Cryptorchidism and Testicular Cancer: Separating Fact From Fiction

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Abbreviations and Acronyms

ASA = American Society of Anesthesiologists

ITGCN = intratubular germ cell neoplasia

UDT = undescended testis

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Purpose: We dissected prevailing assumptions about cryptorchidism and reviewed data that support and reject these assumptions.

Materials and Methods: Five questions about cryptorchidism and the risk of testicular cancer were identified because of their implications in parent counseling and clinical management. Standard search techniques through MEDLINE® were used to identify all relevant English language studies of the questions being examined. Each of the 5 questions was then examined in light of the existing data.

Results: The RR of testicular cancer in a cryptorchidism case is 2.75 to 8. A RR of between 2 and 3 has been noted in patients who undergo orchiopexy by ages 10 to 12 years. Patients who undergo orchiopexy after age 12 years or no orchiopexy are 2 to 6 times as likely to have testicular cancer as those who undergo prepubertal orchiopexy. A contralateral, normally descended testis in a patient with cryptorchidism carries no increased risk of testis cancer. Persistently cryptorchid (inguinal and abdominal) testes are at higher risk for seminoma (74%), while corrected cryptorchid or scrotal testicles that undergo malignant transformation are most likely to become nonseminomatous (63%, $p < 0.0001$), presumably because of a decreased risk of seminoma.

Conclusions: Orchiectomy may be considered in healthy patients with cryptorchidism who are between ages 12 and 50 years. Observation should be recommended in postpubertal males at significant anesthetic risk and all males older than 50 years. While 5% to 15% of scrotal testicular remnants contain germinal tissue, only 1 case of carcinoma in situ has been reported, suggesting that the risk of malignancy in these remnants is extremely low.

Key Words: testis, testicular neoplasms, cryptorchidism, abnormalities, risk

Cryptorchidism, also known as UDT, is the most common congenital abnormality of the genitourinary tract. Being so, it has earned a good deal of interest by urologists in general and pediatric urologists in particular. Curiously however, cryptorchidism, its causes and its potential associated testicular cancer risk have historically been poorly understood and documented, resulting in a number of misconceptions that have been passed down through generations of urologists.

A major problem with characterizing risk between cryptorchidism and testis cancer relates to diagnosing and documenting cryptorchidism. Retrospective analyses, which represent most data upon which conclusions can be drawn, may include men with retractile testes, men with a history of spontaneous descent during infancy or at puberty, men who un-

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derwent treatment with hormonal stimulation and men with persistent UDT after previous orchiopexy. While estimates of the incidence of cryptorchidism based on pediatrician examination and birth records are 1% to 2% at age 12 months, various groups have suggested that the rate of surgery for cryptorchidism is approximately double the estimated risk (3% to 4%), suggesting that the risk of UDT may vary during childhood depending on linear growth and timing of puberty, retractile testes, ascending testes and missed diagnosis among other things.[1–4]

Part of the confusion as it relates to cryptorchidism and testis cancer may also be because the rates of UDT and testis cancer are heterogeneous and changing.[5] Even in different populations of northern Europe the incidence of testis cancer is widely discrepant, ranging from 0.9/100,000 person-years in Lithuania to 7.8/100,000 person-years in 1980 in Denmark.[6] Some groups have postulated an effect of changing environmental conditions, such as an altered hormonal milieu in utero related to increased exposure to synthetic estrogens and estrogen-like chemicals.[7] The observation that formerly cryptorchid testes demonstrate a higher rate of carcinoma in situ and malignant transformation suggests an association. However, whether the condition of maldescent predisposes to dysplasia or is a marker of aberrant gonadocyte development in fetal life remains unanswered. Data supporting the former is that with unilateral maldescent the UDT is more likely to demonstrate malignant transformation. Evidence supporting the latter is that with unilateral maldescent the normally descended testis has historically been believed to be at increased risk for tumor.[8] We analyzed some of the prevailing assumptions about cryptorchidism and reviewed data that support and reject these assumptions.

METHODS

Five questions relating to cryptorchidism and associated testicular cancer risk were identified. 1) What is the RR of testicular cancer in a cryptorchid or formerly cryptorchid testis? 2) In patients with unilateral cryptorchidism what is the RR of testicular cancer in a contralateral, normally descended testis? 3) Does testis location affect the subsequent pathological subtype of testicular cancer? 4) Does orchiopexy decrease the risk of testicular cancer? 5) Is there a risk of malignant degeneration for testicular remnants? These 5 questions were identified because of their clinical implications in the treatment of a child with UDT, and because of the divergence of opinions on these topics.

Standard electronic search methods were used (MEDLINE database). No limits were set on publication date and MEDLINE contains published literature dating back to 1950. References from review articles were also analyzed to identify studies that were not identified by MEDLINE searches and those that predate 1950. All searches were performed using standard search techniques with foreign language, nonhuman studies, editorials/letters, review articles and case reports excluded. While review articles were obtained and reviewed for references and content, this discussion only includes relevant English language case series, cohort studies, case-control studies and meta-analyses.

In addition, chapters from urological textbooks were reviewed for content and references. When deemed relevant, the material was obtained for further review and inclusion. Extensive literature reviews or meta-analyses have been published on 2 questions that we sought to answer[9–11] and these studies are cited. No additional attempts were made to perform meta-analyses of the remaining 3 questions largely due to a lack of prospective data on these topics as well as to wide variability in the nature of the studies done of these subjects.

RESULTS AND DISCUSSION

Questions 1 to 3 demonstrated significant overlap in the relevant literature and, therefore, they were queried together. An initial search using the keywords testis cancer, risk factor, cryptorchidism and undescended testis revealed more than 900 articles, of which 43 provided relevant information. An additional 8 studies were identified upon reviewing the bibliographies of the relevant studies. Additional reviews for orchiopexy, age and testis (190 articles, of which 23 were relevant), and orchiectomy, age and cryptorchidism (111, of which 10 were relevant) as well as multiple searches using testicular, remnant, nubbin, testis and cancer (14 relevant studies) were done to investigate questions 4 and 5. While not all studies reviewed could be presented in this analysis, table 1 lists those selected for discussion, categorized by study type.

Question 1) What is the RR of Testicular Cancer in a Cryptorchid or Formerly Cryptorchid Testis?

An association between testicular maldescent and testis cancer has been known for more than a century.[12] Few urologists would argue with the statement that there is an association between UDT and testicular cancer. However, a review of major urological textbooks suggests that the risk is poorly quantified. Campbell-Walsh Urology, 9th edition states, “It is a well established fact that children born with undescended testes are at increased risk for malignancy. . . the RR is approximately 40 times greater.”[13] However, in Adult and Pediatric Urology it is stated that “The combined risk for all cryptorchid males, irrespective of the location of the testes, has been calculated at 20 to 46 times greater than for patients with normally located testes.”[14] In Pediatric Urology it is stated that “Individuals born with an undescended testis have approximately a 40-fold incidence of testicular malignancy over those born with scrotal testes.”[15]

Table 1. *Categorization of select articles based on question of interest and study design*

Study Type	References
Questions 1–3:	
Retrospective cohort/pathology review	Johnson et al,[8] Gilbert and Hamilton,[16] Campbell,[17] Kanto et al,[18] Prener et al,[19] Cortes et al,[22] Swerdlow et al,[23] Pinczowski et al,[26] Pettersson et al,[28] Strader et al,[30] Ford et al,[32] Gehring et al,[33] Fonger et al,[34] Batata et al,[35] Jones et al,[58] Kuo et al[59]
Meta-analysis	Martin,[9] Dieckmann and Pichlmeier[10]
Case-control	Coupland et al,[24] Moller et al,[25] Pottern et al,[27] Herrinton et al,[29] United Kingdom Testicular Cancer Study Group,[31] Sabroe and Olsen[37]
Question 4:	
Retrospective cohort/pathology review	Kogan et al,[14] Pinczowski et al,[26] Pettersson et al,[28] Rogers et al,[39] Hornak et al,[40] Rusnak et al[46]
Meta-analysis	Martin,[9] Walsh et al[11]
Case-control	Pottern et al,[27] Herrinton et al,[29] Sabroe and Olsen[37]
Prospective, nonrandomized	Berkowitz et al[2]
Other	Farrer et al,[41] Oh et al[42]
Question 5:	
Retrospective cohort/pathology review	Grady et al,[47] Plotzker et al,[50] Turek et al,[51] Renzulli et al,[54] Emir et al,[52] Storm et al,[53] De Luna et al,[55] Cendron et al,[56] Rozanski et al[57]

The source of these estimates dates back to 2 seminal studies of this topic, each published in the 1940s. The first series by Gilbert and Hamilton used 5 data sets published between 1828 and 1927 to generate an estimate of the incidence of UDT in men.[16] A total of almost 10 million military recruits from the British, French, American, Austrian and Scottish armies were included in these 5 studies, which together suggested a 0.23% incidence of UDT. The methods used to diagnose, document and report these cases are not discussed in the study, so that it is not possible to determine whether the diagnosis of UDT was based on physical examination and/or history. Gilbert and Hamilton reported that approximately 11% of their patients (840 of about 7,000) with testicular cancer had associated "testicular ectopy."[16] They then compared the "background incidence" of UDT, as estimated using military recruit data, with the incidence of UDT in their testicular cancer population, generating a 48-fold (0.11/0.0023) excess risk of cancer in patients with UDT. The other study by Campbell used the same combined army recruit data and, therefore, obtained the same estimate of UDT in the general population (0.23%).[17] Campbell observed a 11.6% rate of UDT in his cohort of patients with testicular cancer,[17] which was similar to the rate observed by Gilbert and Hamilton.[16] Although it is still widely quoted, the RRs generated by these 2 studies have proved to be substantial overestimates.

The 0.23% overall incidence of cryptorchidism used in the 2 historical studies[16,17] likely significantly underestimated the true incidence since modern series a demonstrate rate of UDT of between 1.1% and 1.6% at age 1 year.[1–2,10] Modern analysis suggests that the rate of prior cryptorchidism in men with testicular cancer is around 5% to 10%.[18,19] An accurate estimate of the lifetime risk of testicular cancer in a man who otherwise has no risk factors has often been quoted to be 1 in 500.[20] However, this estimate was generated 30 years ago based on data from a New York State Registry.[21] Table 2 lists relevant studies that reflect a wide variety of populations. A review of these studies showed some variability in risk estimates, ranging between 2.75 and 8.[18,19,22–28] The disparity of RR may be accounted for by several factors. 1) Some of these studies included patients who were treated with hormonal and surgical therapy,[23] others only included patients treated with surgical therapy[26] and yet others did not specify whether patients underwent prior therapy for UDT. 2) These studies reflect many populations, and the incidence of testicular cancer and cryptorchidism is known to be widely heterogeneous.[6] 3) These studies reflect a number of different design types.

Dieckmann et al performed a meta-analysis that included 20 of the modern published series, including those by Prener,[19] Swerdlow,[23] Coupland,[24] Moller,[25] Herrinton,[29] and Strader[30] et al, and determined a 4.0 to 5.7 RR of testis cancer and cryptorchidism.[10] Given the congruity among studies performed on this topic across the globe, there exists strong evidence that the risk of testis cancer in cryptorchid and formerly cryptorchid testes is most probably an order of magnitude less than that initially estimated by Campbell,[17] and Gilbert and Hamilton.[16]

While early reports may have overstated the RR of testicular cancer and UDT, they correctly identified settings that significantly increase risk, including bilateral UDT, which often coexists with abnormalities of the external genitalia, endocrinopathy and/or an abnormal karyotype, and abdominally retained testes compared with inguinal or scrotal testes. These 2 observations have endured as our understanding of cryptorchidism and testicular cancer has been refined in the last 70 years.[22,31] Rates of testicular neoplasia and ITGCN appear to be higher

Table 2. *Testis cancer in UDT and contralateral normally descended testis, and association between orchiopexy and testis cancer risk*

References	Country	Study		No. Pts	Calculated Risk		Age at Orchiopexy-Risk Association
		Period	Type		UDT	Contralar Testis	
Pottern et al[27]	United States	1976–1981	Retrospective case control	530	RR 3.7	RR 1.1	Age at correction-risk
Strader et al[30]	Washington State	1974–1988	Case-control	1,436	RR 8.0	RR 1.6 (95% CI 0.6–4.1)	Not provided
Pinczowski et al[26]	Sweden	1965–1983	Prospective database	2,918	RR 7.4	Not provided	Age at correction-risk
Moller et al[25]	Denmark	1986–1988*	Prospective case-control	803	RR 3.6†	1.3‡	Weak age at correction-risk ($p = 0.07$)
Prener et al[19]	Denmark	1941–1957	Retrospective case-control	549	Adjusted RR 5.2	RR 3.6§	Age at correction-risk
Swerdlow et al[23]	United Kingdom	1951–1964	Prospective database	1,124	RR 7.5	RR 2.1‡	None
Coupland et al[24]	United Kingdom	1984–1986	Retrospective case-control	794	OR 3.82	Not provided	Not provided, trend toward more seminoma in late (after age 15 yrs) or uncorrected UDT
Kanto et al[18]	Japan	1975–2002	Retrospective database	240	RR 5.4	RR 1	Age at orchiopexy not discussed
Cortes et al[22]	Denmark	1971–2004	Prospective database	1,466	RR 4	Not provided	Not provided
Pettersson et al[28]	Sweden	1965–2000	Prospective database	16,983	IR 2.75	Not provided	Age at correction-risk

* Cases, not controls.
† After excluding spontaneously descended UDT.
‡ Only 1 affected patient (CI not provided).
§ Five affected patients (CI not provided).

in cases of retained intra-abdominal testes. In 1 series 7 of 60 UDTs (12%) that were biopsied in adults demonstrated ITGCN, of which 4 of 16 (25%) were intra-abdominal and 3 of 44 (7%) were inguinal.[32] This suggests a higher risk associated with malignant degeneration in abdominally retained testes compared to that in inguinally retained testes.[32]

Question 2) In Patients With Unilateral Cryptorchidism What is the RR of Testicular Cancer in a Contralateral, Normally Descended Testis?

Multiple publications emphasize that in a man with a history of UDT the contralateral, normally descended testis also is at increased risk for malignant degeneration. Campbell-Walsh Urology states, "Between 5% and 10% of patients with a history of cryptorchidism develop malignancy in the contralateral, normally descended gonad."[20] Pediatric Urology similarly states that "In about 10% of individuals with unilateral cryptorchidism and cancer, the tumor develops in the contralateral testis, suggesting a possible genetic predisposition."[14] Finally, Pediatric Urology states, "The observation that 10 to 20% of testicular tumors in patient with cryptorchidisms occurs in the normally descended testis suggests that an intrinsic abnormality is present in both testes even when only one is undescended."[15] While the evidence for an approximately 5-fold risk of testis cancer in formerly cryptorchid gonads exists, data supporting an increased risk in a contralateral, normally descended testis are weaker.

Some investigators have attempted to characterize the RR of cancer in a contralateral, normally descended testis (table 2).[18,19,23,25,27,30] Four such studies indicated an excess risk in these gonads.[19,23,25,30] Three series indicated a RR of between 1 and 2.[23,25,30] However, in 2 series the number of individuals affected was low (1% or less of the study population) and the CI was not provided,[23,25] suggesting that these findings may have reflected the background risk (table 2). Strader et al reported an increased risk to the contralateral descended testis (RR 1.6) in patients with a history of testicular cancer in Washington State.[30] However, these data were based on patient recall and were not validated by patient examination or record, while the lower limit of the reported CI for the estimate was less than 1. In another study Prener et al reported an RR of 3.6 for a normally descended contralateral testis based on a case-control study from the Danish Cancer Registry.[19] This group reported that 5 of 155 testicular cancer cases (3%) were observed in normally descended testes opposite a UDT. This series stands alone in demonstrating a meaningful increased risk associated with normally descended

testes. Other studies have failed to show an increased risk to the contralateral testis.[18,27]

Of 147 cases of testis cancer at Wilford Hall Medical Center the neoplasm was in the contralateral, normally descended testis in only 3 (2%).[8] Gehring et al presented a series of 529 patients with testicular cancer, of whom 7 (1.3%) had tumor in the normally descended testicle.[33] Fonger et al reported testis cancer in normally descended contralateral testes in 6 of 646 patients with testis cancer.[34] Finally, Batata et al reported a series of 125 testicular cancers in patients with cryptorchidism from among "approximately 1,000" with testicular cancer.[35] Ten of these cases developed in a contralateral, normally descended testis, suggesting that the rate of tumors in contralateral, normally descended testes is about 1% (10 of 1,000), while the risk of testis cancer in formerly or currently cryptorchid testes is about 10-fold higher (115 of 1,000). Combining these case series shows that 26 of 2,322 men (1.1%) in whom testicular cancer developed had tumor in the normally descended testis opposite a cryptorchid or formerly cryptorchid testis.

Mathematically an increased risk of testicular cancer in a normal contralateral testis seems unlikely. If 10% of men with testicular cancer have tumor in a UDT and only 1.1% of testis tumors develop in the normally descended contralateral testis, the risk of a tumor in the UDT is 8.33 times higher than the risk in the contralateral testis. However, results from the study by Dieckmann and Pichlmeier indicate that the risk of testicular cancer in the UDT is 5.4 times that in the normal population,[10] suggesting that the risk of a tumor in the contralateral testis is similar to that in the normal male population.

Viewed another way, while the incidence of UDT in the general population of children is estimated to be between 1% and 4%,[1–4,36] only approximately 1% to 2% of testis tumors develop in normally descended testes contralateral to a UDT. This suggests that a tumor in these otherwise normal testes is most probably circumstantial and not indicative of an increased predisposition toward malignancy in a man with a unilateral undescended testis.

Question 3) Does Testis Location Affect the Subsequent Pathological Subtype of Testicular Cancer?

The first thorough analysis of this question was provided in an historical review of 220 cases of testicular cancer that occurred following orchiopexy in 43 case series dated from 1950 to the mid 1970s.[9] Therefore, this study represents a time when orchiopexy was generally not performed before puberty. Overall 40% of cases demonstrated seminoma, followed by embryonal tumors and teratocarcinoma in 25% and 19%, respectively.[9] A chart review of Air Force patients entered into a testicular cancer registry between 1954 and 1967 included men who underwent postpubertal orchiopexy at a mean age of 16 years and also had similar types of tumors, although with a lower rate of seminoma (27%)[8] than in the study by Martin.[9] Gehring et al reported a similar pattern with a 46%, 21% and 32% rate of seminoma, embryonal tumors and teratocarcinoma, respectively, in testicles that underwent malignant degeneration following orchiopexy.[33] These values compare with an 89% predominance of seminoma in patients who had uncorrected cryptorchidism and later had testicular cancer.[33]

Subsequently Batata et al reported a series of men with testicular cancer and a history of cryptorchidism.[35] They compared men who underwent orchiopexy between ages 4 and 42 years to patients who had not undergone orchiopexy and noted a similar time to tumor detection and a similar survival rate in the 2 groups. However, when comparing pathological types between cases with and without orchiopexy or hormonal treatment, a predominance of seminoma was observed in uncorrected cases (30 of 42 or 71.4%). However, in corrected cases the distribution of tumor type was remarkably similar to that in the series by Johnson et al,[8] including seminoma in 29% of cases, embryonal tumors in 33% and teratocarcinoma in 35%. The reason for this discrepancy may be that a predominance of abdominal testes was represented by the uncorrected group, which is a group more likely to undergo negative inguinal exploration as well as failed hormone therapy. Indeed, one of the most compelling findings in this study is that 13 of 14 abdominal testes later demonstrated seminoma compared with 63% with seminoma in the inguinal region and only 30% with seminoma in scrotal testes.[35]

While treatment patterns for orchiopexy have trended toward earlier surgical correction, more contemporary series have confirmed the findings suggested by these 3 early studies. Approximately a third of corrected UDTs that undergo malignant transformation are seminomatous, while almost three-quarters of uncorrected UDTs that undergo malignant degeneration are seminomatous ($p < 0.0001$, table 3).

Unfortunately the initial location of scrotal testicular tumors in corrected cases was not documented in all studies that included patients who had undergone orchiopexy. Consequently while these data suggest that a cryptorchid abdominal testis left in situ is more likely to become seminomatous, it does not answer the question of whether orchiopexy simply results in a trade-off of the risk of seminoma for nonseminoma or decreases the risk of seminoma altogether, resulting in a lower but still increased

Table 3. *Seminoma and nonseminoma in patients with history of cryptorchidism based on testis location at cancer diagnosis (chi-square 42.35, p <0.0001)*

	No. Scrotal Testes		No. UDTs	
References	Seminoma	Nonseminoma	Seminoma	Nonseminoma
Johnson et al[8]	3	8	1	0
Gehring et al[33]	13	15	8	1
Martin[9]	34	50		
Fonger et al[34]	13	9	25	6
Batata et al[35]	26	67	30	14
Jones et al[58]	2	7	16	9
Kuo et al[59]			9	2
Totals (%)	91 (37)	156 (63)	89 (74)	32 (26)

risk of testicular cancer. While these 2 possibilities exist, data suggest that the latter is more likely, that is orchiopexy does in fact decrease the overall risk of testicular cancer.

Question 4) Does Orchiopexy Decrease the Risk of Testicular Cancer?

The prevalence of UDT in hospital based prospective cohorts has been estimated to be between 3% and 4% at birth,[1,2] although the prevalence is higher in low birth weight, pre-term and small for gestational age males.[1] Importantly while more than two-thirds of these cases demonstrate descent by age 3 months, the rate of UDT is estimated to be near 1% after age 12 months.[2,4,36] This value is important since improved medical expertise and technology in perinatal care have led to a greater number of pre-term infants surviving the neonatal period and, although many of these infants have UDT, spontaneous descent often occurs before age 1 year. These values suggest that at least half of all testes that are undescended at birth will descend on their own and little is known about the potential oncological risk to this group of patients. A Danish group compared rates of testicular cancer in controls and patients diagnosed with cryptorchid testes at birth who were born from 1950 to 1968 and found no increased risk.[37] It is quite possible that the failure of this study to identify an association between UDT at birth and testicular cancer may have been related to the high prevalence of UDT in neonates and the high rate of early spontaneous descent, which diluted the number of true or persistently cryptorchid testicles. All other studies presented that suggest a link between UDT and testicular cancer are retrospective. As such, they rely on a history of hormonal or surgical therapy, or a diagnosis of maldescent found in adult life and, therefore, they exclude or under represent patients who may have undergone spontaneous descent in infancy. Moreover, because these studies predominantly involve patients born in the 1930s to 1960s, they likely do not reflect the relatively larger number of pre-term infants who now survive to adulthood, a group that commonly demonstrates UDT at birth with spontaneous descent in infancy. Therefore, these data suggest that orchiopexy and forewarnings to parents of an increased cancer risk should be restrained before ages 3 to 12 months, especially in infants born pre-term.

Moreover, several investigators have suggested that the rate of cryptorchidism or at least surgery for cryptorchidism may increase after age 1 year secondary to a testis migrating to an ectopic location with linear growth, retractile testes, missed diagnoses or acquired undescended testes, while the oncological risk for these testes and any potential benefit that may be gained with early treatment remain to be determined.[3–4,36,38]

The evidence that orchiopexy before puberty is protective is strong and 2 studies published in 2007 point toward a decreased risk of malignancy in testes that are subjected to orchiopexy before ages 10 to 12 years.[11,28] The first study from Sweden included almost 17,000 men treated for UDT between 1965 and 2000, and identified 56 who were subsequently diagnosed with testicular cancer.[28] The RR of testicular cancer was then estimated based on age at orchiopexy, including 0 to 6, 7 to 9, 10 to 12, 13 to 15 and 16 to 19 years. While the 3 younger groups had an RR of between 2.02 and 2.35, the 2 postpubertal groups were at significantly increased risk with an RR of 5.06 and 6.24, respectively. The second series is a meta-analysis that included 3 case-control[25,29,30] and 2 cohort[23,26] studies that used age at orchiopexy in the analysis.[11] This analysis determined an OR of 5.8 (range 1.6 to 19.3) for testicular cancer in men who never underwent orchiopexy or underwent postpubertal orchiopexy compared with that in men in whom orchiopexy was performed before puberty.[11] The suspicion that prepubertal orchiopexy may be protective dates back to the review by Martin, in which only 6 of 72 patients underwent orchiopexy before age 10 years.[9] However, even when consider-

ing the risk in children who undergo orchiopexy at ages less than 10 years, the lowest incidence of cancer is seen in children undergoing orchiopexy in the 0 to 6-year age range.[28] Other studies have shown a greatly increased risk for cancer in testicles left in situ that have not been brought down or have been brought down later than age 10 years. Herrinton et al evaluated orchiopexy timing and testis cancer risk in a modern cohort of patients from California.[29] Of men with testis cancer 7% had a history of treated or untreated ectopic testes compared to a 1.4% rate in healthy controls. In the 12 patients with testicular cancer the earliest documented orchiopexy was done after age 5 years, while in the control group 6 of 8 patients had undergone orchiopexy by age 11 years. An OR of 0.6 was calculated for testicular cancer in patients treated before age 11 years and an OR of 32 was noted in those treated later. Likewise Pinczowski et al presented a population based cohort study of 2,900 men who underwent orchiopexy and 30,000 who underwent hernia repair between 1965 and 1983.[26] In the orchiopexy group 4 patients had testicular cancer, including 1 and 3 who underwent orchiopexy at age 10 to 14 years and greater than 15 years, respectively. No testicular cancers were noted in patients who underwent orchiopexy at ages less than 11 years.

In a patient older than 12 years the decision to observe, remove or fix a UDT is complex. The risk of malignancy is increased. Moreover, these gonads are likely to be atrophic and have negligible fertility value.[39] Hornak et al reported that 12% of UDTs removed from a cohort of men with a mean age of 28 years demonstrated atypia and 1 (3%) demonstrated ITGCN.[40] However, a decision to operate (orchiopexy or orchiectomy) involves anesthetic risk. This risk has been evaluated by multiple groups.

In 1985 Farrer et al compared the risk of malignant degeneration and subsequent death from testicular cancer to the risk of anesthetic or postoperative mortality after orchiopexy.[41] They concluded that men with UDT who are between ages 15 and 32 years should undergo orchiectomy because the risk of death due to cancer outweighed the surgical risks associated with orchiectomy, whereas men older than 32 years should be treated nonoperatively. While this group used the most contemporary data available to estimate the anesthetic risk, testicular cancer mortality and the RR of malignant transformation in a retained testis, these risks have significantly changed because of improved anesthetic drugs and techniques, improved operative management and improved testicular cancer survival rates. A study published in 2002 revisited this question by stratifying anesthetic risk by ASA class and using more modern mortality estimates for testicular cancer.[42] According to that risk analysis all ASA class I patients with UDT are recommended to undergo orchiectomy and all ASA class III and IV patients are recommended to undergo observation. The risk of death due to anesthesia exceeds the risk due to testicular cancer in ASA class II adults with UDT at age 43 years. Therefore, the investigators recommended that orchiectomy be performed up to age 50 years in postpubertal ASA class I and II men with UDT, while nonoperative treatment should be done in all postpubertal ASA class III and IV men, and all men older than 50 years.

A confounding issue is whether the testis is palpable. If the testis is inguinal or ectopic, a testicular neoplasm should be palpable before it becomes large and it certainly would be visible on sonography. On the other hand, a neoplasm in an abdominal or peeping testis would be impossible to palpate or image by sonography at an early stage. Consequently since abdominal testes are at highest risk for neoplasia and screening is difficult, reasonably healthy adults with unilateral nonpalpable testes should undergo definitive evaluation by laparoscopy or possibly gadolinium enhanced magnetic resonance angiography.[43,44] Orchiectomy should be advised unless medical circumstances preclude anesthesia.

Briefly, these data suggest that pre-term infants with testicular maldescent should be allowed at least 3 to 12 months to provide a window during which spontaneous descent may occur. If a testis has not descended before age 12 months (corrected for pre-term birth), consideration should be given to perform orchiopexy before age 10 to 11 years to decrease the cancer risk. A number of studies suggest that even earlier orchiopexy (younger than age 2 years) is beneficial to maximize fertility potential but a critical analysis of this literature is not within the scope of our discussion. In patients with bilateral maldescent parents should strongly be advised toward orchiopexy even before age 12 months because these patients are at higher risk for testicular malignancy and infertility in adulthood.[45,46] Finally, reasonably healthy postpubertal men younger than 50 years who seek consultation for a nonpalpable UDT should be offered orchiectomy and a testicular prosthesis since the fertility potential of that testis is likely to be negligible and the cancer risk is likely substantial (at least 1%). Men with a palpable UDT who are older than 50 years or at significant operative risk should be treated nonoperatively because the risk of operative mortality exceeds the risk of death due to testis cancer and germ cell tumors are uncommon at ages greater than 50 years.

Patients with a unilateral solitary UDT or bilateral UDTs who are seen after ages 10 to 12 years can be appropriate candidates for orchiopexy with close surveillance. Testicular biopsy may be useful for

Table 4. *Intratesticular tissue pathological findings reported in testicular remnants in retrospective reviews of the literature*

References	Location	Study Period	No. Nubbins Evaluated	Ring Status	Age	Intratesticular Tissue Pathological Findings (No. pts)
Rozanski et al[57]	Ann Arbor, Michigan	1984–1994	50 Inguinal + scrotal	Not reported	1–17 Yrs (81% of pts younger than 4 yrs)	Viable germ cells (5), intratubular germ cell neoplasia (1 age 9 yrs)
Grady et al[47]	Seattle, Washington	1993–1997	14 Inguinal + scrotal	Closed	Mean 23 mos	No germinal tissue (13), several seminiferous tubules (1 age 13 mos)
Cendron et al[56]	West Lebanon, New Hampshire	1983–1997	29 Inguinal + scrotal	Not reported	Mean 28.6 mos (range 3–168)	No testicular elements (29)
Emir et al[52]	Istanbul, Turkey	1922–2004	39 Inguinal + scrotal	Closed	Mean 4.1 yrs (range 1–13)	No testicular elements (34), seminiferous tubules only (3), seminiferous tubules + viable germ cells (2)
Storm et al[53]	Danville, Pennsylvania + Norfolk, Virginia	1994–2006	56*	—	Median 44.5 mos (range 11–216)	Viable germ cell elements (8), seminiferous tubules without germ cell elements (4)
Renzulli et al[54]	New Haven, Connecticut + Providence, Rhode Island	1981–2003	110 Inguinal + scrotal	Closed	Median 33 mos (range 6 mos–14 yrs)	Viable germ cell elements (8), No. specimens with vas but no germ cell elements not reported
De Luna et al[55]	New Orleans, Louisiana	1990–2000	71 Inguinal + scrotal	Not reported	9 Mos–10 yrs (no mean or median reported)	Residual viable tubules without germ cells (7),† residual viable tubules with germ cells (4)
Plotzker et al[50]	Washington, D.C.	1987–1989	23 Inguinal + scrotal	Not reported	Not reported	Viable seminiferous tubules (3)
Turek et al[51]	Philadelphia, Pennsylvania	1985–1991	105 Inguinal + scrotal	Not reported	Mean 26.8 mos (range 5 mos–14 yrs)	Testis (7), müllerian (2)

When possible, only inguinal nubbins are reported that were found after laparoscopy confirmed vessels and vas going into closed ring.
* Remnants were retrieved laparoscopically, suggesting that they were intra-abdominal, or removed retrograde through an open inguinal ring.
† Associated hernia (open ring) in 5 of 7 patients.

deciding the course of action in this select subgroup of patients.

Question 5) Is There a Risk of Malignant Degeneration in Testicular Remnants?

Approximately 50% of nonpalpable testes are abdominal/inguinal and the remaining 50% are atrophic nubbins or remnant testes resulting from perinatal spermatic cord torsion.[47,48] These structures are almost always in the scrotum.[49] They are often found after laparoscopy reveals testicular vessels and a vas deferens entering a closed inguinal ring[47,48] and subsequent exploration demonstrates a small, hemosiderin containing nubbin. The question arises of whether these testes carry an increased risk of testicular cancer and, therefore, they should be removed. These testes are abnormal because of a mechanical event (spermatic cord torsion), rather than maldevelopment. Therefore, the increased risk of malignancy associated with an undescended testis should not be applied to testicular remnants associated with spermatic cord torsion.

Multiple histological studies of these remnants have demonstrated that few contain seminiferous tubules (0% to 14%) and even fewer demonstrated viable germ cells (table 4).[47,50–56] Grady et al identified 14 of 35 nonpalpable testes that were inguinal/scrotal vanishing testes.[47] Only 1 remnant contained seminiferous tubules and no germ cells were identified on histological evaluation. These findings are in agreement with the findings of Cendron et al, who did not identify any testicular elements in 29 testicular nubbins.[56] None showed evidence of malignancy, which is not surprising since most of these boys were prepubertal. However, Rozanski et al performed histological analysis of 50 testicular remnants and reported that 5 (10%) contained germ cells.[57] However, more importantly 1 remnant in a 9-year-old boy demonstrated intratubular germ cell neoplasia. Theoretically, testicular remnants without germ cells are not at risk for later malignant degeneration into a germ cell tumor even if the remnant gonad is inguinal. Consequently the likelihood of a scrotal testicular remnant becoming malignant is extremely low and it does not need to be removed if the clinician is certain that the testis is atrophic and in the scrotum. However, if there is any uncertainty regarding the diagnosis or exploration has been performed, removal of the nubbin through a scrotal incision and histological evaluation are quite appropriate.

CONCLUSIONS

Despite countless studies of the risks associated with cryptorchidism and cancer many misconceptions still exist (see Appendix). It is important that we understand the limitations and conclusions of the data that have been generated to date and design studies that more accurately and prospectively define the risks better. In addition, it is important to establish guidelines for treating patients with cryptorchidism, including when orchiopexy is appropriate, when orchiectomy is appropriate, when testicular biopsy has a role, and how cryptorchid or formerly cryptorchid patients should be monitored for testis cancer.

APPENDIX

Conclusions

Question	Summary
1) What is the RR of testicular cancer in a cryptorchid testis?	RR of testicular cancer in all patients with UDT is 2.75 to 8 with lower risk (RR 2 to 3) in patients undergoing prepubertal orchiopexy Higher risk in patients with bilateral UDT, associated genitourinary anomalies, or late (after age 10-12 years) or uncorrected UDT
2) In patients with unilateral cryptorchidism, what is the RR of testicular cancer in a contralateral normally descended testis?	The contralateral, normally descended testis has a negligible or no increased risk of testicular cancer
3) Does testis location affect the subsequent pathological subtype?	Of malignant tumors developing in uncorrected abdominal or inguinal testes 74% are seminoma Of malignant testis tumors developing following orchiopexy 63% are nonseminomatous Orchiopexy appears to decrease the risk of seminoma
4) Does orchiopexy decrease the risk of testicular cancer?	Orchiopexy by age 10 to 12 years results in a 2 to 6-fold RR decrease compared with orchiopexy after age 12 years or no orchiopexy Orchiectomy should be discussed with health postpubertal men with UDT up to age 50 years Risk of testis cancer in men with persistent UDT after age 50 years is undefined Testicular biopsy may serve a role in determining whether orchiopexy or orchiectomy should be performed in children 10 years or older with bilateral UDT and solitary unilateral UDT
5) Is there a risk of malignant degeneration in a testicular remnant (nubbin)?	There exists a single case of carcinoma in situ identified in a 9-year-old child Of testicular nubbins 5% to 15% contain seminiferous material but few have viable germ cells, the nubbin is almost always scrotal and the risk of malignant degeneration is minimal

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