AUA **Update Series** 2020

Lesson 24 Volume 39

Undescended Testis in the Postpubertal Patient*

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to describe the optimal timing for diagnosis and treatment of the undescended testis, recognize the risks of endocrinopathy, infertility and malignancy associated with the postpubertal undescended testis, and identify the advantages of orchiopexy vs orchiectomy as treatment options.

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Release date: August 2020

Expiration date: August 2023

Key Words: cryptorchidism, orchiopexy

INTRODUCTION

Cryptorchidism, or undescended testis, is one of the most common pediatric disorders of the male endocrine glands and the most common genital disorder identified in male infants at birth. Defined as failure of a testis to descend to a dependent scrotal position, cryptorchidism is estimated to occur in 1%-4% of full-term and up to 45% of preterm newborn males.[1,2] Spontaneous descent of a testis observed to be cryptorchid at birth is not uncommon and generally occurs before corrected gestational age 6 months, with an estimated 1% of male infants still having undescended testes by age 1 year.[3] Data regarding the incidence of undescended testes in postpubertal boys and adults are much more limited and heterogeneous than for infants but the incidence is estimated to be to 0.79%-2.2% based on older cohort studies.[3,4]

Cryptorchidism can be further categorized as congenital, in which the testis is extrascrotal from the time of birth, or acquired, in which the testis is present in the scrotum at birth but subsequently is observed in an extrascrotal location on examination. Peak age at diagnosis of acquired UDT is 5-7 years. The majority of cases are unilateral, with about 20%-30% of cases involving bilateral UDTs.[3] Cryptorchid testes may be located in the abdomen, inguinal canal, superficial inguinal pouch or upper scrotum, or ectopically. Approximately 70% of UDTs are palpable, and of testes that are non-palpable approximately 30% are in the inguinoscrotal region, 55% are intra-abdominal and 15% are absent.[5,6]

The goals of treating cryptorchidism include optimizing endocrine and reproductive function, decreasing testicular malignancy risk and permitting easy testicular self-examination, preventing testicular torsion and correcting associated inguinal hernia. **In 2014 the American Urological Association published guidelines on the evaluation and treatment of cryptorchidism based on an extensive review of the published literature.[1] According to these guidelines, any infant in whom the testis has not descended spontaneously by corrected gestational age 6 months should be referred to a specialist, and surgery should be performed within the next year, ie by age 18 months.** It is additionally recommended that boys with the possibility of newly diagnosed (acquired) cryptorchidism after age 6 months be referred promptly to an appropriate surgical specialist.

The AUA guidelines recommend against use of hormonal therapy to induce testicular descent given the low response rates and lack of evidence supporting long-term efficacy. **In prepubertal boys with palpable UDTs scrotal or inguinal orchiopexy is the recommended treatment.** In 2016 the European Association of Urology published similar guidelines for the management of UDT, which also recommend early surgical correction of cryptorchidism (before age 18 months).[7]

Although clear and consistent guidelines exist regarding the management of prepubertal UDTs, the optimal management of cryptorchidism in adolescent boys is less clear. The AUA guidelines state that in the presence of a normal contralateral testis orchiectomy may be performed if the testicular vessels and vas deferens are very short, the testis is dysmorphic or very hypoplastic, or the patient is postpubertal. However, this recommendation is stated as a clinical principle because of the limited evidence that exists to support it. This Update reviews the primary concerns regarding postpubertal UDTs, including testicular function and oncologic risk, as well as the suggested evaluation and management of these patients.

CONCERNS REGARDING POSTPUBERTAL UDT

As stated, strong guidelines exist recommending evaluation of all boys with cryptorchidism by age 6 months and treatment by age 18 months. While there are indications that a cryptorchid testis is inherently and biologically different than a normal, descended testis, it is clear that moving the undescended testis out of the suboptimal, warm environment of the abdomen or groin and into the scrotum improves both testicular functional parameters and malignancy risk.

The age at which UDT is treated has gradually decreased as growing evidence has suggested that a decline in testicular function, from both a reproductive and an endocrine standpoint, and a rise in malignancy risk occur with a delay in treatment. **Although the precise age at which these irreversible changes occur has not been well elucidated, it is widely accepted that cryptorchid testes not treated before puberty have a higher risk of malignancy and poor functional outcomes compared to those treated earlier. However, there are still adolescents and adults who present with UDTs, and it is important to understand what can be expected to occur in terms of malignancy risk and function in order to adequately counsel these patients and, if appropriate, their parents.**

Testicular function (endocrine and reproductive). Endocrine and reproductive testicular function is negatively impacted by delay in correcting or failure to correct UDT, although reproductive function seems to be more susceptible to progressive damage. This problem is well illustrated by the fact that virtually all men with uncorrected bilateral cryptorchidism will have azoospermia and infertility, while approximately 49% of those with persistent unilateral cryptorchidism will have a normal sperm concentration. However, after orchiopexy in childhood 71% of patients with unilateral and 28% of those with bilateral cryptorchidism will have normal semen analysis parameters, with paternity rates of around 90% (essentially normal) for those with corrected unilateral cryptorchidism vs 65% for those with corrected bilateral UDTs.[8-12]

In the cryptorchid testis the number of germ cells declines more quickly during the first 3 years of life than in the contralateral normal testicle, which is reflected in slow growing UDT volume compared to normal testicles.[12] A randomized controlled trial in Sweden indicated that orchiopexy performed at 9 vs 36 months resulted in increased catch-up growth of the corrected testes,[13] findings that are supported by studies conducted in Denmark and Korea.[14-16]

Histological evidence from testicular biopsy at the time of orchiopexy has supported early orchiopexy as well, with biopsy in boys younger than 2 years showing significantly higher mean tubular fertility index and germ cell counts and lower interstitial fibrosis vs biopsy performed after age 2 years.[17] Similarly

ABBREVIATIONS: ASA (American Society of Anesthesiologists), AUA (American Urological Association), FSH (follicle-stimulating hormone), MRI (magnetic resonance imaging), UDT (undescended testicle), US (ultrasound)

testicular biopsy in patients randomized to orchiopexy at 9 vs 36 months showed larger numbers of Sertoli cells at 9 months and an 86%-98% reduction in germ cells during this interval.[18] Tasian et al reviewed testicular biopsies performed at the time of orchiopexy in 187 patients and found that patient age at orchiopexy predicted germ cell depletion and Leydig cell loss.[19] Compared to baseline rates for patients undergoing orchiopexy before age 12 months, odds ratio of germ cell depletion was 3.9 for those undergoing orchiopexy at 13 to 24 months, 8.3 at 25 to 96 months and 16.8 after age 96 months. Similarly, the odds of having Leydig cells present in the biopsy were lowest for the oldest group of patients (greater than 96 months at correction). In addition to impaired spermatogenesis, histological changes seen in testes with delayed treatment of cryptorchidism include basement membrane thickening, decreased diameter and atrophy of seminiferous tubules, hyperplasia of Sertoli cells with Sertoli cells only and abnormal hyperplasia of the remaining Leydig cells.

Although these studies all evaluated markers of reproductive and hormonal testicular function during infancy and early childhood, one can assume that progressive decline continues during and after puberty. Several retrospective reviews of orchiectomy specimens from postpubertal males who presented with UDT have supported this assumption. Ryang et al examined surgical specimens from 31 patients who underwent orchiectomy for postpubertal unilateral cryptorchidism for assessment of intratubular germ cell neoplasia as well as spermatogenesis.[20] Of the patients 1 had intratubular germ cell neoplasia, 12 had no germ cells present and 27 had impaired spermatogenesis. Rogers et al evaluated 52 orchiectomy specimens from adults with UDTs and similarly found complete absence of germ cells in 69% and mature spermatozoa in only 1 patient (2%).[21] In their cohort 2 patients (4%) had carcinoma in situ. Findings from these studies support the belief that untreated cryptorchid testis in postpubertal males cannot be expected to contribute to fertility, may harbor malignancy and is therefore best managed by orchiectomy.

Studies evaluating long-term outcomes in adults who previously underwent orchiopexy have also suggested that prepubertal orchiopexy is beneficial in optimizing reproductive and endocrine function of the testes. Rohayem et al compared reproductive hormone levels and semen analysis data from 357 men with previously treated UDTs and 709 men who had normal testes at birth and normal semen analysis.[22] They found that men with previous UDTs had significantly higher luteinizing hormone and FSH values, and lower total testicular volume and sperm concentration vs controls. Age at orchiopexy was significantly inversely correlated with total testicular volume and sperm concentration, and positively correlated with FSH and luteinizing hormone values. Coughlin et al compared hormone levels and semen analysis in 84 men who had undergone orchiopexy between ages 1 month and 11 years.[23] They found that age at orchiopexy correlated inversely with inhibin B levels and positively with FSH, again suggesting a benefit to early orchiopexy. Similarly adult testosterone levels have been observed to correlate negatively with age at orchiopexy.[24]

History of undescended testis does not typically affect onset of puberty, although testicular growth during puberty may be impaired in the undescended testis. A recent longitudinal study comparing 51 cases of congenital cryptorchidism and 65 controls indicated that mean age at onset of puberty did not differ significantly (11.7 vs 11.8 years in cases vs controls).[25] However, a nonlinear mixed effects model comparing individual pubertal testicular growth curves demonstrated that congenitally cryptorchid testes had smaller postpubertal volume compared to scrotal testes in controls. There was no difference in postpubertal volume between testes subjected to orchiopexy earlier in life and those that descended spontaneously. These findings suggest that the hypothalamic-pituitary axis remains intact in patients with cryptorchidism, while poor perinatal testicular development may result in smaller testes following puberty. Therefore, patients and their families should be counseled that undescended testes may be smaller following completion of pubertal development.

As malignancy risk increases, particularly as patients with undescended testis approach adulthood, fertility testing including a semen analysis can be performed to assess fertility potential and help appropriately counsel patients. In the setting of azoospermia testicular sperm extraction may be considered at the time of either orchiopexy or orchiectomy, with the goal of finding mature spermatozoa. This approach has been described in small case series but it should be noted that the likelihood of finding adequate sperm, even for use with assisted reproductive techniques, is low, particularly in cases of intra-abdominal testes.[26]

Malignancy risk. **Cryptorchidism is a well-known and long accepted risk factor for testicular malignancy, and a history of UDT is associated with a twofold to eightfold increased risk of testicular germ cell tumor.[2, 16] Evidence suggests that performing orchiopexy before puberty does not eliminate but helps to mitigate this effect to about a twofold to threefold increased risk compared to the general population.** Bilateral UDTs, associated anomalies and late (postpubertal) or uncorrected UDTs have all been observed to carry an increased risk of malignancy.[27]

Pettersson et al evaluated a cohort of almost 17,000 men in Sweden who underwent orchiopexy for cryptorchidism before age 20 years to determine the risk of malignancy and whether it was associated with age at treatment.[28] They found an overall risk ratio of 2.75 in their cohort compared to the standard risk of testicular malignancy in Sweden. The incidence ratio was 2.23 for those who underwent orchiopexy before age 13 years vs 5.4 for those treated at age 13 years or after.

Walsh et al performed a meta-analysis of 5 studies that investigated whether cryptorchidism was associated with an increased risk of testicular neoplasm and specifically whether age at orchiopexy changed this risk.[29] The included studies showed that testicular neoplasm was 1.6 to 7.5 times more likely to occur in men with a history of cryptorchidism, with an increased risk in all 5 studies if orchiopexy was delayed or not performed. Using a cutoff of 10 to 11 years, the odds of malignancy were 2.9 to 32 times greater among patients who had not yet undergone orchiopexy at this age compared to those who had. Combining the data from these studies revealed that testicular cancer was 3.4 times more likely to develop in men in whom orchiopexy was delayed or not performed.

Although all males with cryptorchidism are at increased risk for testicular malignancy during their lifetime, these studies provide evidence that early treatment of UDT modulates this risk. Interestingly seminoma is the most common pathology in patients with uncorrected UDT and testicular malignancy, occurring in almost three-quarters of these cases, whereas

non-seminomatous germ cell tumors make up the majority of cases of testicular malignancy after orchiopexy. This outcome is believed to be the result of a true decrease in risk of seminoma as opposed to an exchange of risk of seminoma for non-seminomatous germ cell tumor.[25]

EVALUATION OF POSTPUBERTAL UDT

In all patients presenting with cryptorchidism evaluation should begin with a thorough physical examination, which is the cornerstone of initial diagnosis. This also applies in postpubertal patients presenting with UDT. In patients with a palpable UDT either orchiopexy or orchiectomy can be considered. Any patient with concern for testicular mass on examination should undergo a standard evaluation for testicular malignancy before surgical management, including imaging and tumor markers. **Similar to younger age groups, imaging should not be part of the standard evaluation of adolescents presenting with UDT.**[30–32] The figure provides an algorithm for initial evaluation and management of these cases.

The 2014 AUA guidelines and the 2016 European Association of Urology guidelines recommend that providers not perform ultrasound or other imaging in the assessment of boys with cryptorchidism before referral as these studies rarely assist in decision making.[1, 7] Similarly the Choosing Wisely® campaign, a collaborative effort across multiple medical specialties to identify testing that is costly and does not change clinical outcomes in order to reduce waste of resources, advises against performing US in boys with cryptorchidism.[33]

More than 70% of UDTs will be palpable by a specialist on examination, and imaging is therefore not needed to locate the testes. Imaging, regardless of its findings, will not change management. The theoretical role of imaging is greater in cases of non-palpable testes. The ideal imaging technique would accurately localize a viable testis requiring intervention, identify a vanishing or absent testis not requiring intervention, and identify and localize testicular nubbins that may or may not require removal.[34] This assessment not only would allow for preoperative planning, but also would allow some patients to forgo unnecessary procedures. Unfortunately at this point there is no imaging technique that is 100% sensitive for presence of a testis, and diagnostic laparoscopy is therefore considered the gold standard for localizing non-palpable testes against which imaging techniques are compared. Laparoscopy offers the additional benefit of definitive intervention at the time of diagnosis, further increasing its utility.

US is the imaging modality most commonly ordered by providers. However, this technique is not particularly helpful as it only has 45% sensitivity and 78% specificity for localizing a non-palpable testis. Therefore, US cannot be used to change management or obviate surgical intervention.[30, 31] Computerized tomography, although more sensitive and specific, is generally not recommended due to the cost and the risks of ionizing radiation, particularly in children. While magnetic resonance imaging is attractive because of the absence of radiation and greater sensitivity and specificity than US, the high cost, low availability and requirement of anesthesia in younger patients limit its usefulness.

Some studies have demonstrated sensitivity and specificity as high as 96% and 100%, respectively, with the authors proposing diagnostic algorithms that incorporate MRI.[35] However, even with use of contrast medium the absence of a testis on imaging does not completely exclude its presence on exploration. Given the possibility of a retained dysgenetic testis harboring malignancy, it is difficult to justify forgoing diagnostic laparoscopy based on imaging results alone and performing MRI preoperatively as this unnecessarily increases treatment costs if the findings cannot change management.[34] Additionally a systematic review of the ability of MRI to identify non-palpable testes has revealed an accuracy rate of 42%-88%, with a false-positive rate of 14% and, most importantly, a false-negative rate up to 38%, meaning that more than a third of viable testes may be missed.[34-37]

Although these studies were primarily performed in younger children, it is reasonable to extrapolate their findings to postpubertal males as the performance and cost of imaging should not change between these groups. Kucheria et al reported a series of 12 adults with non-palpable UDTs who underwent diagnostic laparoscopy.[38] They observed that diagnostic laparoscopy was feasible in an adult population and also that orchiectomy could be completed during the same procedure with reasonable ease. Consistent with findings in younger patients, US was accurate in 37.5% of cases, MRI in 66.7% and laparoscopy in 100%.

There may be some instances when the use of imaging is justified in postpubertal patients presenting with UDT. Suggestions have included ruling out malignancy in a patient presenting with non-palpable UDT and surveillance for malignancy in those patients who are observed rather than treated with orchiopexy or orchiectomy.[27] This is particularly true for patients presenting for the first time as adults, in whom laparoscopy may not be feasible and observation is the preferred management strategy assuming there is no concern for malignancy. However, in the majority of patients diagnostic evaluation should consist of physical examination alone, with laparoscopy as needed for localization of the non-palpable testis.

MANAGEMENT: ORCHIECTOMY VS ORCHIOPEXY

As discussed, decline in fertility potential of UDT is believed to begin before age 18 months and increases the longer the testis remains cryptorchid, with almost no fertility potential remaining in testes that are not brought down into the scrotum before puberty. Therefore, treatment for UDT in the postpubertal patient should focus primarily on decreasing the risk of mortality from testicular malignancy as opposed to preserving fertility. Given these circumstances, orchiectomy has traditionally been the recommended treatment for males presenting with UDT after puberty.

Multiple groups have compared the mortality risk of testicular malignancy and the perioperative risk of orchiectomy of UDT in patients presenting after puberty in an attempt to provide an evidence-based guide for management of these cases. Martin and Menck were the first to investigate this question in 1975 and concluded that orchiectomy should be performed in men younger than 50 years old, with observation in older patients since 50 years is the age at which perioperative mortality begins to outweigh the risk of death from testicular malignancy.[39] Since that time, perioperative mortality and outcomes for patients diagnosed with testicular malignancy have greatly improved due to standard perioperative anesthesia monitoring and the discovery of highly effective platinum based chemotherapy regimens for testicular malignancy.

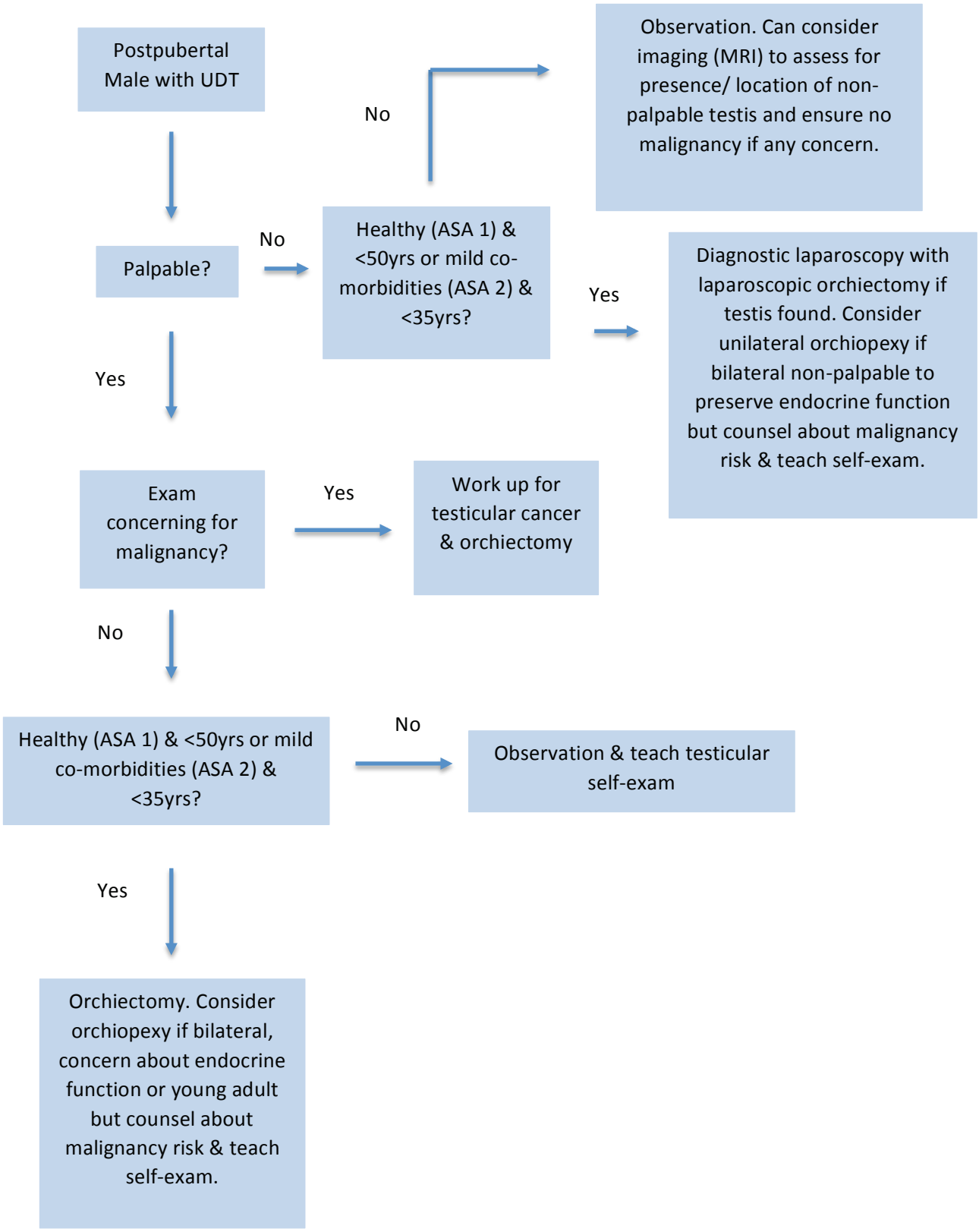

Figure. Evaluation and treatment of postpubertal cryptorchidism.

Shah et al recently reexamined this management question using updated germ cell mortality data as well as recent data for perioperative mortality risk stratified by ASA® classification.[40] They concluded that prophylactic orchiectomy should be advised for ASA class 1 (healthy) males younger than 50 years old and class 2 (mild systemic disease) males younger than 35 years old. In men with significant comorbidities (ASA class 3 or 4) the risk of perioperative mortality outweighed the risk of death from testicular malignancy at all ages, and it was therefore recommended that these men be observed.

While many studies have indicated significant germ cell deterioration or absence in postpubertal orchiectomy specimens (justifying orchiectomy in these cases), specimens from younger men have shown that there may still be some benefit to testicular preservation in terms of fertility. Koni et al reviewed orchiectomy specimens from 51 men 20 to 24 years old who had unilateral cryptorchidism on physical examination at the time of military recruitment who underwent orchiectomy.[41] In contrast to other histological studies that generally included older patients, half of these patients had germ cells at different maturation levels present, although other changes, including basal membrane thickening, decreased seminiferous tubule diameter, dystrophic calcification and Leydig cell hyperplasia, were also evident. While the presence of germ cells alone on pathological specimen does not necessarily mean that these testes would be able to contribute to paternity, it may suggest that a discussion of testicular preservation is reasonable, particularly given recent improvements in assisted reproductive technology.

It is important to consider each case on an individual basis. In patients with a solitary testicle or bilateral UDTs presenting after puberty it is reasonable to consider testicular preservation to maintain endocrine function even though these testicles may not contribute to fertility.[37] Testicular biopsy may be helpful in determining whether orchiopexy is feasible and safe in these unique cases, and in instances of bilateral UDTs may help with the decision of whether to preserve 1 or both testicles.[25] In younger postpubertal males, as opposed to adults presenting with UDT, it may also be reasonable to perform orchiopexy instead of orchiectomy. Again, testicular biopsy may be helpful in this situation.

Because of the known increased risk of malignancy in postpubertal patients with untreated UDT, it is important that these patients and their parents be extensively counseled. **Any patient who is observed or undergoes orchiopexy rather than orchiectomy should be taught how to perform a monthly testicular self-examination and understand the risk of malignancy.** An important consideration before choosing to observe patients is whether a self-examination is feasible. In older patients with non-palpable UDT it may be safer to perform orchiectomy to avoid the possibility of delayed diagnosis and advanced presentation of malignancy due to inability to perform a self-examination.[42]

CONCLUSIONS

Cryptorchidism is a common genitourinary condition primarily affecting males at birth, although patients can present later in life. When confronted with a postpubertal patient with untreated UDT, there are several important and unique considerations. The clinician should remember that physical examination, rather than imaging or laboratory tests, is the cornerstone of initial diagnosis. **Additionally a postpubertal patient should be counseled that uncorrected UDT at this age is likely to have minimal fertility potential but increased malignancy risk. Neither the function of the testis nor the risk of malignancy is likely to be changed by postpubertal orchiopexy. For this reason orchiectomy rather than orchiopexy may be the best treatment choice in older patients.**

DID YOU KNOW?

- Patients with UDT should be referred to an appropriate surgical specialist by age 6 months or at the time of diagnosis, and surgical correction should be performed by age 18 months in order to mitigate long-term effects on testicular function and malignancy risk.
- Failure to surgically treat UDT before puberty results in decreased testicular function (both endocrine and reproductive) with minimal fertility potential from the cryptorchid testis and an up to eightfold increased risk of testicular malignancy.
- Postpubertal orchiopexy is not believed to increase fertility potential or decrease malignancy risk of UDT, and orchiectomy may therefore be the best treatment strategy for these patients if they are healthy and younger than 50 years. Otherwise, observation can be considered since the risk of anesthesia outweighs the potential decrease in malignancy risk offered by orchiectomy.
- Imaging is not part the standard diagnosis or management of postpubertal UDT and should be used sparingly, and only if it will change management in these cases.

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Study Questions Volume 39 Lesson 24

1. Cryptorchid testes treated after age 18 months do not adversely affect the
   a. onset of puberty
   b. sperm concentration
   c. paternity rate
   d. malignancy rate

2. An adolescent male presents with a history of a left undescended testis. The best risk/benefit ratio of localization of the testis is offered by
   a. physical examination
   b. gonadotropin and anti-müllerian hormone levels
   c. US
   d. MRI

3. In addition to germ cell maturation changes, signs of abnormal histology in late cryptorchid testes include
   a. increased seminiferous tubule diameter
   b. basal membrane thinning
   c. Leydig cell aplasia
   d. Sertoli cell hyperplasia

4. The paternity rate for patients with bilateral cryptorchidism corrected in childhood is
   a. 90%
   b. 65%
   c. 35%
   d. 10%

5. The most common malignancy in men with an uncorrected undescended testis is
   a. intratubular germ cell neoplasia
   b. choriocarcinoma
   c. seminoma
   d. yolk sac

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