Testicular Cancer in Trans People Using Feminising Hormone Therapy—A Brief Review

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The number of transgender (or trans) individuals, including those who have a binary and/or non-binary gender identity, seeking gender-affirming hormone therapy is increasing.[1] In this brief review, we aim to provide an overview of gender affirmation and synthesise current literature describing case reports and management of testicular cancer in trans people using feminising hormone therapy.

In the United States, utilizing sampling-based telephone interviews, approximately 0.3%-0.53% of people identify as transgender.[2] Gender dysphoria is characterized by psychological distress caused by a mismatch between the biological or presumed sex of a person (normally assigned at birth), and the subjective experience each person has of their own gender identity throughout their life.[3] Gender is now considered a diverse human trait, and whilst the precise origins are unclear, there is evidence that gender is, in part, innate with a genetic basis.[4] Whilst many individuals will have a binary gender identity (ie, male or female), roughly 1/3 of transgender individuals identify with a gender outside of the binary or non-binary which includes many identities including genderfluid, genderqueer, and agender.[5] The general goal of gender dysphoria care is to minimize the distress, anxiety, depression, and other sequalae of gender dysphoria. Gender affirmation varies considerably between people and may include social transition, medical transition (with gender-affirming hormone therapy), surgical transition and/or legal transition.

Testicular cancer is the most common cancer among males aged 15-34 years old, and the frequency is increasing worldwide.[6] Testicular cancers are exceedingly survivable, with 5-year survival rates of >95%. With cancer confined to the testicle, the survival rate is greater than 99%.[7] Risk factors for testicular cancer development include cryptorchidism (undescended testes) and congenital abnormalities.

We sought to evaluate the effect of feminising hormone therapy on testicular cancer and testicular biology. A literature search was conducted in August 2021 encompassing the years 1900-2021, using PubMed, JSTOR, ScienceDirect, EMBASE, and Web of Science. Search terms utilized in each search were: testicular cancer, testicular neoplasm, testes, testicle, transgender, estrogen, and testosterone.

EFFECTS ON THE TESTIS

The effect of gender affirmation therapies on the testes themselves are observed in histologic analysis of orchiectomy specimens in three studies[8-10] where hormone therapy was used for >1 year in all or most trans people using feminising hormone therapy. Microscopic evidence of spermatogenesis ranged from 21% to 40% while germ cells were present in 80% with strong correlation to testicular size. However, another study demonstrated greatly reduced motility counts in trans people using feminising hormones (0.2 million per mL) compared to those who were not (63.2 million per mL).[11]

Testicular development and function depend on estrogen, and it has been demonstrated that estrogens stimulate proliferation of human malignant testicular germ cells[12] via a non-classical estrogen receptor that activates MAPK1/MAPK3 (previously called ERK1/2) and protein kinase A. Epidemiological evidence points to a possible link with perinatal exogenous estrogen exposure, for example, to diethylstilbestrol, and testicular cancer[13] but the association with later in life exposure is not clear.

REGISTRY STUDIES

A nationwide study in the Netherlands linked patients attending a gender identity clinic and the national database of pathology results.[14] This included trans women that attended the clinic between 1972 and 2017. A total of 3026 trans women were included in the analysis, with a

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mean follow-up of 2.3 years. Two testicular cancers were found during clinical care, and one was found incidentally at orchiectomy. For those with more than 5 years of follow-up, there were no cases of testicular cancer. The authors conclude that the rate of testicular cancer in trans women is the same as cis men by comparing the expected incidence in the Netherlands versus the encountered rate. The absence of testicular cancer cases after 5 years of follow-up supports the safety of long-term hormonal treatment. Data from the North American Association of Central Cancer Registries suggests that the testicular cancer rate in trans women is lower than in cis men (Proportional incidence ratio: 0.3, (95%CI: 0.1-0.6)),[15] however there were low numbers of evaluable cases.

CASE STUDIES OF TESTICULAR CANCER IN TRANS PEOPLE USING FEMINISING HORMONE THERAPY

We identified six case studies from our literature search (Table 1).

Case 1[16]: A 38-year-old prescribed estradiol and spironolactone for 15 months, presented to emergency with progressive right sided scrotal swelling, abdominal pain, back pain, fatigue, and recent weight loss of 7 kg. On CT, a 6.4*4.9*6.3 cm testicular lesion and 11.5*10.6*17.4 cm retroperitoneal mass, a large thrombosis in the right common iliac and femoral vessels, and right sided hydronephrosis were found. The diagnosis was seminoma. Treatment was four cycles of BEP (bleomycin, etoposide, cisplatin) chemotherapy before right sided orchiectomy. The patient was followed for 2 years with PET/CT with no evidence of recurrence.

Case 2[17]: A 31-year-old had been on estradiol, leuprorelin for several years. Despite the addition of spironolactone and increasing estrogen doses, there was a failure to achieve feminising effects. An investigation revealed high beta human chorionic gonadotrophin, and elevated dehydroepiandrosterone sulphate. A testicular ultrasound revealed a 3.1*3.1*2.3 cm lesion in the right testicle. PET/CT demonstrated significant uptake in the right testicle. A right sided orchiectomy was performed, which revealed a seminoma completely confined to the testicle. Six months later, feminising goals were achieved.

Case 3[18]: A 30-year-old received estradiol and progesterone for 2 years. The patient had a rapidly growing painless mass in the right testicle (5 cm in diameter) on physical examination. A whole-body CT showed no evidence of metastatic disease. A right sided orchiectomy was performed which demonstrated a mature teratoma that was estrogen receptor beta positive, but estrogen receptor alpha negative and progesterone receptor negative. The other testicle was removed later to complete gender transition, with no evidence of recurrence.

Case 4[19]: A 30-year-old with a history of scrotal trauma (due to physical assault on multiple occasions) was prescribed 2 mg estradiol and 100 mg spironolactone per day for a year. The following year, estradiol dose increased to 6 mg, spironolactone increased to 200 mg per day, and commenced 5 mg finasteride and 100 mg progesterone daily. At 21 months following the initial consultation, serum testosterone remained persistently high and the patient felt unsatisfied with feminising progress. Gender affirming surgery was performed, including bilateral orchiectomy and vaginal reconstruction. Routine histology demonstrated seminoma with indeterminate lymphovascular invasion. Serial CT scans and tumour markers were performed for 5 years with no evidence of metastatic disease, and the authors concluded the surgery was probably a complete excision.

Case 5[20]: A 28-year-old received 2 mg estradiol and 100 mg spironolactone per day for 3 months. At 3 month follow up, testosterone levels remained high, therefore, feminising hormone therapy was increased to 4 mg estradiol and 200 mg spironolactone per day. After a further 4 months, testosterone remained high, so the spironolactone was increased to 300 mg and 5 mg medroxyprogesterone was added. Despite this, testosterone levels remained persistently high, therefore at 18 months after initial commencement of therapy, medroxyprogesterone was increased to 10 mg per day, spironolactone was reduced to 200 mg per day, and estradiol was kept at 4 mg per day. Two years after beginning feminising hormone therapy, the patient reported testicular pain that went away by itself (the patient could not recall a specific timeline and denied having a testicular mass), the left testicle was enlarged on physical examination, and an ultrasound demonstrated a 1.7*1.2*1.3 cm mass in the left testicle. On investigation, a contrast CT of the abdomen and pelvis showed a hypodense region on the hepatic dome, and CT of the chest was normal. The patient underwent a left orchiectomy, which showed a non-seminomatous tumour: 75% embryonal carcinoma, 15% immature teratoma, 9% seminoma, <1% yolk sac tumour; intravascular invasion was found but did not extend beyond the tunica albuginea. Testosterone remained persistently elevated, so a right radical orchiectomy was performed. The right testicle was normal on histology, as were the lymph nodes. After removal of the right testicle the persistently high testosterone went away.

Case 6[21]: A 37-year-old who had been taking estradiol for 22 years. The initial presentation was a 1-month history of severe left groin, testicle, and flank pain. Her initial CT staging scan showed a large left para-aortic retroperitoneal mass measuring 9.5*6.8*7.6 cm. The mass was completely obstructing the left proximal ureter and causing hydronephrosis. Biopsy of the mass demonstrated choriocarcinoma. There were also multiple metastatic pulmonary nodules in both lungs. She underwent four cycles of BEP chemotherapy, and 3 cycles of TIP (paclitaxel, ifosfamide, cisplatin) chemotherapy. The patient underwent a left orchiectomy, retroperitoneal lymph node dissection, and left nephrectomy. Upon histological examination, there was no viable tumour remaining, and

Table 1. Cases of Testicular Cancer Reported in Trans People Using Feminising Hormone Therapy.

Case	Reference	Year	Age at Diagnosis	GAT	Length of GAT	Tumour	Treatment	Outcome
1	Chandhoke[16]	2018	38	Estradiol Spironolactone	15 mo	Seminoma	Orchiectomy 4 cycles of BEP chemotherapy	No recurrence at 2 y. Followed with PET/CT for surveillance
2	Elshimy[17]	2020	31	Estradiol Leuprorelin Spironolactone	Several years	Seminoma	Orchiectomy	Histology demonstrated tumour completely confined to the right testicle. No evidence of recurrence
3	Kobori[18]	2015	30	Estradiol Progesterone	2 y	Teratoma	Orchiectomy	Right testicle removed initially. GAS completed later with both testes removed. No evidence of disease
4	Kvach[19]	2019	30	Estradiol Spironolactone Progesterone Bicalutamide Finasteride	21 mo	Seminoma	Orchiectomy	Patient followed with CT for 5 years. Probably completed excision. No evidence of recurrence or metastasis
5	Wolf-Gould[20]	2016	28	Estradiol Spironolactone Progesterone	2 y	Nonseminoatous tumour	Orchiectomy	Complete excision
6	Hannoush[21]	2016	37	Estradiol	22 y	Choriocarcinoma	4 cycles of BEP chemotherapy 3 cycles of TIP chemotherapy Orchiectomy	Completed BEP and TIP before orchiectomy. Histology showed no viable tumour remaining. In remission

BEP, bleomycin etoposide platinum (Cisplatin); GAT, gender affirming therapy; GAS, gender affirming surgery; TIP, taxane (Paclitaxel) ifosfamide platinum (Cisplatin).

the patient was in remission. This is the first reported case of a choriocarcinoma in this setting.

CONCLUSION

The registry evidence would suggest that the rate of testicular cancer in trans people using feminising hormone therapy is at worst not different from cis men, and at best considerably lower than cis men. The six cases presented here do not appear to follow a common pattern; they were all on similar gender affirming feminising therapies but for varying lengths of time, the tumour types encountered are similar to cis males, and their ages reflect the peak incidence of testicular cancer. There is minimal evidence that long-term feminising gender affirming therapy results in an altered risk of testicular cancer or differing tumour types. The rarity of testicular cancer likely relates to the unfavourable hormonal environment due to feminising hormonal therapy, under-reporting of cases, and orchiectomy as part of gender affirming therapy.

References

1. Zhang Q, Rechler W, Bradlyn A, et al. Changes in size and demographic composition of transgender and gender non-binary population receiving care at integrated health systems. *Endocr Pract*. 2021;27:390–395.
2. Crissman HP, Berger MB, Graham LF, Dalton VK. Transgender demographics: a household probability sample of US adults, 2014. *Am J Public Health*. 2017;107:213–215.
3. Zaliznyak M, Bresee C, Garcia MM. Age at first experience of gender dysphoria among transgender adults seeking gender-affirming surgery. *JAMA Netw Open*. 2020;3: e201236.
4. Foreman M, Hare L, York K, et al. Genetic link between gender dysphoria and sex hormone signaling. *J Clin Endocrinol Metab*. 2019;104:390–396.
5. Cheung AS, Leemaqz SY, Wong JWP, et al. Non-binary and binary gender identity in Australian trans and gender diverse individuals. *Arch Sex Behav*. 2020;49:2673–2681.
6. Bray F, Richiardi L, Ekbom A, Pukkala E, Cuninkova M, Moller H. Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. *Int J Cancer*. 2006;118:3099–3111.
7. Bertuccio P, Santucci C, Carioli G, Malvezzi M, La Vecchia C, Negri E. Mortality trends from urologic cancers in Europe over the period 1980-2017 and a projection to 2025. *Eur Urol Oncol*. 2021;4:677–696.
8. Jiang DD, Swenson E, Mason M, et al. Effects of estrogen on spermatogenesis in transgender women. *Urology*. 2019;132:117–122.
9. Kent MA, Winoker JS, Grotas AB. Effects of feminizing hormones on sperm production and malignant changes: microscopic examination of post orchiectomy specimens in transwomen. *Urology*. 2018;121:93–96.
10. Schneider F, Neuhaus N, Wistuba J, et al. Testicular functions and clinical characterization of patients with gender dysphoria (GD) undergoing sex reassignment surgery (SRS). *J Sex Med*. 2015;12:2190–2200.
11. Adeleye AJ, Reid G, Kao CN, Mok-Lin E, Smith JF. Semen parameters among transgender women with a history of hormonal treatment. *Urology*. 2019;124:136–141.
12. Bouskine A, Nebout M, Mograbi B, Brucker-Davis F, Roger C, Fenichel P. Estrogens promote human testicular germ cell cancer through a membrane-mediated activation of extracellular regulated kinase and protein kinase A. *Endocrinology*. 2008;149:565–573.
13. Giannandrea F, Paoli D, Figa-Talamanca I, Lombardo F, Lenzi A, Gandini L. Effect of endogenous and exogenous hormones on testicular cancer: the epidemiological evidence. *Int J Dev Biol*. 2013;57:255–263.
14. de II N, Wiepjes CC, de Blok CC, et al. Incidence of testicular cancer in trans women using gender-affirming hormonal treatment: a nationwide cohort study. *BJU Int*. 2021. https://bjui-journals.onlinelibrary.wiley.com/doi/10.1111/bju.15575.
15. Nash R, Ward KC, Jemal A, Sandberg DE, Tangpricha V, Goodman M. Frequency and distribution of primary site among gender minority cancer patients: an analysis of U.S. national surveillance data. *Cancer Epidemiol*. 2018;54:1–6.
16. Chandhoke G, Shayegan B, Hotte SJ. Exogenous estrogen therapy, testicular cancer, and the male to female transgender population: a case report. *J Med Case Rep*. 2018;12:373.
17. Elshimy G, Tran K, Harman SM, Correa R. Unmasked testicular seminoma during use of hormonal transgender woman therapy: a hidden hCG-secreting tumor. *J Endocr Soc*. 2020;4:bvaa074.
18. Kobori Y, Suzuki K, Iwahata T, et al. Mature testicular teratoma with positive estrogen receptor beta expression in a transgendered individual on cross-sex hormonal therapy: a case report. *LGBT Health*. 2015;2:81–83.
19. Kvach EJ, Hyer JS, Carey JC, Bowers M. Testicular seminoma in a transgender woman: a case report. *LGBT Health*. 2019;6: 40–42.
20. Wolf-Gould CS, Wolf-Gould CH. A transgender woman with testicular cancer: a new twist on an old problem. *LGBT Health*. 2016;3:90–95.
21. Hannoush ZC, Ayala A. Estrogen exposure and testicular choriocarcinoma: case report of a male to female transgender patient. Endocrine Society's 98th Annual Meeting and Expo; April 1—4, 2016; Boston, Massachusetts. *Endocr Rev*. 2016; 37(1):i411—i412, https://doi.org/10.1093/edrv/37.supp.1.