Sexual Function in a Nationwide Cohort of 2,260 Survivors of Testicular Cancer after 17 Years of Followup

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Purpose: Evidence on the long-term impact of testicular cancer treatment on sexual function is not clear. Our aim was to estimate the effect of testicular cancer treatment on the risk of sexual dysfunction in long-term survivors of testicular cancer.

Materials and Methods: We performed a cross-sectional study of 2260 long-term survivors of testicular cancer with a median followup of 17 years (IQR 12–24), including 1,098 who underwent orchiectomy alone (surveillance), 788 treated with bleomycin, etoposide and cisplatin alone or post-chemotherapy retroperitoneal surgery, 300 treated with abdominal radiotherapy and 74 who received more than 1 line of treatment. Sexual function was evaluated by the IIEF-15 (International Index of Erectile Function) questionnaire. Results were compared between treatment groups using logistic regression analysis with the results on each of the 5 IIEF-15 dimensions as the outcome and treatment as exposure using surveillance as the referent.

Results: The risk of erectile dysfunction was increased in all treatment groups compared to surveillance, including bleomycin, etoposide and cisplatin alone (OR 1.5, 95% CI 1.0–2.1, p <0.05), bleomycin, etoposide and cisplatin with post-chemotherapy surgery (OR 2.1, 95% CI 1.4–3.4, p <0.005), radiotherapy (OR 1.7, 95% CI 1.1–2.5, p <0.05) and more than 1 line of treatment (OR 3.2, 95% CI 1.6–6.3, p <0.005). Orgasmic dysfunction was associated with radiotherapy, bleomycin, etoposide and cisplatin with post-chemotherapy surgery and more than 1 line of treatment.

Conclusions: Treatment with bleomycin, etoposide and cisplatin, radiotherapy and more than 1 treatment line increased the risk of erectile dysfunction in long-term survivors of testicular cancer compared to surveillance. Patients should be informed about this as part of the information on treatment related late effects.

Key Words: testicular neoplasms, erectile dysfunction, radiotherapy, drug therapy, survivors

Abbreviations and Acronyms

BEP = bleomycin, etoposide and cisplatin

DaTeCa = Danish Testicular Cancer

HADS = Hospital Anxiety and Depression Scale

IIEF-15 = International Index of Erectile Function-15

MTOL = more than 1 treatment line

PDE5 = phosphodiesterase type 5

RT = radiotherapy

TC = testicular cancer

TCS = TC survivor

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As the majority of patients with TC become long-term survivors,[1] addressing patient reported late effects such as sexual dysfunction after TC treatment becomes increasingly important. In a systematic review Nazareth et al reported a significantly increased risk of ejaculatory, orgasmic and erectile dysfunction up to 2 years after TC treatment.[2] It was emphasized that

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there is a lack of knowledge about how different treatment modalities (cisplatin based chemotherapy, abdominal radiotherapy and surgery) as well as psychological factors affect sexual function in TCSs. In a cross-sectional study from Norway Dahl et al found increased an risk of ejaculatory dysfunction in patients treated with retroperitoneal surgery and a possible association of cisplatin based chemotherapy and neurotoxicity with ejaculatory dysfunction among 1,084 TC survivors at a median followup of 11 years.[3] In a similarly designed study of 401 Danish long-term TCSs Rossen et al confirmed the association between retroperitoneal surgery and ejaculatory dysfunction while not confirming other associations between treatment modality and sexual dysfunction.[4] Thus, it is still unclear how current TC treatment, especially cisplatin based chemotherapy and abdominal radiotherapy, affects different aspects of sexual function in long-term TCSs.

We present data from a large nationwide and population based cross-sectional study of 2,572 long-term TCSs treated with the current standard of care.[5] The aims of the study were to 1) clarify the association between treatment modalities and different aspects of sexual function, and 2) investigate whether possible associations between treatment modalities and sexual function were mediated through psychological or physiological factors.

PATIENTS AND METHODS

Study Population

Between 2014 and 2016 we performed a questionnaire survey, DaTeCa-LATE (late treatment effects), evaluating patient reported outcomes in Danish TCSs with a median followup of 17 years after diagnosis.[5] All Danish TCSs included in the national DaTeCa database, including patients with TC treated from 1984 to 2007,[6] were invited. Of the 4,271 eligible TCSs 2,572 (60%) completed the 167-item questionnaire. Detailed information about the design of DaTeCa-LATE was previously reported.[5] Briefly, responders were older than nonresponders and in line with other studies more responders were in a relationship[7] while there was no difference in the Charlson comorbidity index between responders and nonresponders.

In the current study we excluded 71 responders (3%) with extragonadal germ cell cancer, 8 (0.3%) treated with high dose chemotherapy and bone marrow transplantation, and 233 (9%) with bilateral TC including contralateral germ cell neoplasia in situ, yielding a total of 2,260 TC survivors for analysis.

Treatment Protocol

Patients with stage I disease were treated with orchiectomy alone and followed on a surveillance program, except for some patients with large seminomas (6 cm or greater), who were offered adjuvant radiotherapy.[8] If there was primary disseminated disease or relapse, patients were initially treated with 3 or 4 courses of BEP. Those with small retroperitoneal seminomas (stage IIA) could be offered abdominal RT. In cases of residual disease after BEP surgical resection was performed.

In the current study TC survivors were divided into 5 treatment groups, including surveillance as the reference group, BEP with or without post-chemotherapy surgical resection of residual disease (BEP alone or BEP with post-chemotherapy surgery), RT and MTOL as previously described.[9,10]

Outcome Measures

All patients completed the IIEF-15 questionnaire, which covers erectile function (score 1 to 30), intercourse satisfaction (score 0 to 15), orgasmic function (score 1 to 10), sexual desire (score 2 to 10) and overall satisfaction (score 2 to 10).[11] A lower score on each of the 5 scales indicates a higher symptom burden. To evaluate erectile function and intercourse satisfaction only patients who reported having had sexual activity within the last 4 weeks were included.[4,12]

To evaluate neurotoxicity, which is a common side effect of cisplatin, patients completed the 11-item FACT/GOG (Functional Assessment of Cancer Therapy/Gynecologic Oncology Group)-NTX (Neurotoxicity) subscale, version 4.[13] This questionnaire evaluates patient reported symptoms of neurotoxicity such as numbness, tingling or discomfort of hands and feet, and difficulty walking or buttoning buttons. In the current study we included the total neurotoxicity score, which ranges from 0 to 44 with a higher score indicating a higher symptom burden. We applied the HADS[14] to evaluate the influence of coexisting anxiety and depression. A score greater than 7 on each of the 2 scales (HADS-Anxiety and HADS-Depression) served as the cutoff value for caseness.[14]

Some supplementary questions were asked regarding other factors with a possible influence on sexual function, including 1) the use of PDE5 inhibitors, 2) the use of testosterone substitution, 3) the patient assessment of the treatment influence on sexual function and 4) sexual activity during the last 4 weeks. The supplementary Appendix (http://jurology.com/) presents these items.

Information on marital status was obtained from the Danish Civil Registration System.[15] Information on comorbidity (Charlson comorbidity index excluding TC) as defined by Quan et al[16] was obtained from the DNPR (Danish National Patient Registry), which has registered the diagnoses of all patients admitted to hospitals since 1977.[15]

The regional ethical committee of the Capital Region of Denmark approved the study (file No. H-2-2012-044).

Statistics

To evaluate erectile dysfunction we used a composite end point of a IIEF-Erectile Function score less than 22[12] or the use of PDE5 inhibitors. The composite end point was determined since erectile dysfunction is the primary indication of PDE5 inhibitor use. For the other 4 domains of the IIEF-15 a score in the lowest quartile was defined as the outcome. We constructed a logistic regression model with each of the 5 domains of the IIEF-15 scale as the outcome and the treatment, including BEP alone or with post-chemotherapy surgery, RT and MTOL vs surveillance