

## **Testicular cancer in men with undescended testis: Insights from the Thames Valley Testicular Cancer database**

### **Abstract:**

#### **Objective:**

Undescended testis (UDT) increases the risk of testicular cancer (TCa) development. Historical evidence suggests malignant transformation of uncorrected UDT primarily results in seminomas, whereas mixed germ cell tumours (MGCTs) predominate in corrected UDT, however the risk of malignancy in the “normal” contralateral testis is unclear. We investigated the contemporary Oxford TCa cohort to report the frequency of prior UDT and types of tumours developing in the prior UDT and normal contralateral testis.

#### **Patients and Methods:**

A 607 patient contemporary TCa cohort within the Thames Valley Testicular Cancer database.

#### **Results:**

8% of men with new TCa had a history of UDT. 61% of men with TCa and prior UDT developed seminomas, whereas 56% of men with TCa without previous UDT developed this subtype. Among men with prior UDT, 77% developed tumours in the UDT, whilst 23% developed TCa in the contralateral “normal” testis.

#### **Conclusion:**

Seminoma was the most frequent malignancy following UDT, with a greater frequency than without prior UDT. Around one in four TCa patients with UDT developed contralateral tumours, emphasising the need for self-examination of both testes. Advice should be given to any patient with a history of UDT stressing the importance of ongoing self-examination of both testes.

**Keywords:**

Testicular cancer; undescended testis

## **Introduction:**

Testicular cancer (TCa) comprises 0.7% of male cancers in the United Kingdom (UK), with 2,418 new cases in 2014 (1), commonly affecting adolescents and young men. Whilst TCa is usually curable with chemotherapy, it is increasing in incidence (2) and resulted in 60 UK deaths in 2014 (1).

Undescended testis (UDT) is a testis that has not descended into the scrotum by birth, occurring in 3-5% of term male infants, though in most cases the testis reaches its normal scrotal position by 3 months of age (3,4). UDT can however persist, or a retractile testis may become UDT (5,6). UDT is associated with an increased TCa risk (3,7,8), and the British Association of Paediatric Urologists recommend early surgical correction (orchidopexy) between 3-12 months of age (9). 6000 orchidopexy procedures are performed in England each year (9). Early orchidopexy may reduce, though does not eliminate, future TCa risk (10,11) and enables self-examination of a previously non-palpable testis (3).

Historical evidence suggests uncorrected UDT undergoing malignant transformation has a propensity to become a seminoma, whereas mixed germ cell tumour (MGCT) is more common in a previously corrected UDT (12), however the molecular mechanism underlying this observation is unknown. The incidence of previous UDT in TCa is reportedly between 5-12% (13–17), and the relative risk (RR) of TCa if prior UDT is 5.2 (CI 95% 2.1-13) (13). 1% of individuals with previous UDT develop TCa (13,18,19), with the RR in men with previous

unilateral UDT being 15 (95% CI 10-23) (13), rising to 33 (95% CI 20-55) for bilateral UDT.

The increased TCa risk following UDT occurs in both the ipsilateral and contralateral testis.

We report the Oxford TCa cohort to provide a contemporary overview of the frequency of prior UDT and types of tumours that currently develop.

## **Patients and Methods:**

We retrospectively evaluated the Oxford Cancer Centre Testicular Cancer database to investigate the features of UDT in a contemporary cohort of men diagnosed with TCa. A dedicated data manager collects the Oxford Cancer Centre Testicular Cancer database prospectively, with Institutional approval. 607 consecutive patients with a history of newly developed TCa between 2004 and 2016 were included for analysis. Demographic, TCa laterality, histology and stage, prior history of UDT features, age at historical orchidopexy, and testicular examination findings of the contralateral non-malignant testis (where applicable) were extracted from the database and reported.

## **Results:**

The median age of men with newly diagnosed TCa treated in our Institution between 2004 and 2016 was 36 years (range 15-82 years), with an equal split regarding laterality (53% of tumours right-sided, 47% left-sided) (**table 1**). Seminoma was the commonest histological subtype of TCa in the entire cohort (56%), followed by MGCTs (39%). Less common testicular tumours included teratomas (4%), embryonal carcinomas (4%), Sertoli/Leydig cell tumours (3%), yolk sac tumours (<1%) and choriocarcinomas (<1%). 407 (72%) of individuals presented with stage I tumours.

43 of 511 (8%) individuals with available data had a previous history of UDT (**table 2**), and the median age of development of TCa in this subgroup of men was 37 years (range 19-75 years). 31 of 42 (74%) men with available data had previous unilateral UDT, with the other 11 (26%) men having prior bilateral UDT. 30 of 39 (77%) individuals had developed TCa in the testis ipsilateral to the previous UDT, with the other 9 (23%) developing malignancy in the contralateral normally descended testis. 26 of 43 (61%) men with prior UDT developed seminoma, a further 13 (30%) developed MGCTs, and 4 (9%) developed Sertoli/Leydig or other tumours.

13 of 15 patients with available data had historically undergone an orchidopexy as a child for an UDT ipsilateral to the eventual malignant testis, this being performed at a median (range) age of 10 (5-17) years. Where data was available for patients with UDT of the testis contralateral to the side of malignancy, 9 of 15 individuals had undergone prior orchidopexy, at a median (range)

age of 8 (1-14) years. Clinical examination findings were available for half of all men with a prior history of UDT (regardless of orchidopexy history), and 30% of these individuals had a soft and/or atrophic contralateral testis, whilst 70% had a normal volume contralateral testis.

## **Discussion:**

We present data from a large contemporary cohort of men treated for newly diagnosed TCa to provide an up to date overview of the current incidence of prior UDT among these individuals, and to inform the uro-oncology community of the histological features of TCa developing in men with a prior history of UDT. Whilst the association between UDT and increased risk of TCa has been recognised for many decades (20), the rising rates of TCa, along with changes in the classification of these tumour types (17), taken together with the variable rates of UDT, make it important to report an up to date cohort of patients with TCa.

The incidence of a history of UDT in 8% of our contemporary cohort of individuals with new TCa is consistent with previous reports suggesting that anywhere between 5-12% of men who develop TCa were, or are, cryptorchid (13–17). Our data also accords with the established dogma that the commonest type of testicular malignancy to arise in cryptorchid testes is seminoma (20), and whilst the overall number of men with a prior history of UDT (n=43) in our series is small, the observation that seminoma was slightly more common in those with a prior history of UDT compared with the entire cohort (61% versus 56% in our series) suggests the possibility that the drivers behind the development of seminoma may be common with those underlying the process of UDT, or that an UDT may be more prone to developing seminomatous change for environmental or genetic reasons. Indeed, the rate of seminomas developing against a background of UDT has been reported as being higher (at 41%) than for any other subtype of TCa in a previous historical series (21). The mechanism behind the well-established association between UDT and TCa remains unknown. Two models, which are not mutually exclusive, may



explain the association (21). Firstly, the ectopic position of the testis may directly or indirectly increase the risk of malignant change, and secondly the underlying development of UDT and TCa may share common intrauterine, environmental and/or genetic causes. Intriguingly, we observed no difference in the median age of development of TCa among men with a history of prior UDT versus those with developmentally normal testes. This suggests that the underlying genetic cause of UDT may not link directly with the aetiology of testicular malignancy, as one would predict that testicular malignancy might occur at an earlier age in those with UDT if the molecular drivers of these conditions were similar. These hypotheses require formal investigation. It is noteworthy that the age at orchidopexy of individuals in our cohort with a prior history of UDT was considerably older than the recommended age of 3-12 months for this corrective procedure advocated by the British Association of Paediatric Urologists (9), which would not have been in practice for individuals in our dataset. It would be interesting for a future study to determine whether earlier orchidopexy, as now recommended, influences both the incidence and type of TCa development in a cryptorchid testis.

Seminomas often develop from a precursor lesion termed “germ cell neoplasia *in situ*” which can arise *in utero*, remaining quiescent during infancy and then proliferating during puberty to become a seminoma under the influence of gonadotrophins and testicular steroid (17). Whilst numerous molecular and genetic changes have been described which may promote the development of seminoma (17), none of these have to date provided a tangible link to account for the propensity of UDT to form this particular subtype of testicular tumour. Further research to investigate the potential molecular aetiology of seminoma may benefit by paying particular

attention to those developing this subtype of TCa against a background of UDT, given the increasingly common nature of this malignant condition in this subgroup of men.

A strength of our study is the large number of patients within the database, in part due to its supra-regional nature. However, this supra-regional nature of the database is also a weakness, as we are unable to collect many features of the historical orchidopexy in cases where this has been performed, and this aspect of the history, along with the examination findings of the non-malignant testis, may not always be obtained by the tertiary referral oncologist, or be provided by the referring out-of-area urologist. A further weakness is the absence of formal fertility data, which historically has not been collected. It would be useful for future studies to collect this data prospectively, especially as many men with TCa opt for sperm storage ahead of adjuvant treatment.

The observation that approximately 1 in 4 men who develop TCa against a background of a prior history of UDT will do so in the contralateral normally descended testicle is consistent with data from a previously reported meta-analysis (21). Among 199 patients with both unilateral UDT and TCa from 12 studies, it was reported that 79% of tumors were ipsilateral to the UDT whilst 21% of tumours were contralateral (21). The relative risk of TCa was 6.33 (95% CI 4.3-9.31) on the ipsilateral side, and 1.74 (95% CI 1.01-2.98) on the contralateral side (21).

**Conclusion:**

8% of men with TCa in this contemporary cohort had a history of UDT, and these individuals had a slightly higher proportion of seminomas (61%) than the entire cohort (56%). Among these individuals, 3 in 4 developed TCa in the ipsilateral testis, however 1 in 4 men developed malignancy in the contralateral normally descended testicle. In view of this observation, advice should be given to any patient with a history of UDT of the importance of continuing self-examination of both testes throughout life. The observation that TCa can develop in the contralateral testis in men with a prior history of unilateral UDT also provides indirect evidence to support the possibility that certain unidentified genetic and/or environmental factors may play a role in the association between UDT and testicular malignancy. This hypothesis warrants further investigation.

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