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LETTER TO THE EDITOR

Organ Sparing Approach in Bilateral Testis Tumors: A Short Review of the Literature with a Featuring Case

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Dear Editor,

Testicular cancer (TC) is very rare in clinical practice. It represents only 1-2% of all cancers.[1] However, TC is the most common malignancy in men between 15 and 40 years old.[2] Race, cryptorchidism, genetics, maternal estrogen exposure, and previous TC are main known risk factors.[3,4] Western and Northern Europe populations have significantly high incidence for TC.[5] Pathological classification of TCs consists of germ cell tumors (GCT), stromal tumors, ITGCN, and others. More than 90% of TC has GCT histology.[6] GCT is divided into 2 main subgroups such as seminomas and non-seminomatous tumors. Non-seminomatous GCT has 5 subtypes such as embryonal carcinoma, yolk sac tumors, choriocarcinoma, teratoma, and mixed tumors. Our patient has mixed GCT histology. Average age of presentation of mixed GCT is 30 years old.[7] Any combination of histological subtypes is formally possible, although admixture of embryonal carcinoma and teratoma is more frequent.[8]

Our patient was 24 years old. He did not have any other comorbidity. He has noticed swelling in his scrotum and was timely administered to hospital. A 3.5 cm solid mass was reported in his left testicle with USG. Serum β-Hcg, AFP, and LDH levels were 437 mIU/ml, 903 ng/mL, 362 IU/L, respectively. Left inguinal orchiectomy was performed to the patient in August 2011. There was no complication after surgery. Admixture of yolk sac and teratoma were reported by pathologists. Serum β-Hcg, AFP and LDH levels decreased to 25.7 mIU/ml, 289 ng/mL, 179 IU/L, respectively, in the 1st post-operative week. Regression of tumor markers was continued within 1½ months after the surgery. They were at completely normal levels by the 6th post-operative week. Systemic evaluation was made with thoracic and abdominopelvic CT scan. There was no sign of metastasis in the body. Although serum tumor marker levels decreased to normal values, the normalization time was longer than expected. Two cycles of BEP (cisplatin 100 mg/m^2, etoposid 150 mg/m^2, and bleomycin 30 U) were given to the patient in October 2011. Then, the patient followed up with testing of tumor marker levels in every 3 months and radiologic imaging in every 4 months. While the patient was screening with stable disease, prominent progression of tumor marker levels was detected in routine laboratory tests in December 2013. Serum β-Hcg, AFP levels were 173.5 mIU/ml and 36 ng/mL, respectively. Scrotal USG showed 1.5 cm mass at the inferior pole of the right testicle. Right testis sparing surgery (TSS) was performed immediately after USG result. During surgery, 2 punch biopsies were taken from normal testis parenchyma. Pathology report revealed a mixed GCT with a combination of embryonal carcinoma (65%), yolk sac (20%), teratoma (10%), and choriocarcinoma (5%). Lymphovascular invasion was seen. Surgical margins were intact. Furthermore, ITGCN reported in the residual testis parenchyma. Therefore, 20 Gy radiotherapy (RT) (Figs. 1, 2) was given to residual testis in 10 fractions in January 2014. Serum β-Hcg, AFP levels were 3600 mIU/ml and 255 ng/mL, respectively, in the 1st post-operative week. Serum β-Hcg, AFP levels were 2400 mIU/

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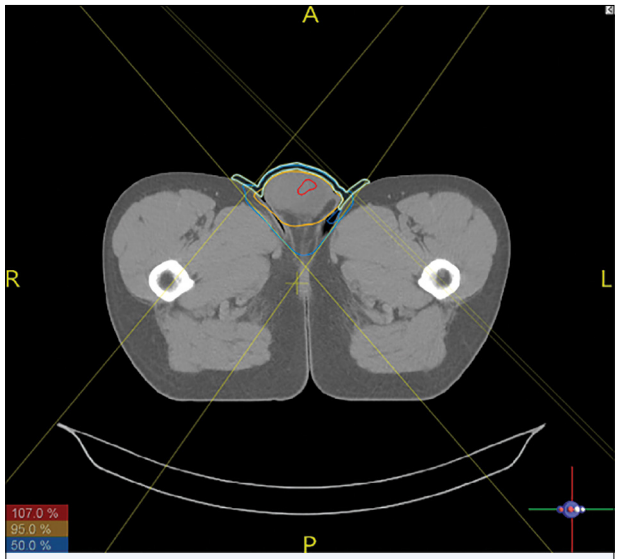

Fig. 1. Coronal view of the radiotherapy (RT) plan. Isodose lines red, yellow, and blue represent 107%, 95%, and 50% of the total dose, respectively. IGRT (image-guided radiotherapy) is used to minimize setup errors and interfraction differences. A bolus was placed superficially to the skin to maintain an adequate surface dose.

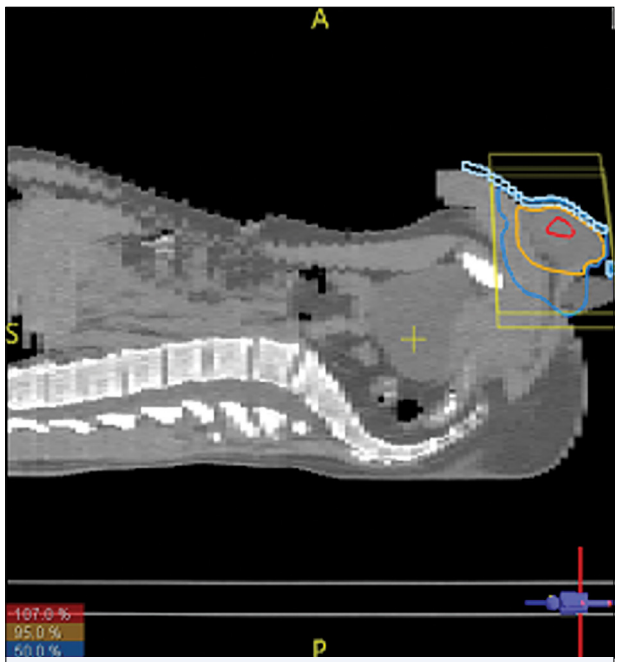

Fig. 2. Sagittal view of the radiotherapy (RT) plan. Isodose lines red, yellow, and blue represent 107%, 95%, and 50% of the total dose, respectively. The penis retracted superiorly to avoid from RT field. The 95% isodose line covers all of the remaining testis volumes.

ml and 180 ng/mL, respectively, after the RT. PET scan showed increased FDG uptake at the distal paraaortic lymph node (SUVmax 7.3). Consequently, the patient was referred to medical oncology for systemic therapy. Afterward, 4 cycles of EP chemotherapy were applied to the patient. EP chemotherapy was completed in March 2014. Serum β-Hcg, AFP levels were 1.6 mIU/ml and 7.8 ng/mL, respectively, after EP chemotherapy. Regression of involved lymph node and decreased uptake of FDG (SUVmax 2.6) were reported in control PET scan in May 2014. During follow-up, 3 consecutive measurements of serum β-Hcg levels were seen progressively increased in June 2014 (64→122→223 mIU/ml). Accordingly, 3 cycles of TIP chemotherapy were planned. TIP (paclitaxel 250 mg/m^2, ifosfamide 1.5 g/m^2, mesna 1.5 mg/m^2, and cisplatin 25 mg/m^2) chemotherapy was completed in August 2014. Serum tumor marker levels were totally normal in September 2014. There is still no evidence of disease (NED). Survival is 110 months and disease-free survival is 74 months now. There is no long-term complication of treatment except testosterone deficiency due to the Leydig cells destruction.

Radical orchiectomy is the gold standard treatment for TC. However, TSS may be alternative to radical orchiectomy, especially in bilateral tumors to prevent testosterone deficiency. Although there are several publications about TSS in the literature, there is no scientific consensus on this topic. The common idea is being cautious for assigning patients to TSS.[9,10] EAU guidelines recommend the use of TSS to patients, which have solitary testis, for preserving infertility and hormonal function, which is compatible with our patient.[11]

ITGCN is a precursor lesion of cancer. Heidenreich et al. stated that ITGCN is seen at the residual testis parenchyma in 82% of 73 patients after TSS in their study. Existence of ITGCN ends up with TC in 50-80% of cases.[12,13] Therefore, RT is required in case of ITGCN. Although RT is effective for controlling the disease, it damages Leydig cells and causes testosterone deficiency at the same time. In this regard, determination of RT dose is very crucial. Leydig cells are very sensitive to radiation. It is showed that doses as low as 6 Gy can affect Leydig cells.[14] On the other hand, according to literature, optimal RT dose for ITGCN is 20 Gy.[15] There are several studies in the literature comparing 20 Gy with lower doses (14-16 Gy) in the aspects of both disease control and hormone profile. However, decreasing the RT dose may lead to an increasing risk of disease relapse.[16-18] Consequently, hypogonadism rates after RT are reported as 25-30% in the literature.[18,19] In

compliance with literature findings, we applied 20 Gy RT. Unfortunately, our patient ended up with testosterone deficiency and required hormone substitution. He is getting 1000 mg testosterone replacement every 3 months.

Testosterone deficiency is a consequence of both RT and chemotherapy. Recent researches indicated that cisplatin-based regimens cause subclinical hypogonadism by affecting Leydig cells' function.[20,21] Furthermore, another effect of radio and chemotherapy is reported in the literature. Higher serum LH levels are associated with a decrement in testosterone production in the remaining irradiated testicular tissue. Furthermore, platinium-based chemotherapeutics have a cumulative effect on Leydig cells.[22] According to this data, testosterone deficiency was inevitable in this case as a result of intense treatment.

Overall survival (OS) rates for bilateral synchronous TC are lower than metachronous contralateral TC according to SEER database. The 10-year OS rate for patients diagnosed with metachronous contralateral TC has been reported as 93% in SEER analysis.[23] However, there are many publications reporting different OS time for bilateral TC patients with different histology, stage, and risk factors in the literature. Klatte et al. reported that all of the patients were alive after a median follow-up of 95 months for 11 metachronous bilateral TC patients. However, only 1 of 11 patients had non-seminomatous mixed GCT histology.[24] Similarly, in the study by Hentrich et al.,[25] 32 of 33 metachronous bilateral TC patients were reported as alive with NED after a median follow-up of 41 months. Furthermore, in the study by MD Anderson Cancer Center for bilateral TC, it has been stated that only 1 of 24 patients died due to the metastatic disease.[26] In parallel with literature findings, our patient survived for 110 months and is still following up with NED.

Our patient evaluated as stage 1S at the time of diagnosis, according to serum tumor marker levels (S1). Therefore, despite return of tumor marker levels to normal at 1.5 months after surgery, 2 cycles of BEP were given to the patient according to recommendations from NCCN guidelines.[27,28] At the time of relapse, our patient had stage 2A disease because of N1 lymph node. Serum tumor marker levels were prominently high after TSS. Persistent marker elevation after surgery was a significant independent predictor of recurrence.[29] Four cycles of EP were applied to the patient. After EP chemotherapy, markers turned down to normal levels in March 2014. However, β-Hcg values elevated on 3 serial measurements in June 2014. Therefore, the patient was accepted again with the relapsed disease and received 3 cycles of TIP chemotherapy as the second-line regimen. TIP regimen is very useful for relapsed GCT. Motzer et al. reported of a complete positive response from 24 out of 30 patients with relapsed GCT who were treated with TIP regimen.[30]

Although CT is the standard modality for detecting abdominal or retroperitoneal lymphadenopathies, its false negative rates have been observed as high as 30-59% in the literature.[31,32] However, potential of PET/CT to improve clinical staging of TCs has reported recently.[33] Besides, prospective studies of the German multicenter PET study group revealed that PET/CT is only slightly better than CT as a primary staging tool for stage 1/2 non-seminomatous GCTs.[34] Furthermore, they reported that PET/CT is not better than serum tumor markers and CT for evaluating treatment response after chemotherapy for non-seminomatous GCTs.[35] In light of this information, we performed CT scans for routine radiological follow-up and treatment response evaluation of our patient. In addition, we further combined PET/CT with CT scans for improving the accuracy of clinical staging and treatment response evaluation.

Management of bilateral testis tumors requires a wide consideration of several issues all together, including control of disease, following of serum tumor markers, making decisions on necessity of adjuvant treatments, timing of therapies assigned, applying of proper RT techniques, and controlling of long-term side effects. Our patient has been treated with the multimodality approach under cooperation of different departments. BTCs may have an excellent prognosis. However, close follow-up of the disease and multimodality approach should always be considered. Organ sparing approach can be a useful treatment alternative in selected patients.

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