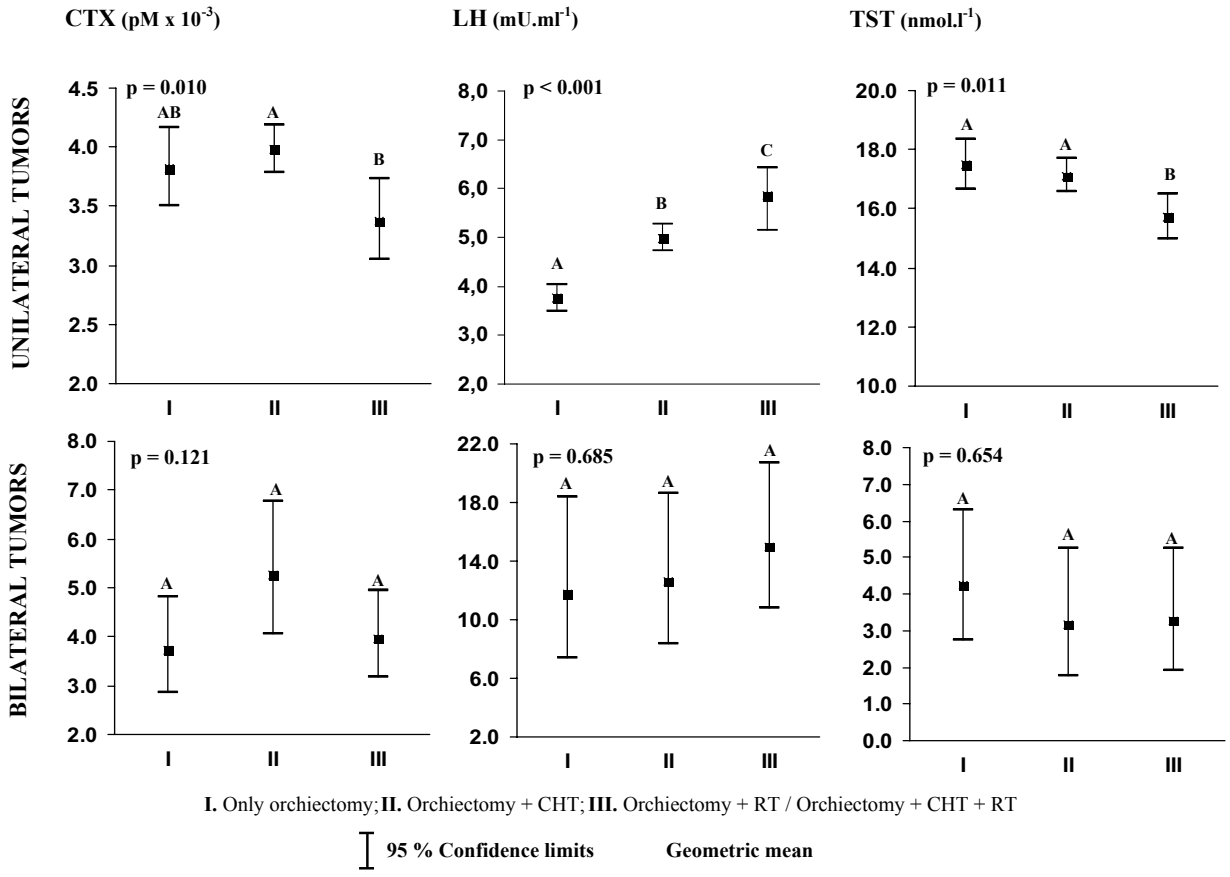

Figure 2. Biochemical markers in relation to modality of cancer therapy

p value: one ANOVA model; A-C: marks of statistical significance - therapeutic regimens I-III marked by the different letter are mutually statistically significant ($p < 0.05$).

References

[1] BERRINO F, DE ANGELIS R, SANT M et al. Survival for eight major cancers and all cancers combined for European adults in 1995-1999: results of the EUROCARE-4 study. Lancet Oncology, 2007; 8, 773–783. doi:10.1016/S1470-2045(07)70245-0

[2] DOHLE GR, JUNGWIRTH A, COLPI G et al. Guidelines on Male inferility. Arnhem EAU 2008.

[3] NIESCHLAG E, BEHRE HM. Testosterone: Action, Deficiency, Substitution. 2nd ed: Berlin, Springer Verlag 1998.

[4] FINKELSTEIN, JS Androgens and bone metabolism, pp. 178–207. In: Nieschlag E, Behre HM, editors. Testosterone: Action, Deficiency, Substitution. 2nd ed: Berlin, Springer Verlag 1998.

[5] HUDDART RA, NORMAN A, MOYNIHAN C et al. Fertility, gonadal and sexual function in survivors of testicular cancer. Br J Cancer 2005; 93: 200–207. doi:10.1038/sj.bjc.6602677

[6] NUVER J, SMIT AJ, WOLFFWENBUTTEL HR et al. The metabolic syndrome and disturbances in hormone levels in long-term survivors of disseminated testicular cancer. J Clin Oncol 2005; 23: 3718–3725. doi:10.1200/JCO.2005.02.176

[7] NORD C, BJORO T, ELLINGSEN D et al. Gonadal hormones in long-term survivors 10 years after treatment for unilateral testicular cancer. Eur Urol 2003; 44: 322–328. doi:10.1016/S0302-2838(03)00263-X

[8] LONDEN VAN GJ, TAXEL P, POYNAK VAN C. Cancer therapy and osteoporosis: approach to evaluation and management. Sem Oncol 2008; 35: 643–651. doi:10.1053/j.seminoncol.2008.08.008

[9] BOEHNKE MICHAUD L, GOODIN S Cancer-treatment-induced bone loss, part 1. Am J Health Syst Pharm 2006; 63: 419–430. doi:10.2146/ajhp050045.p1

[10] KHAN MN, KHAN AA. Cancer treatment – related bone loss: a review and synthesis of the literature. Curr Oncol 2008; 15: Suppl. 1, S30–S40. doi:10.3747/co.2008.174

[11] DUPREE K, DOBS A. Osteopenia and male hypogonadism. Rev Urol 2004; 6: Suppl. 6, S30–S34.

[12] EBERHARD J, STAHL O, CWIKIEL M et al. Risk factors for post-treatment hypogonadism in testicular cancer patients. Eur J Endocrinol 2008; 158: 561–570.

[13] FOSSA SD, LEHNE G, HEIMDAL K et al. Clinical and biochemical long- term toxicity after postoperative cisplatin-based chemotherapy in patients with low-stage testicular cancer. Oncology 1995; 52: 300–305.

[14] PETERSEN PM, HANSEN SW, GIWERCMAN A et al. Dose-dependent impairment of testicular function in patients treated with cisplatin-based chemotherapy for germ cell cancer. Ann Oncol 1994; 5: 355–358.

[15] MURUGAESU N, POWLES T, BESTWICK J et al. Long-term follow-up of testicular cancer patients shows no predisposition to osteoprosis. Osteoporos Int 2008 (epub ahead of print) doi:10.1007/s00198-008-0793-x

[16] LACKNER JE, MÄRK I, SCHATZL G et al. Hypogonadism and androgen deficiency symptoms in testicular cancer survivors. Urology 2008; 69: 754–758. doi:10.1016/j.urology.2007.01.002

[17] WANG C, NIESCHLAG E, SWERDLOFF R et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. Eur J Endocrinol 2008; 159: 507–514. doi:10.1530/EJE-08-0601

[18] TUCK SP, FRANCIS RM. Testosterone, bone and osteoporosis, pp. 121–130. In: Jones TH (editor). Advances in the management of testosterone deficiency. Front Horm Res. Basel, Karger 2008, Vol. 37.