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Retrospective Study

Outcomes in Patients with Testicular Maldescent and Germ Cell Neoplasia: A Retrospective Assessment and Review of the Literature

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ABSTRACT

Introduction

Cryptorchidism is not an uncommon problem in young males, yet the ideal management of the undescended testes (UDT) is not clear-cut. Multiple issues influence the patient-physician decision process regarding treatment including fertility, hormone-production, cosmesis and the risk of testicular germ cell tumors (TGCT's).

Methods

A retrospective review of 2204 men presenting to Indiana University Medical Center or Baylor College of Medicine affiliated hospitals with TGCT during a 20 year period was conducted, and individuals with a history of UDT were identified. Clinical outcomes of the 94 men with UDT and TGCT who did, and did not, undergo orchidopexy were compared. Statistical analysis included chi-square, Fischer's exact test and confidence intervals.

Results

Of the 94 patients identified with UDT and TGCT, 87 had a complete evaluable dataset. Fifty-two patients out of the 87 had tumors ipsilateral to the UDT (in the previously undescended testicle). Forty-nine of the 52 patients with UDT (94%) were corrected by orchidopexy at ages ranging from one to twenty-six. Of the 49 orchidopexies in the ipsilateral tumor group, 48 (98%) were successful and 1 failed. Two patients had spontaneous testicular descent and 2 patients had descent with hormonal therapy. Ten patients had no treatment. The average interval from the time of UDT diagnosis and the development of GCT ipsilateral to the previously UDT was 18 years. Twenty-four patients had tumors contralateral to the UDT. 54.1%(13/24) with tumors developing in the contralateral testes had successful orchidopexy at an average age of 7 years. Of the remaining 11 of 24, four patients had contralateral orchiectomy at the time of treatment of the UDT. Exploration was conducted and no tissue identified in 3. Two patients had spontaneous descent. Two patients had no treatment. The average time interval from diagnosis of UDT to the diagnosis of GCT was 22 years. A much greater percentage of patients developed tumors in the previously undescended testicle if the orchidopexy was performed after the age of 10 years. Performing orchidopexy prior to the age of 5 years, however, did not protect the testes from the development of cancer. There is no statistical difference between the groups with ipsilateral and contralateral tumors with respect to age at tumor presentation or the time interval from orchidopexy to tumor diagnosis. Sixty-three percent of patients with tumors developing in untreated testes or testes suffering from failed orchidopexies, presented with advanced disease (B3 or C), compared with 43% of patients with treated UDT's and 34% of patients with tumors developing in descended testes contralateral to UDT's, an odds ratio of 2.39, but not statistically significant. The mortality for patients who had untreated or failed orchidopexies, 27%(3/11) was 4.5 times higher than those with successful orchidopexies 8% (4/52), p=0.06 at 95% confidence limit, or 3.3 times higher than for patients with normally descended testes.

Conclusion

Germ cell tumors occurred on average 7-10 years earlier in patients with UDT ipsilateral to the side of TGCT than in those where GCT developed in the contralateral normally descended testes. Orchidopexy did not confer protection to testes in the development of TGCTs, however, there was a non-significant delay in the time to onset of tumor and the percentage of the advance stage at presentation compared to untreated testes or normally descended testes. In this series, early orchidopexy was associated with 4.5 less likelihood of dying from GCT compared with non-treated testes, a difference which approached, but did not reach, statistical significance.

Keywords

Testes cancer; Germ cell tumor; Undescended testes; Maldescent; Cryptorchidism; Orchidopexy; Retroperitoneal lymph node dissection.

Abbreviations

UDT: Undescended Testes; TGCT's: Testicular Germ Cell Tumors; CIS: Carcinoma-*In-Situ*; TDS: Testicular Dysgenesis Syndrome.

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INTRODUCTION

Incidence and Prevalence of UDT

Cryptorchidism or undescended testicle (UDT) is a relatively common entity occurring in approximately one per 120 live male births. This constitutes 0.8% of the male population.[1] Cryptorchidism persists and is found in at least 0.23-0.30% of adult males,[2-5] yet is reported as high as 0.78-3.0% by Scorer, Swerdlow and Beard.[3,5,6] Thus, while some populations are affected at a higher frequency than others, approximately 2-4% of boys are globally diagnosed with either unilateral or bilateral cryptorchidism.[7] The prevalence of cryptorchidism varies somewhat internationally with a range of the highest to near the lowest incidence reported from the western to the eastern fringes of Scandinavia: 9.0% in Denmark and 2.4% in Finland.[8] Several reports in Lithuania and the USA note an increase in incidence during the 1970s and 1980s, however, in England rates have been declining since the 1990s.[9-11]

Secondary disease diagnoses occur more commonly in patients with UDT than in normally descended testes, and cryptorchidism is one of the strongest risk factors for infertility and testicular cancer.[12] Infertility can occur in up to 30% of patients with UDT.[13-16] Seven to twelve point five percent of males with germ cell tumors (GCT's) of the testes have a history of UDT.[3,17-22]

Incidence and Risk of Germ Cell Tumors

The incidence of testicular malignancy in patients with UDT is not precisely known, but has been reported to be anywhere from 3.6 to 30%. Although quite variable, as seen in the review by Farrer,[5] 7-11% seem to be commonly reported numbers.[2,23-27] This amounts to ~0.0013% of the general population.[1] So as many as 10% of all cases of testicular germ cell tumors (TGCT) are associated with men who have a history of cryptorchidism.[28] Numerous reviews have attempted to define the incidence of GCT's in patients with testicular maldescent, but there is not an agreed upon rate, perhaps due to differences in definitions/terminology for both undescended testes and whether carcinoma-*in-situ* (CIS) was included with TGCT.[80,81] For example, Ford, et al reported on 112 testes finding a higher incidence of CIS in abdominal and high-inguinal testes than in other locations.[4]

The relative risk for TGCT has been reported to be as high as 50 times greater in males with UDT compared with those with a normal testicular descent. More recent reports have placed the relative risk at a 3-10 fold increase, with several calculating the risk at 4.5-6 times that of the general male population.[5,23,29-30] Some of the variability reported may be related to the degree of testis descent arrest.

Cryptorchidism thus appears to be an accepted risk factor for GCT with a conservative estimate relative risk of 3.7-7.5 times higher than the normally descended testicle population.[23,29-31]

Interestingly, there appears to be ethnic variation in predisposition as both cryptorchidism and testicular malignancy are uncommon in American blacks and Asians, and this may account for much of the international variation in reported rates, due to different ethnic make-up of the population.[32-34] Also of interest, is a similar rate of TGCT in dogs with UDT of 14%.[35]

Mortality Risk

Farrer et al discussed the observation that a man with cryptorchidism has a 9.7 times increased risk of dying of TGCT than men in the normal population. This was considered in the light of suggestions that stage of presentation and mortality were no different between cryptorchid and normal populations.[36-39] After much analysis, Farrer and colleagues concluded, however, that post-pubertal men with unilateral UDT < age 32 should undergo orchiectomy, while those >32, warrant close observation, due to considerations of low overall mortality risk in this cohort. They did relate this recommendation as a framework rather than dogma, because of a multiplicity of factors including fertility, endocrine function, cosmetics, morbidity of cancer treatment, the expense of follow-up examinations, and patient psychosocial concerns.

Effect of Surgical Correction

Although, there is no definitive evidence that orchiopexy prevents malignant degeneration of the cryptorchid testis, there are reports that the relative risk of tumorigenesis is less in patients who had orchidopexy performed prior to the age of 10 years.[16,26,32,36,40,85] Other reports have failed to show any change in tumor risk with orchidopexy.[16,41,42] Some authors purport a direct correlation between the time a testes is in a cryptorchid position and the incidence of TGCT. Most, but not all, of the data on surgical correction of UDT show some reduction in the rate of TGCT. Batata and colleagues reported 13/14 uncorrected cryptorchid testes developed TGCT.[36] Petterson's group reported 56 cases of TGCT in approximately 17,000 men with orchidopexy for UDT, with a tumor incidence of 2.2% if performed before age of 13, and 5.4% if after age 13.[43] Thus, some have recommended that the age of surgical correction should be lowered, and in modern practice is usually performed before the age of two.[44]

Orchidopexy has otherwise been recommended predominantly because a testis tumor may be easier to diagnose and treat if the gonad is located intra-scrotally rather than intra-abdominally or in the inguinal canal. Orchidopexy has also been advocated to prevent the morphologic changes that lead to infertility in the UDT, specifically to allow normal development of spermatogenic tissue. The hypothesis has been that the earlier the orchidopexy, the better the chance of preserving normal spermatogenesis.[4,14-16]

Recommendations for patients and families regarding management of undescended testicle(s) remains controversial. The controversy exists because of the actual risk of developing germ cell tumors (GCT's) or Carcinoma-*In-Situ* (CIS) and cancer-related morbidity/mortality in patients with UDT's is not completely defined, nor is the effect of surgical correction of the condition.[53] In this manuscript, the presentation and outcome of cryptorchid patients with and without surgical correction is evaluated, in order to better define treatment for this patient population. The effect of surgical correction of UDT on fertility is a separate topic and will

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not be addressed in this discussion.

PATIENTS AND METHODS

A retrospective review was conducted of 2204 patients in the urology databases with TGCT identified 1520 patients treated with RPLND for germ cell tumors of the testis at Indiana University Medical Center (IUMC) or Baylor College of Medicine (BCM) over a 20-year period ending July 2017. Institutional Review Board (IRB) approval was obtained to review the charts of patients with GCT's for outcomes results. Both IUMC and BCM are tertiary medical centers and many patients are referred after the primary tumor has been treated, so there is some skewing of patients with more advanced disease in these centers. Patients were stratified based on the presence or absence of undescended testes, orchidopexy, stage at presentation and survival.

Statistical testing was performed using the SAS statistical package. Subgroup variables were tested with continuity-adjusted chi-square, both one-tail and two-tail analyses. After constructing 2×2 tables for the relevant subgroups, hazard ratios, relative risk and Chi-square with Fischer's exact test were used to evaluate differences between groups for statistical significance. Confidence intervals were also calculated for the comparison of stage and mortality between the orchidopexy and no orchidopexy groups.

RESULTS

Ninety-four patients were identified with a history of UDT and TGCT. Eighty-seven of the 94 had complete datasets which included a minimum follow-up of 2 years after treatment of their GCT. Ninety-four of 2204 represents 4.5% of the total group. Eighty-seven of 1520 RPLND's represents 5.7%. The average age at diagnosis of GCT in the 87 patients were 29.7 years. 68 of 1520 (4.1%) patients had tumors in an ipsilateral UDT while 26 of 1520 (1.5%) had a contralateral UDT from the site of GCT.

Fifty-two patients with treatment of the ipsilateral UDT (in the previously undescended testicle) developed GCT, and their average age at presentation was 30 years. Forty-nine of the 52 patients with ipsilateral UDT (94%) were corrected by orchidopexy at ages ranging from one to twenty-six. The average age at the time of orchidopexy for the 49 patients was 10.8 years. Of the 49 orchidopexies in the ipsilateral tumor group, 48 were successful and 1 failed. Two patients had spontaneous testicular descent and 2 patients had descent with hormonal therapy. Ten patients had no treatment, leaving a total of 11 pts with residual undescended testes due to no or failed treatment. The average age at the time of diagnosis/treatment was 12 years and the average time interval from the time of UDT diagnosis and the development of GCT was 18 years for tumors ipsilateral to the side of UDT.

Twenty-six patients had tumors contralateral to the UDT, 24 with complete data available. Their average age of presentation was 28.9 years. 54%(14/26) with tumors developing in the contralateral testes had successful orchidopexy at an average age of 7 years. Of the remaining 11 of 24, four patients had contralateral orchiectomy at the time of treatment of the UDT. Exploration was conducted and no tissue identified in 3. Two patients had spontaneous descent. Two patients had no treatment. The average time interval from diagnosis of UDT to diagnosis of GCT was 21.9 years.

Of the 66 total successful orchidopexies performed (52 with ipsilateral GCTs and 14 with contralateral GCTs), 52 were unilateral and 14 were bilateral orchidopexies.

A comparison of the ages at the time of orchidopexy between patients developing ipsilateral *vs.* contralateral tumors is present in Table 1. A much greater percentage of patients developed tumors in the previously undescended testicle if the orchidopexy was performed after the age of ten years. Performing orchidopexy prior to the age of 5 years, however, did not protect the testes from the development of cancer. The location of the neoplastic testicle at the time of presentation with testes cancer is shown in Table 2. There is no statistical difference between the groups with ipsilateral and contralateral tumors with respect to age at tumor presentation or the time interval from orchidopexy to tumor diagnosis; however, patients with GCTs in UDT developed tumors 4 years earlier than in patients who had an GCT in the normally descended testes contralateral to a UDT.

Histology

The histology of the testes lesions in this population differs significantly from previously reported series. The majority of the cancers are of a mixed non-seminoma histologic pattern with embryonal cancer being the most common singular germ cell element. The histologic subtype is not a predictor of outcome in this series of patients with UDT. The data are summarized in Table 3. No pattern of histology could be identified by the level of testicular descent arrest.

Table 1. *Breakdown by Age and Side of Testes Tumor and Timing of Successful Orchidopexy in 87 Patients with Complete Data Available*

Age at orchidopexy (years)	Total Patients	Tumors Ipsilateral to UDT (n=52)	Tumors Contralateral to UDT (n=24)
<5	(20/76) 32%	(6) 24%	(14) 58%
5-10	(7/76) 12%	(4) 6%	(3) 13%
>10	(49/76) 56%	(42) 71%	(7) 29%
	100%	100%	100%

Table 2. *Location of the 87 Neoplastic Ttesticles at Time of Presentation with Testes Cancer*

Location	Total	Ipsilateral	Contralateral
Scrotum	76 (87%)	52 (68%)	24 (32%)
Inguinal Canal	5 (5.7%)	5 (100%)	0 (0%)
Intra-abdominal	6 (6.8%)	6 (100%)	0 (0%)

Table 3. *Histology of the Orchiectomy Specimen in All 94 Patients with Testicular Maldescent*

	Number of Cases	Percentage of Total
Pure Seminoma	10	11%
Pure Embryonal	19	20%
Pure Teratoma	7	7%
Pure Choriocarcinoma	1	1%
Pure Yolk sac	2	2%
Mixed w NSGCT	55	58%
Unknown	1	1%

Stage

The stage of the cancers at the time of presentation is summarized in Table 4 of the 87 patients with full datasets. Sixty-three percentage of patients with tumors developing in untreated testes or testes suffering from failed orchidopexies, presented with advanced disease (B3 or C) (7/11), compared with 43% of patients with treated UDT's (22/52) and 34% of patients with tumors developing in descended testes contralateral to UDT's (8/24). The hazard ratio of presenting with the advanced disease if the UDT was not treated *versus* treated is 2.39; however, the calculated 95% confidence intervals using the logistical regression method assuming standard distribution of the log odds ratios are [0.621, 9.169] which is not statistically significant. Additional Chi-square testing between the treated and untreated UDT groups gave a *p*-value of 0.057, suggesting statistical non-significance.

Inguinal Lymph Nodes

Five point seven percent (5/87) of patients had hemiscrotectomies due to previous operative scrotal contamination, but none of these specimens contained viable tumor. No patients developed inguinal lymphadenopathy at the time of GCT treatment (none underwent inguinal adenectomy) and none relapsed in the inguinal region or scrotum.

Survival

Ninety percent (77/87) of the patients with UDT who developed GCT's are currently alive having NED with a greater than a 5-year average follow-up. One patient died of causes unrelated to testes cancer. One patient 1% (1/87) is alive with persistent disease and is undergoing further treatment. Ten percent (9/87) have died secondary to progression of disease or during therapy for the cancer. This compares to 90.6% who are NED, 2.4% living with disease, and 6.2% died of disease progression or during therapy for the total group of 1520 with TGCT's. These differences are not statistically different. There was also no difference found in the relapse rate of 14.7% of all GCT patients and those with UDT-16%.

Stage-specific mortality by groups is shown in Table 5. The mortality for patients who had untreated or failed orchidopexies is greater 27% (3/11) than for patients with successful orchidopexies 8% (4/52) or for patients with normally descended testes 6.2% (89/1433). This is in comparison to the overall mortality for all 1520 patients- 6.25% (98/1520) and for all those presenting with advanced disease (B3 + C)- 15.6% (59/512).

The data for the patients with ipsilateral UDT developing GCTs, between the untreated and treated groups, was evaluated by 2×2 matrix and hazard ratio was determined to be 4.5. The regression confidence intervals at the 95% level for the odds ratio were calculated to be [0.844, 23.99], again including 1.0, indicating non-significance but this time even larger interval (indicating too small a sample size) and skewed to right, suggesting a larger hazard than the 4.5 calculated. The differences between the groups was also assessed by chi-square analysis (3.52) and found to be significant at the 90% confidence level but not at the 95% level with a *p*-value= 0.06. Fischer's exact test gave a *p*=0.095.

DISCUSSION

Etiology

The pathogenesis of the increased risk of TGCT in UDT's has been the subject of extensive debate and may involve both intrinsic gonadal defects and the effects of abnormal gonadal position.[85] The question arises: "are the testes maldescended due to abnormal gonads or are the gonads abnormal due to the maldescent?"

Table 4. *Clinical Staging at the Time of Presentation with Testes Ccancer in Patients with Complete Data Available*

Patient Group	Total No. Patients	A	B1	B2	B3	C	Advanced (B3+C)
All GCT	1520	699(46)*	147(10)	162(11)	172(11)	340(22)	512(33)
All UDT	87	31(35)	8(9)	11(13)	12(14)	25(29)	37(43)
UDT total ipsilateral	63	23(37)	7(11)	4(6)	9(14)	20(32)	29(46)
Tumor Ipsilat to Rx'd UDT	52	23(44)	4(8)	3(6)	6(12)	16(31)	22(43)
Tumor Contralat to Rx'd UDT	24	8(33)	1(4)	7(29)	3(13)	5(21)	8(34)
Tumor Ipsilat. to Untreated UDT or Failed pexy	11	0(0)	3(27)	1(9)	3(27)	4(36)	7(63)

**numbers in parenthesis denote percentages of total for that patient group*
The Advanced stage is the arithmetic sum of patients presenting with B3 and C stage disease

Table 5. *Stage Specific Mortality*

Group	# Patients	A	B1	B2	B3	C	Advanced (B3+C)	Total All Stages
All GCT	1520	1.7% (12/699)	7.5% (11/147)	9.9% (16/162)	12.8% (22/172)	10.9% (37/340)	11.5% (59/512)	6.4% (98/1520)
NI descent	1433	1.8% (12/668)	7.7% (11/142)	9.9% (15/152)	12.5 (20/160)	9.8% (31/315)	10.7% (51/475)	6.2% (89 /1433)
All UDT	87	0% (0/35)	0% (0/5)	10% (1/10)	17% (2/12)	24% (6/25)	22% (8/37)	10% (9/87)
All Ipsilat UDT	63	0% (0/26)	0% (0/5)	0% (0/3)	22% (2/9)	25% (5/20)	24% (7/29)	11% (7/63)
Tumor Ipsilat to Rx'd UDT	52	0% (0/23)	0% (0/4)	0% (0/3)	17% (1/6)	19% (3/16)	18% (4/22)	8% (4/52)
Tumor Contra to Rx'd UDT	24	0% (0/9)	0% (0/0)	14% (1/7)	0% (0/3)	20% (1/5)	13% (1/8)	8% (2/24)
Tumor Ipsilat to Untreated UDT or Failed Orchiopexy	11	0% (0/3)	0% (0/1)	0% (0/0)	33% (1/3)	50% (2/4)	43% (3/7)	27% (3/11)

Mostofi defines 5 factors which may be operative in the etiology of UDT: 1) abnormal germ cells, 2) elevated temperature, 3) altered blood supply, 4) endocrine disturbances, 5) gonadal dysgenesis.[4] Evidence of each factor is multifactorial, but the preponderance to date does not lead to any definite conclusion regarding etiology. [94]

In support of factor, one is the report of increased risk of GCT's developing in the contralateral, descended testes. (see discussion below) Therefore, it appears that both testes are quite often abnormal in patients with unilateral UDT.[87,88] Also in support of the notion that the germ cells are primarily abnormal leading to maldescent is the finding that CIS originates from malignant gonocytes and that CIS cells have been identified in fetal and neonatal testes.[45,46,84] The Scandinavian group and others have performed histologic, ultrastructural and immunohistochemical analyses of thousands of biopsies and pathological specimens to come to these conclusions.[3,47-54] However, a study performed Muffly and associates in 1983 failed to confirm the histologic alterations in UDT's in men < age 16 years.[51] A recent Danish study by Cortes et al, revealed no cases of CIS in 100 consecutive boys median age 10.8 evaluated for impalpable testes.[55,56] Therefore, CIS may not be as common or as early a finding as suggested in other studies of Scandinavian patients.

Support for factor 2, elevated temperature, comes from animal studies showing morphological changes in the testes of experimental animals whose testes were subject to elevated temperatures and surgical placement in the inguinal canal.[57-61]

Evidence for factor 3 comes from animal studies which found abnormal capillaries in boar abdominal testes *vs.* scrotal testes.[62] Certainly vascular changes associated to the performance of orchidopexy could contribute to alterations in blood supply to the pexed gonad, and thus potentially change the metabolic clearance of important molecules, such as steroid hormones.[93]

The notion of factor 4, endocrine factors stems from reports of increased risk of GCT's in individuals who were exposed to hormones *in utero*.[24,63-65,95,96] Reports that exposure to other agents (non-endocrine) can also increase the risk of maldescent, lends credence to this hypothesis.[44]

Regarding factor 5; the predisposition of dysgenetic gonads to carcinoma in patients with disorders of sexual differentiation, especially secondary to chromosomal anomalies, is well recognized.[27,55,66,67] Numerous cytogenetic and HLA pattern studies of testes tumors and somatic DNA of individuals with familial patterns of gonadal malignancy has failed to reveal a putative testes tumor gene.[33,68,69] The only consistent cytogenetic findings include iso (12 p) which is present in the vast majority if GCT's, and appears to be an early event in tumorigenesis. Inconsistent findings include structural changes in chromosomes 1, 11, 12, 17, 22, X and Y.[27,70]

In 2001, Neils Skakkebaek proposed the Testicular Dysgenesis Syndrome (TDS) which hypothesized a single developmental disorder producing the constellation of cryptorchidism, hypospadias, testicular cancer, and reduced semen quality.[71] Since the presence of all four is uncommon, this could represent a spectrum of embryonic gonadal development disorder, perhaps related to a disruption in androgen receptor signaling.[90-92]

Ferguson and Agoulnik have comprehensively reviewed other possible factors-somatic, tumor and somatic mutations, gene expression, and epigenetics. They cite breakdown in the blood-testis barrier and other Sertoli cell and Leydig cell dysfunction as possible somatic factors in spermatogonia abnormalities, as well as number of environmental factors and candidate genetic mutations.[44]

Subset Analysis

This retrospective review possesses all the limitations of any retrospective study, including limited power in establishing significance in subgroup analysis. With stratification of the patients by stage at presentation and location of testes, the numbers of patients in each group are relatively small, but the largest single institution series yet reported. These issues must be borne in mind

in assessing the data results.

Only 5.7% (87/1520) of patients in this series had a history of undescended testes, which is consistent with other reports, but less than the commonly reported 7-10% cited above.

Histology and Degree of Maldescent

Most TGCT's developing in UDT's are seminomas,[16,36,72,73] but the proportion of pure seminoma varies based on final resting location of the testes 87% in abdominal, 78% in inguinal, and 50% in orchidopexy-produced scrotal testes, the same as in normally descended testes.[86-89] The histologic pattern was felt to be more aggressive in patients that had untreated or unsuccessful orchidopexies.[16] Another report showed seminoma in only 43% of patients with UDT and a greater % of teratocarcinoma in UDT patients <30 years of age.[19] Martin found the post orchidopexy tumor distribution as follows: seminoma 40%, embryonal 25%, teratocarcinoma 19%, teratoma 8%, and mixed 8%.[72] An Air Force report in 1968 found 75% of the tumors developing in 12 UDT's to be non-seminomatous.[74] The Toronto experience found the non-seminoma tumors in non-scrotal testes to be more advanced than those found in scrotally-placed testes.[21]

Due to the nature of the referral pattern at Indiana University and Baylor College of Medicine in this series, there is a change in the usual distribution of tumor histology, with fewer seminomas than is usually reported and a higher % of nonseminomatous GCTs (NSGCTs). This skew in histology could clearly affect the potential biologic behavior of the tumors as a whole, and thus the outcome of treatment; therefore, it represents a potential bias in the data reported.[82,83]

Disease Distribution

Because of the potential differences in lymphatic drainage in the UDT, especially after the dissection/manipulation during orchiectomy, several authors have advocated routine/prophylactic inguinal lymph node dissection and or scrotectomy. We have not found the inguinal lymph nodes to be a site of primary disease spread or relapse and do not perform inguinal lymphadenectomy or scrotectomy unless indicated.

Age of Orchidopexy

One problem in interpreting tumor and histology data is the variability in the age at which time orchidopexy was performed. Often, when individual authors attempt to segregate patients by age of treatment, the numbers of patients which have developed tumors is so small that any ability to uncover statistical differences between groups, is eliminated. This has lead to the conclusion, by some, that the age of orchidopexy has no relation to eventual tumorigenesis.[41] However, Gehring and associates reported on 529 patients with GCT's, 37 with UDT's. No testes tumors in the group of 6 UDT patients surgically pexed before the age of 6.[22] Pottern et al, also felt that the testes cancer risk was correlated with the timing of orchidopexy, with the highest risk being in patients with no correction.[40] An Israeli study of 40 patients treated for post-pubertal UDT, showed 15% had tumors at the time of operation with a 5% rate of spermatogenesis. Two patients treated with orchidopexy at ages 9 and 17 developed TGCT's at ages 27 and 31 years respectively. They advocate routine orchiectomy for treatment of all patients diagnosed with UDT after puberty due to low fertility and high malignancy potential.[75]

In this series, a greater percentage of tumors are found in the group of UDT patients that had orchidopexy performed after the age of ten. Yet, early orchidopexy did not protect patients from tumor formation, as 6 patients (6.9% of the 87 total UDT patients) who underwent orchidopexy <5 years developed tumors. The age of orchidopexy did not correlate with the stage at presentation or survival.

Final testes position, however, did correlate with outcome, in that, the untreated and failed orchidopexy group presented with 2.4 increased risk of advanced disease and 4.5 higher likelihood of death from the disease than the successfully treated (orchidopexy) group. However, the differences between these groups approached, but did not reach, statistical significance. Statistical analysis showed that at least 344 UDT patients would be necessary to show significance if the calculated hazard ratio holds true in a larger series. The lack of significance in this review may be a result of inadequate power to detect a difference, due to the relatively small numbers of deaths in each subset; therefore, the results reported should be interpreted with caution. The tendency towards poorer outcome in the non- or failed- treatment group, may be the most significant finding of this review. An important explanatory mechanism for this worsened survival in the non-pexed patients advanced stage at presentation, had a hazard ratio of 2.4 but also was not statistically different from the group undergoing orchidopexy.

Time to Tumor Development

Time intervals of 5-16.4 to even 29 years after orchidopexy have been reported.[17,72,76] Mean intervals vary from 12-19 years.[72,74]

In this study, the mean interval of 18 years for ipsilateral tumors and 22 years for contralateral seems to fall within the previously reported ranges and was not statistically different between groups.

Contralateral Testes

The incidence of tumors developing in normally descended testes contralateral to a UDT has been found in 10-24% of cases.[5,21,22,24,36,41,74] Strader defined the risk as 8X higher in the ipsilateral UDT and 1.6 X higher in the contralateral UDT compared with males with normal descent.[26] Mazanec reported carcinoma in the contralateral testes in 7 of 27 patients with UDT (26%) and CIS in the contralateral testes in 27/500 (5.4%).[27] Nevertheless, there are some studies finding no statistically increased risk in the contralateral testes when proper case controls are applied to the cohort data. In the study by Pottern and associates, the prevalence

of UDT contralateral to a testes tumor is estimated at 1.5% and their calculations of tumors in the contralateral testes to a UDT in three independent series found a frequency of 0.9-1.3%.[40]

The number of tumors developing in the contralateral normally descended testes in this series was 27.6% (24/87) of all UDT patients 1.6% (24/1520), somewhat higher than the 10-24% and 1.3% reported in previous studies, and suggestive of a higher risk than expected in testes contralateral to those with normal descent.

TGCT Diagnosis

Ultrasound of the testes has shown to be a reliable and cost-effective screening modality for gonadal GCT's, both in terms of sensitivity and specificity. However, it does require the testes to be palpable in order to obtain an image. Therefore, this is not an acceptable diagnostic modality for children with non-palpable UDT's, who require initially laparoscopy +/- exploration for evaluation. Laparoscopy has been shown to be a safe and effective method of diagnosis, also Ultrasonography (US), however, does not detect CIS.

There have been some recent encouraging results in attempting to develop testes cancer-specific monoclonal antibodies to detect malignant germ cells, such as detecting CIS not only in pathologic sections, but in semen itself *via* semen analysis. One monoclonal antibody, TRA-1-60 raised against an embryonal cell carcinoma cell line and another M2A are present in 75-100% of fetal germ cells. TRA-1-60 stains positive in 85% of CIS cells, and 100% of ECC a cells from tumor specimens, tested.[30,54,77] Another monoclonal antibody, 43-9F is a marker of CIS cells and also showed positive staining in germ cell carcinoma indicating the pathogenetic link between CIS and invasive cancer.

Genetic Testing

Thus far, a dominant oncogene or tumor suppressor gene mutant has not been identified to be expressed consistently in most TGCT's, aside from the i(12p) variants identified by several research teams.[68] Multiple additional sites of cytogenetic abnormalities have been identified in karyotypically abnormal GCT's at 1p36, 1p13-1qh, 11q23, 19q13 and pericentromeric regions of acrocentric chromosomes.[69] The proto-oncogene *hst* 1, located on 11q, was found to be expressed in 63% of non-seminoma TGCT's but only 4% of seminomas evaluated.[70] C-*kit*, a growth factor receptor with tyrosine kinase activity, the gene of which is found on chromosome 4, has been shown to be involved in normal testicular and hematological cell development. Conversely, c-*kit* is expressed in 83% of seminomas but 7% of non-seminomas. c-*kit* expression may be controlled *via* methylation. Whole genome sequencing has identified 6 susceptibility loci in TGCT: 1) *KITLG* and 2) *ATF7IP* on chromosome 12, 3) *SPRY4* on chromosome 5, 4) *BAK1* on chromosome 6, 5) *TERT-CLPTM1l* on chromosome 5, and 6) *DMRT1* on chromosome 9.[44] The TERT locus, which encodes for telomerase and its transcription factor regulator, *ATF7IP* are often overexpressed in cancers. Both seem to be associated with TGCT in a UK-based whole genome study by Turnbull et al.[78] Karnetsky, identified two SNPs within the zinc finger-like DNA-binding *DMRT1* allele which significantly predisposes to TGCT.[79]

Thus, molecular markers are proving to be valuable in evaluating grade and prognosis of other solid tumors, and continued research along these lines is warranted. Findings such as the diminished level of glutathione S-transferase (a chemotherapy drug detoxifier) in TGCT's compared to normal germ cells is particularly intriguing. The TCGA will be publishing a manuscript, in the near future, which may shed light on which are early and late mutations in possible TGCT progenitor cells.

CONCLUSIONS

In addition to considerations of fertility in the management of undescended testes, the issue of possible tumor development must be discussed with patient or parents. The risk of tumor development in these testes will not be affected by treatment such as orchidopexy, however, the likelihood of presentation with advanced disease and therefore with reduced survival may be higher if orchidopexy is not performed. Therefore, orchidopexy is advocated for patients with UDT.

Recommendations for Managing UDT's

- Early orchidopexy, < age 2 when possible to reduce the risk of impaired spermatogenesis
- Biopsy of all cryptorchid testes at time of orchidopexy

  if + for CIS- possible orchiectomy or close follow-up, due to high progression rate (as high as 70%)[91]
  if - for CIS- routine regular monitoring by self-exam and regular PE +/- U/S, including the contralateral testes
- Consider orchiectomy in patients presenting with UDT after puberty.
- Patients with no or failed treatment for UDT may have higher risk of developing an advanced or potentially lethal disease.
- No routine hemi- or bilateral- scrotectomy or inguinal node dissection should be performed in treating patients with UDT's who develop TGCT's.
- Pursue development of improved diagnostic strategies to facilitate early and reliable detection of TGCT's, in those at risk. Ideally, this methodology would not require open testes biopsy, e.g. a molecular marker for TGCT detectable in blood or semen.

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CONFLICTS OF INTEREST

There are no conflicts of interest with any of the authors related to the content of this manuscript.

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