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Intratubular Germ Cell Neoplasms of the Testis and Bilateral Testicular Tumors: Clinical Significance and Management Options

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1. Introduction

Although rare, testicular cancer is the most common solid tumor in men between ages 20 and 34, with approximately 5.5 new cases per 100,000 men reported in the United States each year (Howlader et al., 2011). For reasons that are still unclear, the incidence of testicular cancer worldwide has doubled in the past 40 years, with the most significant increases seen in industrialized countries in North America, Europe and Oceania (Huyghe et al., 2003). The vast majority of malignant testicular tumors are testicular germ cell tumors (TGCTs), which can be divided into two main categories: seminomas and non-seminomas. The pathogenesis of TGCTs has been the subject of intense interest recently due to the rising incidence (Chia et al., 2010). Skakkebaek was the first to describe the possibility of a pre-invasive lesion for testicular cancer in 1972, when he identified atypical germ cells in the testes of two infertile men who later developed TGCTs (Skakkebaek, 1972). Subsequent work by Skakkebaek et al. confirmed the existence of a precursor lesion for TGCTs. Historically, the terms carcinoma in situ and testicular intraepithelial neoplasia have been used to describe this lesion, but they are no longer preferred because these lesions do not possess epithelial features (Emerson & Ulbright, 2010). The preferred term used in recent literature, including this review, is intratubular germ cell neoplasia, unclassified (ITGCN).

ITCGN plays an important role in the development of TGCTs. Since the seminal work by Skakkebaek, it has been generally accepted that most TGCTs arise from ITGCN, with the notable exception of pediatric germ cell tumors (yolk sac, mature teratoma) and the rare spermatocytic seminomas. Subsequent work by von der Maase et al. demonstrated that patients with ITGCN will ultimately progress to invasive cancer if left untreated(von der Maase et al., 1986). This malignant transformation has led researchers to focus on early detection and treatment in order to improve the outcomes in testicular cancer. Advances in molecular biology have helped us gain insight into the mechanisms involved in the transformation of ITGCN to TGCTs. In this chapter, we will focus on the pathogenesis, risk factors, diagnosis and treatment regimens utilized in the management of ITGCN and bilateral TGCTs.

2. Pathogenesis

A close association between seminoma and non-seminoma was described long before the discovery of ITGCN (Akhtar & Sidiki, 1979; Mark & Hedinger, 1965). Numerous studies have since demonstrated that both histologies can often co-exist in the same tumor and share similar risk factors, hinting toward a common etiopathogenesis (Bray et al., 2006). The likelihood of common origin has also been supported by epidemiological studies. When analyzing the testicular cancer incidence between 1973 and 2002, Chia and colleagues found the incidence trends of seminoma and non-seminoma were similar to each other suggesting common risk factors (Chia et al., 2010). In contrast, these trends were not observed in those with pediatric testicular cancer, indicating different inciting factors are involved in this population (Lacerda et al., 2009). Histologic studies on orchiectomy specimens taken from patients with TGCTs also confirmed the high incidence of a common precursor lesion associated with both seminoma and non-seminoma. Following his initial description of ITGCN in 1972, Skakkebaek identified ITGCN in 77% of orchiectomy specimens taken from patients with seminoma, embryonal carcinoma or terato-carcinoma (Skakkebaek, 1975). ITGCN has also been found in as many as 98% of orchiectomy specimens containing both seminoma and non-seminoma (Jacobsen et al., 1981). Interestingly, while the majority of patients with ITGCN undoubtedly progress to TGCTs, those without evidence of ITGCN tend not to develop invasive testicular tumors (von der Maase et al., 1986). This finding lends support to the concept that ITGCN serves as the initial gateway to TGCTs.

A strong connection between ITGCN and TGCTs can be realized through two large autopsies studies from Europe, which demonstrated similar prevalence of ITGCN to lifetime risk of TGCTs (Giwercman et al., 1991a; Linke et al., 2005). Subsequent studies on infertile men with untreated ITGCN found that many will progress to invasive tumors, with risk approaching 70% at 7 years (von der Maase et al., 1986). There is strong evidence suggesting that ITGCN is present years prior to development of overt cancer. Muller and colleagues followed a 10 year-old cryptorchid boy with repeated testicular biopsies, which showed ITGCN at age 13 and eventually invasive malignant growth at age 21 (Muller et al., 1984; Skakkebaek et al., 1987). This idea was further supported by the morphological similarity between ITGCN and human fetal gonocytes observed by Holstein and Korner in 1974 (Holstein & Korner, 1974). Through immunohistochemical and DNA studies, Jorgense and colleagues were able to support their hypothesis that ITGCN cells are of prenatal origin and may be a consequence of malignant transformation of fetal germ cells *in utero* (Jorgensen et al., 1993).

Histologic and molecular studies have provided strong evidence supporting the close association between ITGCN and TGCTs. Due to its high serum concentration in seminoma patients, placental-like alkaline phosphatase (PLAP), a molecule of unknown biological function, was one of the first tumor markers studied for testicular cancer (Jacobsen & Norgaard-Pedersen, 1984). Through immunohistochemical experiments, PLAP was found to be highly expressed in seminomas, embryonal carcinomas, and ITGCN(Manivel et al., 1987). In contrast, expression of PLAP was not observed in normal testicular tissues (Manivel et al., 1987). As a result of recent advances in molecular pathology, numerous markers specific for ITCGN and TGCTs have been discovered. These markers include M2A (Giwercman et al., 1988a), 49-3F (Giwercman et al., 1990b), TRA-1-60 (Giwercman et al., 1993a), NANOG (Hart et al., 2005; Hoei-Hansen et al., 2005a), *c-kit* (Rajpert-De Meyts & Skakkebaek, 1994), AP-2y (Hoei-Hansen et al., 2004b), and OCT 3/4 (de Jong et al., 2005; Jones et al., 2006). Detailed

discussion of these markers is beyond the scope of this chapter, but some of them deserve further mention here**.** *c-kit* is a cell membrane tyrosine kinase receptor responsible for migration and survival of primordial germ cells. Its expression is seen in both ITGCN and seminoma. Mutations in the *c-kit* gene are frequently encountered in patients with bilateral germ cell tumors but rare in those with unilateral disease (Rajpert-De Meyts, 2006). This finding suggests that mutations had occurred prior to migration of primordial germ cells early in life and patients with *c-kit* mutations are prone to develop bilateral germ cell tumors. Recently, OCT3/4 has become one of the most widely used germ cell tumor markers due to its high specificity and sensitivity for seminoma, embryonal carcinoma and ITGCN (Jones et al., 2006). OCT3/4 has been praised as a possible screening tool for patients at risk for the development of TGCTs (Cheng et al., 2007; Jones et al., 2006).

The exact mechanisms involved in the transformation of ITGCN to overt TGCTs are not well understood, partly due to the lack of good experimental and animal models (Hoei-Hansen et al., 2005b). Down regulation of PTEN and p18 expressions as well as induction of cyclin E have been implicated in the progression of ITGCN to invasive tumors (Bartkova et al., 2000; Di Vizio et al., 2005). Through comparative genomic analysis, Summersgill and colleagues were able to show that the gain of chromosome 12p, a consistent finding in TGCTs, is associated with survival of ITGCN independent of Sertoli cells leading to malignant transformation (Looijenga et al., 2003; Summersgill et al., 2001). While there is strong evidence indicating ITGCN is the precursor for all TGCTs, the question still remains: where does ITGCN come from? The most widely accepted hypothesis suggests that ITCGN originates from fetal gonocytes and the initiation of malignant transformation most likely takes place early in fetal development. This hypothesis was initially based on the close morphological similarities between ITGCN and fetal gonocytes noted by Skakkebaek as well as other investigators (Gondos et al., 1983; Holstein & Korner, 1974). Subsequent studies demonstrating similar expression patterns between ITGCN, TGCTs and fetal gonoctyes of many immunohistochemical markers lend further support to this hypothesis (Jorgensen et al., 1993). Interestingly, expression of these markers is not seen in the adult testis (Jorgensen et al., 1993). Recent development of high throughput expression technology has not only provided better characterization of gene expressions of ITGCN at the RNA level but also helped us gain further insights into the relationship between ITGCN and fetal gonocytes. By comparing the mRNA expression of ITGCN to normal testis tissue, Hoei-Hansen et al. was the first to focus on the expression pattern of ITGCN and subsequently identified several genes that are important to fetal testicular development (Hoei-Hansen et al., 2004a). In 2004, Almstrup and colleagues used genome-wide cDNA microarrays to compare genomic expression profiles of ITGCN and embryonic stem cells, a precursor to fetal gonocytes, and found a remarkable similarity in expression patterns between these two entities, providing additional support that ITGCN is of fetal origin (Almstrup et al., 2004). Similar conclusions have been reached by other investigators as well. A recent microarray analysis by Sonne et al. demonstrated that the expression patterns of ITGCN cells are more similar to those of gonocyte than embryonic stem cells, suggesting that ITGCN may simply be an arrested gonocyte that persisted in a postnatal testis (Sonne et al., 2009).

Two mechanisms regarding the development of ITGCN can be proposed based on the current discussion. Whether the formation of ITGCN is related to spontaneous regression of spermatogonia toward a primordial germ cell state or an abnormal persistence of an

arrested gonocyte beyond the neonatal period remains unanswered. Some researchers have attempted to address this through epidemiologic studies by specifically examining the correlation between cancer incidence and differences in environmental factors during time of fetal development and birth. Moller's work in 1989 demonstrated lower incidence of testicular cancer in men born around the time of World War II than expected from the overall increasing trend. His observation supports the hypothesis that environmental influences early in life, or *in utero*, may be the determining factor for testicular cancer development (Moller, 1989; 1993). Additional evidence supporting this hypothesis can be seen in two cohort studies from Denmark, a country known to have one of the highest incidences of testicular cancer. By looking at the incidence of testicular cancer according to residence at birth within Denmark, Myrup et al was able to show the risk for TGCTs is related to county of birth, rather than county of residence at diagnosis (Myrup et al., 2010). When evaluating the testicular cancer risk in first- and second–generation immigrants to Denmark, it was found that the first-generation immigrants have TGCT risk similar to their country of origin, whereas the second generation has a risk similar to the Danish incidence (Myrup et al., 2008). Similar results have been produced by investigators from Sweden as well (Hemminki & Li, 2002). All of the evidence presented thus far would argue that the fate of testicular cancer is determined early in life, and the transformation of a precursor cell to ITGCN is initiated during fetal development.

3. Risk factors

Since ITGCN is a precursor lesion for TGCTs, the presence of ITGCN is now recognized as a risk factor for TGCTs. However, the incidence of ITGCN in healthy men has not been well characterized as the diagnosis of ITGCN requires testicular biopsy. As mentioned earlier, two landmark pathological studies attempted to address this question. The researchers from Denmark analyzed 399 testes from men between age 18 to 50 years old who died unexpectedly and found the overall prevalence of ITGCN to be 0.8%, comparable to the lifetime risk of TGCTs in the Danish male population (Giwercman et al., 1991a). The autopsy study from Germany also demonstrated similar findings (Linke et al., 2005). A number of conditions with high prevalence of ITGCN haven been identified and will be discussed here.

One of the greatest risk factors for developing TGCTs is a personal history of TGCTs. It has been shown that patients with a personal history of testicular cancer have a 25-fold increased risk of developing TGCTs in the contralateral testis (Dieckmann et al., 1993). Studies on men with TGCTs who underwent contralateral testicular biopsy demonstrated consistent rates of ITGCN at around 5-7% (Berthelsen et al., 1982; Dieckmann & Loy, 1996; von der Maase et al., 1986). Once again, the prevalence of ITGCN in the contralateral testis correlates well with the lifetime risk of developing contralateral TGCTs (Grigor & Rorth, 1993; von der Maase et al., 1986). Additional studies on men with unilateral TGCTs have identified a number of risk factors associated with contralateral ITGCN. Several reports have demonstrated testicular atrophy as an independent risk factor for contralateral ITCGN, with 4.3-fold increased risk of having positive biopsies in this group of patients (Dieckmann & Loy, 1996; Harland et al., 1998). Age at presentation is also a concern for contralateral ITGCN. One study showed that diagnosis of TGCTs in patients younger than 30 is associated with significant increased risk of positive biopsies on the contralateral testes

(Harland et al., 1998). While these findings demonstrate testicular atrophy and age of presentation are both strong risk factors for ITGCN, it has also been shown that the majority of patients with ITGCN do not have these associated risk factors. A large portion of patients with ITGCN would be missed if contralateral biopsies were only performed in patients with these risk factors. Dieckmann et al. have advocated for performing biopsies in all men with a history of testicular cancer (Dieckmann & Skakkebaek, 1999). In addition to atrophy and age of presentation, an irregular echogenic pattern of the contralateral testis on ultrasound has been shown to be predictive of positive testicular biopsy for ITGCN in 78 men with unilateral TGCTs (Lenz et al., 1996).

A recent study of 22,562 men in the US demonstrated that infertility is a strong risk factor for testicular cancer, suggesting that infertility and testicular cancer share a common etiology (Walsh et al., 2009). Similar findings were observed in a study of 2739 patients who underwent testicular biopsy for infertility (Bettocchi et al., 1994). In this cohort, 16 patients had unilateral ITGCN and testicular atrophy, 50% progressed to invasive TGCTs. Previous studies have shown that the incidence of ITGCN in infertile men is about 0.4-1.1% (Pryor et al., 1983; Skakkebaek, 1978). A recent retrospective review of biopsies from 453 subfertile men revealed a 2.2% risk of ITGCN, compared to an estimated risk of 0.45% in an age- and birth-matched cohort, suggesting that infertility is a risk factor for ITGCN (Olesen et al., 2007). In agreement with previous findings, these authors concluded that severe oligospermia and atrophic testes are associated risks for ITGCN.

Patients with cryptorchidism or undescended testes (UDT) are at an increased risk for developing testicular cancer. A recent meta-analysis review of 11 studies demonstrated that men with UDT are at a 6.3-fold increased risk for TGCTs, compared to 1.7-fold increase in the unaffected testes (Akre et al., 2009). Furthermore, there is strong evidence suggesting that orchiopexy before puberty has a protective effect against development of testicular cancer (Wood & Elder, 2009). While there is convincing evidence linking cryptorchidism to testicular cancer, the relationship between UDT and prevalence of ITGCN remains unclear. An early biopsy study on 50 men with cryptorchidism demonstrated the prevalence of ITGCN in this cohort is around 8% (Krabbe et al., 1979). In contrast, a larger study involving 300 patients with UDT found the prevalence of ITGCN to be 1.7% (Giwercman et al., 1989). Furthermore, previous studies on the prevalence of ITGCN in patients with unilateral TCGTs found that history of cryptorchidism is not predictive of ITGCN (Dieckmann & Loy, 1996; Harland et al., 1993). Unlike cryptorchidism, patients with sexual developmental disorders have been shown to have high rates of ITGCN and TGCTs in several small studies (Skakkebaek, 1979; Slowikowska-Hilczer et al., 2001).

Significant controversy surrounds the association between testicular microlithiasis (TM) and the subsequent development of ITCGN and TGCTs. In an otherwise healthy population, TM is not considered a risk factor for TGCTs. One study involving 63 healthy men with TM demonstrated that 98.5% of this cohort remained cancer-free 5 years after the initial screening (DeCastro et al., 2008). Furthermore, the incidence of TM in asymptomatic young men is reportedly to be 1.5-5.6% (DeCastro et al., 2008; von Eckardstein et al., 2001). On the other hand, the association between TM and TGCTs is also well documented, with high incidence of TM observed in patients with testicular cancer (Ikinger et al., 1982; Sanli et al., 2008). Recently, a large meta-analysis attempted to address this issue by looking at the

association of TM with TGCT and ITGCN (Tan et al., 2010). The authors found no association between TM and increased risk of TCGT in the otherwise healthy males. However, in those patients at risk for TGCTs, such as infertility, UDT or history of unilateral TGCT, the presence of TM is associated with approximately a 10-fold increased risk for concurrent diagnosis of TGCT or ITGCN. These findings are in an agreement with previous studies as well. Holm et al. demonstrated the presence of TM in the contralateral testis of men with unilateral TGCTs is associated with about a 30-fold increased risk of ITGCN (Holm et al., 2003). Furthermore, the incidence of TM in infertile men has been shown to be 2-20%, which is considerably higher than that of the general population (de Gouveia Brazao et al., 2004; von Eckardstein et al., 2001). Others have suggested that bilateral microlithiasis and sonographic heterogeneity in subfertile men are associated with increased risk of developing ITGCN (de Gouveia Brazao et al., 2004; Elzinga-Tinke et al., 2010), indicating the need to follow these patients closely with frequent biopsy or ultrasound.

4. Diagnosis

There are no imaging modalities or serum tumor markers to accurately diagnose ITGCN. Currently, testicular biopsy is the only reliable method to diagnose ITGCN. The pathologic morphology of ITGCN is well-defined and is similar to that of seminoma. The ITGCN cells are larger than normal spermatogonia, and possess larger nuclei with prominent nucleoli (Gondos & Migliozzi, 1987). The cytoplasm is rich with glycogen and contains the enzyme PLAP (Dieckmann et al., 2011; Lauke, 1997). These abnormal cells are located at the basement membrane of the seminiferous tubules and the tubules vary from containing adjacent normal Sertoli cells and spermatogonia to complete dominance of ITGCN cells (Jacobsen et al., 1981). A good biopsy sample should be at least 3 x 3 mm in size and contains at least 30-40 tubules on microscopic examination (Holstein & Lauke, 1996). Testicular biopsies should be placed in Boulin's or Stieve's solution; Formalin fixation should be avoided because it can greatly alter the morphology of testicular architecture.

Immunohistochemical markers are routinely used during histological examination to aid the diagnosis of ITGCN. The importance of immunohistochemistry (IHC) was highlighted in a recent review of 20 patients with TGCTs and prior negative testicular biopsy (van Casteren et al., 2009). Seven cases of ITGCNs and TGCTs were diagnosed by experienced pathologists based on morphology alone, but an additional 4 cases were identified with IHC. As mentioned earlier, PLAP has traditionally been the most widely used IHC marker to identify ITGCN, with sensitivity ranging from 83-98% (Jacobsen & Norgaard-Pedersen, 1984; Manivel et al., 1987). Several studies recently have demonstrated a superior IHC marker for detecting ITGCN, OCT3/4, which has sensitivity and specificity approaching 100% (Cheng et al., 2007; de Jong et al., 2005; Jones et al., 2006). A pathologic representation of ITGCN stained with OCT 3/4 is portrayed in Fig. 1.

As open testicular biopsy is invasive and has the potential for complications, detection of ITGCN by semen analysis has been investigated. The ability to use semen to detect ITGCN is based on the original work by Giwercman when he observed the exfoliation of ITGCN cells from the seminiferous tubules into the seminal fluid in men with TGCTs (Giwercman et al., 1988b). However, the detection rate of ITGCN cells in semen is far inferior to open surgical biopsy (Brackenbury et al., 1993). Subsequent studies have attempted to increase the sensitivity

of semen analysis for CIS by combining DNA flow cytometry and in situ hybridization without great success (Giwercman et al., 1990a). Recently, investigators from Denmark sought to improve the detection rate on semen analysis by developing a sophisticated model involving immunocytochemical staining of ejaculates from infertile men (Almstrup et al., 2011). This approach demonstrated an overall sensitivity and specificity of 0.67 and 0.98, respectively, when compared to open surgical biopsy. These non-invasive methods for detection of ITGCN are promising but their clinical feasibility remains to be seen.

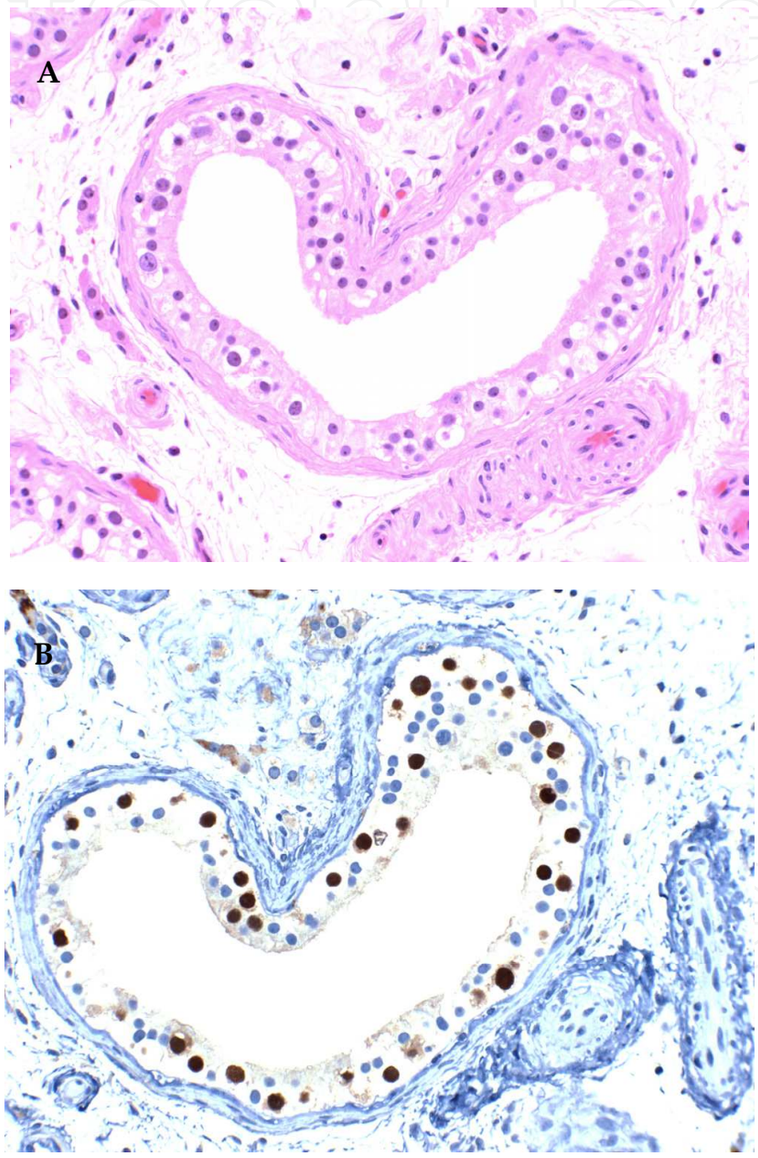


Fig. 1. Pathologic features of ITGCN. A – H&E stained section demonstrates typical features of ITGCN: cells with large nuclei and prominent nucleoli located along the basement membrane of the seminiferous tubules. B – Immunohistochemical staining of ITGCN cells with OCT 4 demonstrating a nuclear staining pattern (Jones et al., 2004). (Courtesy of Liang Cheng, MD, Indiana University School of Medicine, Indianapolis, IN)

4.1 Testicular biopsy

The distribution of ITGCN cells within a testis has been a subject of contention and is directly linked to the accuracy of testicular biopsy. Based on their biopsy simulation experiments, Berthelsen and Skakkebaek hypothesized that ITGCN cells are homogenously dispersed throughout the testis and demonstrated that a 3-mm biopsy is a sufficient representation of the entire testis (Berthelsen & Skakkebaek, 1981). Early studies had supported this theory by demonstrating the low false-negative biopsy rates associated with the single biopsy technique. In a study involving 1859 negative testicular biopsies in the contralateral testes of patients with TGCTs, only 5 patients (0.3%) developed TGCTs (Dieckmann & Loy, 2003). The same authors re-examined their data recently and, again, showed the overall proportion of false-negative biopsies for detecting ITCGN is about 0.5% (Dieckmann et al., 2005). Some investigators have sought to improve the sensitivity of testicular biopsy by performing multiple biopsies on the same testis. In a series of 2318 men with TGCTs who underwent double-biopsy of the contralateral testes, the discordance rate was 31% with an extra yield of 18% in diagnosis (Dieckmann et al., 2007). The high discordance rate in this study suggests that the distribution of ITGCN within a testis is heterogeneous rather than homogenous. This finding is further supported by several ITGCN mapping studies that demonstrated a focal pattern of ITGCN adjacent to TGCTs (Loy et al., 1990; Prym & Lauke, 1994). The heterogeneous distribution of ITGCN would also provide an explanation for the development of TGCTs despite prior negative biopsies. Based on this assumption, Dieckmann and colleagues were able to increase the diagnostic yield of ITGCN by performing a second biopsy at a different site (Dieckmann et al., 2007). This is in accord with a study involving triple biopsies of the contralateral testis, which demonstrated an 8% increase in detection of ITGCN (Kliesch et al., 2003). However, this approach may result in a higher complication rate especially in the setting of a solitary testis. Furthermore, it remains to be seen whether the benefit of multiple biopsies outweighs its risks. Even with this approach subsequent TGCTs in patients with prior negative double biopsy have been reported (Souchon et al., 2006).

Complications associated with testicular biopsy remain a major concern and have prevented many clinicians from adopting this approach as routine screening protocol. Current literature suggests the overall rates of complication secondary to testicular biopsy range from 3 – 20% (Dieckmann et al., 2005; Heidenreich & Moul, 2002). In a prospective study of 1874 men with testicular cancer who underwent contralateral testicular biopsy, the overall complication rate of 2.8% was noted with 0.64% requiring repeat surgery and one testis (0.05%) was lost (Dieckmann et al., 2005). In the same series, a subset of patients were followed with serial scrotal sonographic and magnetic resonance imaging, which demonstrated early post-operative changes, such as hematoma or edema, in 33% - 45% of patients. However, these changes spontaneously resolved in 96% of patients 18 months after the initial biopsy, suggesting testicular biopsy is a procedure with low-surgical risks. Despite resolution of post-surgical changes on imaging, the impact of surgical biopsy on testicular endocrine function remains to be addressed in this cohort of patients. Studies on infertile men have reported decrease in serum testosterone level following testicular biopsy, with some developing hypogonadism (Manning et al., 1998); however, these cases were done with significantly more biopsies per testis and the effect was self-limiting.

The question of which group of patients should undergo testicular biopsy has been a subject of controversy, with varying responses to the same data. The fundamental argument for routine testicular biopsy is early diagnosis of TGCTs at the precursor stages. The most common scenario in which testicular biopsy is performed to detect ITGCN is in the contralateral testes of patients with a history of unilateral TGCTs. Surgical biopsy of the contralateral testis at the time of initial orchiectomy is routinely done in Denmark and Germany, two counties with the world's highest incidences of TGCTs (Dieckmann et al., 2011). Others have advocated for biopsy only in those with TGCTs and risk factors for contralateral ITGCN, such as testicular atrophy, history of cryptorchidism, age less than 30 years, infertility and TM (Dieckmann et al., 2011; Heidenreich, 2009). As demonstrated earlier, those who routinely perform testicular biopsy have consistently demonstrated a 5-7% incidence rate of ITGCN in the contralateral testis, and 70% of them progress to TGCTs at 7 years (Dieckmann & Loy, 1996; von der Maase et al., 1986). Early identification of these high risk patients allows for organ-sparing therapy, which may potentially preserve endocrine function in contrast to a second orchiectomy (Dieckmann & Skakkebaek, 1999). Additionally, diagnostic delay in patients with TGCTs has been shown to significantly impact survival, which highlights the importance of early diagnosis (Huyghe et al., 2007). Since the rate of false-negative biopsy is exceedingly low (0.5%), a negative testicular biopsy translates into a very low probability of having a second TGCTs. This may dictate a less intensive surveillance protocol as well as alleviate psychological distress associated with diagnosis of cancer in high-risk patients.

The arguments against the practice of routine testicular biopsy in these patients are also convincing. In contrast to the standard of care in Denmark and Germany, physicians in the US are less likely to perform routine testicular biopsy in patients with TGCTs partly due to a lower incidence of contralateral cancer (Coogan et al., 1998; Fossa et al., 2005). In a large series of nearly 30,000 patients with unilateral TGCT, the investigators demonstrated an overall risk of developing contralateral TGCTs is 1.9% in the US (Fossa et al., 2005), which is considerably lower than the 5-7% reported by the European studies. Furthermore, these authors demonstrated patients with contralateral TGCTs had excellent long-term prognosis, with an overall survival rate of 93% at 10 years after initial diagnosis, providing support for continuing the US approach of not subjecting contralateral testis to biopsy. Others have also demonstrated good clinical outcomes in patients with bilateral TGCTs who are treated appropriately for histology and stage (Holzbeierlein et al., 2003). Other arguments favoring the omission of routine biopsy include the added cost associated with surgery as well as exposing the majority of patients unnecessarily to the surgical risks in order to benefit a few individuals. As discussed earlier, testicular biopsy to screen for ITGCN is not a perfect technique; many cases of contralateral tumor occurrence have been reported in patients with negative prior biopsies, even with the double biopsy approach (Souchon et al., 2006). Finally, the most widely accepted organ-sparing therapy for ITGCN is radiotherapy, which has been shown to destroy both endocrine and exocrine function of a testis, with one study demonstrating high incidence of hypogonadisim after radiation requiring androgen supplementation (Petersen et al., 2002). Until methods of diagnosis are improved or a survival benefit is demonstrated with early diagnosis of ITGCN, treatment decisions need to be made based on data presented and individualized for patient risk factors and wishes.

5. Treatment

The primary goal of treating ITCGN is to prevent its malignant transformation to TGCT. Presently, there are four options to managing ITGCN: chemotherapy, radiation, orchiectomy and surveillance. With the exception of surveillance, the remaining three treatment modalities put patients at significant risk for infertility, hypogonadism, or both. The decision to proceed with a certain treatment modality has to be individualized based upon specific risk factors as well as patient wishes.

5.1 Chemotherapy

It was initially thought that chemotherapy could completely eradicate ITGCN and prevent development of contralateral TGCT. This idea was based on the observation that patients receiving chemotherapy had no progression of disease and had complete resolution of ITGCN on repeat biopsy, whereas 7 out of 18 patients without chemotherapy progressed to overt cancer (von der Maase et al., 1985). However, three years after their initial publication, the same investigators reported that one patient in the chemotherapy group had recurrence of ITGCN on repeat biopsy (von der Maase et al., 1988). Numerous reports since then demonstrated chemotherapy to be an ineffective regimen for treating ITGCN. One series estimated the risk of recurrent ITGCN 5 and 10 years after termination of chemotherapy to be 21% and 42%, respectively (Christensen et al., 1998). Histological analysis on orchiectomy specimens obtained from patients who had chemotherapy demonstrated persistence of ITGCN in 35% of patients (Bottomley et al., 1990). Possible explanations behind this phenomenon include the presence of blood-testis barrier or insensitivity of ITGCN cells to chemotherapy (Mortensen et al., 2011; Ploen & Setchell, 1992). In a recent study of 11 patients with unilateral TGCTs and biopsy-proven ITGCN in the contralateral testis treated with chemotherapy, 64% of them had ITGCN on repeat biopsy, providing support that chemotherapy is ineffective at eradicating ITGCN (Kleinschmidt et al., 2009).

5.2 Radical orchiectomy

Unlike chemotherapy, orchiectomy is the most definitive treatment with the highest success rate and is the main treatment approach for three patient populations: those with unilateral ITGCN and contralateral normal testis; those with an atrophic testis; and those with infertility and unilateral ITGCN (Dieckmann & Skakkebaek, 1999; Mortensen et al., 2011). In patients with a solitary testis, orchiectomy in this population needs to be weighed against the risk of infertility and permanent dependence on exogenous testosterone replacement.

5.3 Radiation

Local radiation has become the preferred treatment modality for ITGCN because it is organ-sparing and highly effective at eradicating ITGCN cells. The rationale behind employing radiotherapy is based on the finding that radiation has the propensity to destroy ITGCN and germ cells while preserving Leydig cell function (von der Maase et al., 1985). Therefore, it has the potential of preserving testicular endocrine function while eliminating neoplastic cells. Presently, three major concerns have been raised regarding radiotherapy in the treatment of ITGCN. First, the radiation dose for optimal oncologic control has not been determined (Mortensen et al., 2011). The current recommended dose according to guidelines

put forth by the European Association of Urology is 20 Gy delivered over 2 weeks (Albers et al., 2005). This dose has previously been shown to be very effective at eradicating ITGCN cells, with one series demonstrating complete resolution of ITGCN on repeat biopsy at a follow-up of 2 years (Giwercman et al., 1991b). Another group from Denmark studied the effect of radiotherapy in doses 14 to 20 Gy on eradication of ITGCN testes, and demonstrated that all patients treated with radiation dose level 16 to 20 Gy had complete resolution of ITGCN while one patient treated at dose level 14 Gy had a recurrence at a follow up of 5 years (Petersen et al., 2002). However, recurrences of ITGCN have been reported at all dose levels up to 20 Gy (Classen et al., 2003; Dieckmann et al., 2002; Dotsch et al., 2000; Petersen et al., 2002). Currently, there is no consensus on the optimal radiation dose to achieve cancer control, but most would agree that a dose level of 16 to 20 Gy is effective. The second concern is in regards to the effect of radiation on testicular exocrine function. Local radiation to the testis will result in the destruction of both ITGCN and germ cells, subsequently rendering these patients infertile. Proponents of local radiation to solitary testes argue that patients with ITGCN already have severely impaired spermatogensis prior to therapy (Giwercman et al., 1993b; Petersen et al., 1999); therefore, radiation should not have significant impact on the development of infertility. However, improvement in spermatogenesis has been noted following removal of unilateral TGCTs (Carroll et al., 1987) and cases of successful conception in patients with ITGCN have been reported (Heidenreich et al., 1997). Therefore, it is important to consider surveillance or postponing radiation to allow for paternity in patients with ITGCN in the solitary testis. The third concern is the impairment of testicular endocrine function by local radiation. According to one series of patients with ITGCN in solitary testis, serum luteinizing hormone remained significantly elevated post radiation and 25% of patients require permanent androgen supplementation (Giwercman et al., 1991b). This finding led to several investigations on dose reduction, with one study demonstrating the impairment on endocrine function was independent of radiation dose and the need for androgen substitutions was similar at all dose levels (Petersen et al., 2002). Others found less toxic effect on testicular Leydig cell function with lower radiation doses at 13 and 16 Gy (Bang et al., 2009; Sedlmayer et al., 2001). All patients undergoing radiation therapy need to have their hormone function checked on a regular basis in order to identify those where androgen supplementation is needed.

5.4 Active surveillance

For select patients, active surveillance may be the treatment of choice. This is particularly true for those with ITGCN in the solitary testis who desire to preserve fertility and hormone function. Surveillance can be justified in these patients but they must be counseled on the risk of developing invasive cancer and the need for subsequent orchiectomy. Furthermore, these patients need to be compliant with regular follow-up and, more importantly, frequent testicular self-examination. If preserving fertility is the goal, semen analysis should be obtained and cryopreservation of viable sperm should be considered before treatment is initiated (Dieckmann & Skakkebaek, 1999). For those patients who progress to TGCTs, partial orchiectomy may be an acceptable treatment if the tumor is organ-confined and less than 2cm in size (Heidenreich et al., 2001). Consistent with the discussion above, as most patients in this series (82%) had associated ITGCN, most were treated with adjuvant radiation and relapses were only observed in those who did not receive radiation treatment. Partial orchiectomy is

still in the investigational phase, and patients should be counseled on the risk of disease progression and the need for radical orchiectomy if a tumor recurs in that testis.

6. Bilateral testicular cancer

While the risk of developing contralateral testicular cancer is high in patients with unilateral TGCTs, there is no clear consensus on how these patients should be managed. Perhaps, we can gain further insight into this issue by looking at the outcome data of patients with bilateral testicular cancer. The reported incidence of bilateral TGCTs in the US and Europe is estimated to be 1- 4% (Bokemeyer et al., 1993; Che et al., 2002; Coogan et al., 1998; Fossa et al., 2005; Hentrich et al., 2005; Holzbeierlein et al., 2003; Pamenter et al., 2003). In these contemporary series, metachronous presentations were the majority (62-88%) and the median interval between first and second testicular tumor was 50 – 76 months. Recent studies demonstrated that the clinical outcomes of metachronous TGCTs were excellent (Albers et al., 1999; Che et al., 2002; Coogan et al., 1998; Fossa et al., 2005), with the majority of patients presenting with clinical stage 1 disease (44 – 90%). Furthermore, the 10-year survival rate following a diagnosis of metachronous bilateral testis cancer was 93%, which is comparable to patients diagnosed with unilateral TGCTs (95%)(Fossa et al., 2005). Single institution studies from Indiana, M.D. Anderson, and Memorial-Sloan-Kettering also demonstrated excellent prognosis in these patients, with most reporting very low mortality from TGCTs (Che et al., 2002; Coogan et al., 1998; Holzbeierlein et al., 2003). Despite such a high cure rate, most patients in these studies did not undergo contralateral testicular biopsy. This finding certainly questions the value of contralateral testicular biopsy to screen for ITGCN. Based on the excellent outcomes observed in bilateral TGCTs, active surveillance, perhaps, should play an important role in the management of patients with contralateral ITGCN.

7. Conclusions

The incidence of testicular cancer is increasing worldwide and it has nearly doubled in the last 40 years. This increasing incidence has led researchers to focus on the pathogenesis of ITGCN, which has now been established as the precursor lesion for most TGCTs. Several theories have been proposed regarding the origin of ITGCN, and recent studies seem to suggest it is abnormal persistence of an arrested gonocyte beyond the neonatal period. The fate of testicular cancer is determined early in life, and the transformation of a precursor cell to ITGCN cell is initiated *in utero*. Incidence trends of testicular cancer can potentially be altered by continued exploration of the contributing factors in the pre- and peri-natal period. The diagnosis and management of patients with ITGCN remain a challenging problem for clinicians, and indications for testicular biopsy to detect ITGCN are controversial. The decision to proceed with a certain treatment modality should be individualized and needs to be based on specific risk factors as well as patient wishes. Radical orchiectomy and radiation therapy are the only two effective means of preventing subsequent TGCTs in a testis with ITGCN. Both treatment options can result in infertility as well as hormone dysfunction. Metachronous bilateral TGCTs occur infrequently but the clinical outcomes are excellent, suggesting that the role of active surveillance needs to be emphasized in the management of contralateral ITGCN in a solitary testis.

8. References

Akhtar, M. & Sidiki, Y. (1979). "Undifferentiated intratubular germ cell tumor of the testis: light and electron microscopic study of a unique case." Cancer 43(6): 2332-2339.

Akre, O., Pettersson, A. & Richiardi, L. (2009). "Risk of contralateral testicular cancer among men with unilaterally undescended testis: a meta analysis." Int J Cancer 124(3): 687-689.

Albers, P., Albrecht, W., Algaba, F., Bokemeyer, C., Cohn-Cedermark, G., Horwich, A., Klepp, O., Laguna, M. P. & Pizzocaro, G. (2005). "Guidelines on testicular cancer." Eur Urol 48(6): 885-894.

Albers, P., Goll, A., Bierhoff, E., Schoeneich, G. & Muller, S. C. (1999). "Clinical course and histopathologic risk factor assessment in patients with bilateral testicular germ cell tumors." Urology 54(4): 714-718.

Almstrup, K., Hoei-Hansen, C. E., Wirkner, U., Blake, J., Schwager, C., Ansorge, W., Nielsen, J. E., Skakkebaek, N. E., Rajpert-De Meyts, E. & Leffers, H. (2004). "Embryonic stem cell-like features of testicular carcinoma in situ revealed by genome-wide gene expression profiling." Cancer Res 64(14): 4736-4743.

Almstrup, K., Lippert, M., Mogensen, H. O., Nielsen, J. E., Hansen, J. D., Daugaard, G., Jorgensen, N., Foged, N. T., Skakkebaek, N. E. & Rajpert-De Meyts, E. (2011). "Screening of subfertile men for testicular carcinoma in situ by an automated image analysis-based cytological test of the ejaculate." Int J Androl 34(4 Pt 2): e21-30; discussion e30-21.

Bang, A. K., Petersen, J. H., Petersen, P. M., Andersson, A. M., Daugaard, G. & Jorgensen, N. (2009). "Testosterone production is better preserved after 16 than 20 Gray irradiation treatment against testicular carcinoma in situ cells." Int J Radiat Oncol Biol Phys 75(3): 672-676.

Bartkova, J., Thullberg, M., Rajpert-De Meyts, E., Skakkebaek, N. E. & Bartek, J. (2000). "Cell cycle regulators in testicular cancer: loss of p18INK4C marks progression from carcinoma in situ to invasive germ cell tumours." Int J Cancer 85(3): 370-375.

Berthelsen, J. G. & Skakkebaek, N. E. (1981). "Value of testicular biopsy in diagnosing carcinoma in situ testis." Scand J Urol Nephrol 15(3): 165-168.

Berthelsen, J. G., Skakkebaek, N. E., von der Maase, H., Sorensen, B. L. & Mogensen, P. (1982). "Screening for carcinoma in situ of the contralateral testis in patients with germinal testicular cancer." Br Med J (Clin Res Ed) 285(6356): 1683-1686.

Bettocchi, C., Coker, C. B., Deacon, J., Parkinson, C. & Pryor, J. P. (1994). "A review of testicular intratubular germ cell neoplasia in infertile men." J Androl 15 Suppl: 14S-16S.

Bokemeyer, C., Schmoll, H. J., Schoffski, P., Harstrick, A., Bading, M. & Poliwoda, H. (1993). "Bilateral testicular tumours: prevalence and clinical implications." Eur J Cancer 29A(6): 874-876.

Bottomley, D., Fisher, C., Hendry, W. F. & Horwich, A. (1990). "Persistent carcinoma in situ of the testis after chemotherapy for advanced testicular germ cell tumours." Br J Urol 66(4): 420-424.

Brackenbury, E. T., Hargreave, T. B., Howard, G. C. & McIntyre, M. A. (1993). "Seminal fluid analysis and fine-needle aspiration cytology in the diagnosis of carcinoma in situ of the testis." Eur Urol 23(1): 123-128.

Bray, F., Ferlay, J., Devesa, S. S., McGlynn, K. A. & Moller, H. (2006). "Interpreting the international trends in testicular seminoma and nonseminoma incidence." Nat Clin Pract Urol 3(10): 532-543.

Carroll, P. R., Whitmore, W. F., Jr., Herr, H. W., Morse, M. J., Sogani, P. C., Bajorunas, D., Fair, W. R. & Chaganti, R. S. (1987). "Endocrine and exocrine profiles of men with testicular tumors before orchiectomy." J Urol 137(3): 420-423.

Che, M., Tamboli, P., Ro, J. Y., Park, D. S., Ro, J. S., Amato, R. J. & Ayala, A. G. (2002). "Bilateral testicular germ cell tumors: twenty-year experience at M. D. Anderson Cancer Center." Cancer 95(6): 1228-1233.

Cheng, L., Sung, M. T., Cossu-Rocca, P., Jones, T. D., MacLennan, G. T., De Jong, J., Lopez-Beltran, A., Montironi, R. & Looijenga, L. H. (2007). "OCT4: biological functions and clinical applications as a marker of germ cell neoplasia." J Pathol 211(1): 1-9.

Chia, V. M., Quraishi, S. M., Devesa, S. S., Purdue, M. P., Cook, M. B. & McGlynn, K. A. (2010). "International trends in the incidence of testicular cancer, 1973-2002." Cancer Epidemiol Biomarkers Prev 19(5): 1151-1159.

Christensen, T. B., Daugaard, G., Geertsen, P. F. & von der Maase, H. (1998). "Effect of chemotherapy on carcinoma in situ of the testis." Ann Oncol 9(6): 657-660.

Classen, J., Dieckmann, K., Bamberg, M., Souchon, R., Kliesch, S., Kuehn, M. & Loy, V. (2003). "Radiotherapy with 16 Gy may fail to eradicate testicular intraepithelial neoplasia: preliminary communication of a dose-reduction trial of the German Testicular Cancer Study Group." Br J Cancer 88(6): 828-831.

Coogan, C. L., Foster, R. S., Simmons, G. R., Tognoni, P. G., Roth, B. J. & Donohue, J. P. (1998). "Bilateral testicular tumors: management and outcome in 21 patients." Cancer 83(3): 547-552.

de Gouveia Brazao, C. A., Pierik, F. H., Oosterhuis, J. W., Dohle, G. R., Looijenga, L. H. & Weber, R. F. (2004). "Bilateral testicular microlithiasis predicts the presence of the precursor of testicular germ cell tumors in subfertile men." J Urol 171(1): 158-160.

de Jong, J., Stoop, H., Dohle, G. R., Bangma, C. H., Kliffen, M., van Esser, J. W., van den Bent, M., Kros, J. M., Oosterhuis, J. W. & Looijenga, L. H. (2005). "Diagnostic value of OCT3/4 for pre-invasive and invasive testicular germ cell tumours." J Pathol 206(2): 242-249.

DeCastro, B. J., Peterson, A. C. & Costabile, R. A. (2008). "A 5-year followup study of asymptomatic men with testicular microlithiasis." J Urol 179(4): 1420-1423; discussion 1423.

Di Vizio, D., Cito, L., Boccia, A., Chieffi, P., Insabato, L., Pettinato, G., Motti, M. L., Schepis, F., D'Amico, W., Fabiani, F., Tavernise, B., Venuta, S., Fusco, A. & Viglietto, G. (2005). "Loss of the tumor suppressor gene PTEN marks the transition from intratubular germ cell neoplasias (ITGCN) to invasive germ cell tumors." Oncogene 24(11): 1882-1894.

Dieckmann, K. P., Heinemann, V., Frey, U. & Pichlmeier, U. (2005). "How harmful is contralateral testicular biopsy?--an analysis of serial imaging studies and a prospective evaluation of surgical complications." Eur Urol 48(4): 662-672.

Dieckmann, K. P., Kulejewski, M., Heinemann, V. & Loy, V. (2011). "Testicular biopsy for early cancer detection--objectives, technique and controversies." Int J Androl 34(4 Pt 2): e7-13.

Dieckmann, K. P., Kulejewski, M., Pichlmeier, U. & Loy, V. (2007). "Diagnosis of contralateral testicular intraepithelial neoplasia (TIN) in patients with testicular germ cell cancer: systematic two-site biopsies are more sensitive than a single random biopsy." Eur Urol 51(1): 175-183; discussion 183-175.

Dieckmann, K. P., Lauke, H., Michl, U., Winter, E. & Loy, V. (2002). "Testicular germ cell cancer despite previous local radiotherapy to the testis." Eur Urol 41(6): 643-649; discussion 649-650.

Dieckmann, K. P. & Loy, V. (1996). "Prevalence of contralateral testicular intraepithelial neoplasia in patients with testicular germ cell neoplasms." J Clin Oncol 14(12): 3126-3132.

Dieckmann, K. P. & Loy, V. (2003). "False-negative biopsies for the diagnosis of testicular intraepithelial neoplasia (TIN)--an update." Eur Urol 43(5): 516-521.

Dieckmann, K. P., Loy, V. & Buttner, P. (1993). "Prevalence of bilateral testicular germ cell tumours and early detection based on contralateral testicular intra-epithelial neoplasia." Br J Urol 71(3): 340-345.

Dieckmann, K. P. & Skakkebaek, N. E. (1999). "Carcinoma in situ of the testis: review of biological and clinical features." Int J Cancer 83(6): 815-822.

Dotsch, M., Brauers, A., Buttner, R., Nolte-Ernsting, C., Eble, M. J. & Jakse, G. (2000). "Malignant germ cell tumor of the contralateral testis after radiotherapy for testicular intraepithelial neoplasia." J Urol 164(2): 452-453.

Elzinga-Tinke, J. E., Sirre, M. E., Looijenga, L. H., van Casteren, N., Wildhagen, M. F. & Dohle, G. R. (2010). "The predictive value of testicular ultrasound abnormalities for carcinoma in situ of the testis in men at risk for testicular cancer." Int J Androl 33(4): 597-603.

Emerson, R. E. & Ulbright, T. M. (2010). "Intratubular germ cell neoplasia of the testis and its associated cancers: the use of novel biomarkers." Pathology 42(4): 344-355.

Fossa, S. D., Chen, J., Schonfeld, S. J., McGlynn, K. A., McMaster, M. L., Gail, M. H. & Travis, L. B. (2005). "Risk of contralateral testicular cancer: a population-based study of 29,515 U.S. men." J Natl Cancer Inst 97(14): 1056-1066.

Giwercman, A., Andrews, P. W., Jorgensen, N., Muller, J., Graem, N. & Skakkebaek, N. E. (1993a). "Immunohistochemical expression of embryonal marker TRA-1-60 in carcinoma in situ and germ cell tumors of the testis." Cancer 72(4): 1308-1314.

Giwercman, A., Bruun, E., Frimodt-Moller, C. & Skakkebaek, N. E. (1989). "Prevalence of carcinoma in situ and other histopathological abnormalities in testes of men with a history of cryptorchidism." J Urol 142(4): 998-1001: discussion 1001-1002.

Giwercman, A., Hopman, A. H., Ramaekers, F. C. & Skakkebaek, N. E. (1990a). "Carcinoma in situ of the testis. Detection of malignant germ cells in seminal fluid by means of in situ hybridization." Am J Pathol 136(3): 497-502.

Giwercman, A., Lindenberg, S., Kimber, S. J., Andersson, T., Muller, J. & Skakkebaek, N. E. (1990b). "Monoclonal antibody 43-9F as a sensitive immunohistochemical marker of carcinoma in situ of human testis." Cancer 65(5): 1135-1142.

Giwercman, A., Marks, A., Bailey, D., Baumal, R. & Skakkebaek, N. E. (1988a). "A monoclonal antibody as a marker for carcinoma in situ germ cells of the human adult testis." APMIS 96(8): 667-670.

Giwercman, A., Marks, A. & Skakkebaek, N. E. (1988b). "Carcinoma-in-situ germ-cells exfoliated from seminiferous epithelium into seminal fluid." Lancet 1(8584): 530.

Giwercman, A., Muller, J. & Skakkebaek, N. E. (1991a). "Prevalence of carcinoma in situ and other histopathological abnormalities in testes from 399 men who died suddenly and unexpectedly." J Urol 145(1): 77-80.

Giwercman, A., von der Maase, H., Berthelsen, J. G., Rorth, M., Bertelsen, A. & Skakkebaek, N. E. (1991b). "Localized irradiation of testes with carcinoma in situ: effects on Leydig cell function and eradication of malignant germ cells in 20 patients." J Clin Endocrinol Metab 73(3): 596-603.

Giwercman, A., von der Maase, H., Rorth, M. & Skakkebaek, N. E. (1993b). "Semen quality in testicular tumour and CIS in the contralateral testis." Lancet 341(8841): 384-385.

Gondos, B., Berthelsen, J. G. & Skakkebaek, N. E. (1983). "Intratubular germ cell neoplasia (carcinoma in situ): a preinvasive lesion of the testis." Ann Clin Lab Sci 13(3): 185-192.

Gondos, B. & Migliozzi, J. A. (1987). "Intratubular germ cell neoplasia." Semin Diagn Pathol 4(4): 292-303.

Grigor, K. M. & Rorth, M. (1993). "Should the contralateral testis be biopsied? Round table discussion." Eur Urol 23(1): 129-135.

Harland, S. J., Cook, P. A., Fossa, S. D., Horwich, A., Mead, G. M., Parkinson, M. C., Roberts, J. T. & Stenning, S. P. (1998). "Intratubular germ cell neoplasia of the contralateral testis in testicular cancer: defining a high risk group." J Urol 160(4): 1353-1357.

Harland, S. J., Cook, P. A., Fossa, S. D., Horwich, A., Parkinson, M. C., Roberts, J. T. & Stenning, S. P. (1993). "Risk factors for carcinoma in situ of the contralateral testis in patients with testicular cancer. An interim report." Eur Urol 23(1): 115-118; discussion 119.

Hart, A. H., Hartley, L., Parker, K., Ibrahim, M., Looijenga, L. H., Pauchnik, M., Chow, C. W. & Robb, L. (2005). "The pluripotency homeobox gene NANOG is expressed in human germ cell tumors." Cancer 104(10): 2092-2098.

Heidenreich, A. (2009). "Contralateral testicular biopsy in testis cancer: current concepts and controversies." BJU Int 104(9 Pt B): 1346-1350.

Heidenreich, A. & Moul, J. W. (2002). "Contralateral testicular biopsy procedure in patients with unilateral testis cancer: is it indicated?" Semin Urol Oncol 20(4): 234-238.

Heidenreich, A., Vorreuther, R., Neubauer, S., Zumbe, J. & Engelmann, U. H. (1997). "Paternity in patients with bilateral testicular germ cell tumors." Eur Urol 31(2): 246-248.

Heidenreich, A., Weissbach, L., Holtl, W., Albers, P., Kliesch, S., Kohrmann, K. U. & KP, D. I. (2001). "Organ sparing surgery for malignant germ cell tumor of the testis." J Urol 166(6): 2161-2165.

Hemminki, K. & Li, X. (2002). "Cancer risks in second-generation immigrants to Sweden." Int J Cancer 99(2): 229-237.

Hentrich, M., Weber, N., Bergsdorf, T., Liedl, B., Hartenstein, R. & Gerl, A. (2005). "Management and outcome of bilateral testicular germ cell tumors: Twenty-five year experience in Munich." Acta Oncol 44(6): 529-536.

Hoei-Hansen, C. E., Almstrup, K., Nielsen, J. E., Brask Sonne, S., Graem, N., Skakkebaek, N. E., Leffers, H. & Rajpert-De Meyts, E. (2005a). "Stem cell pluripotency factor NANOG is expressed in human fetal gonocytes, testicular carcinoma in situ and germ cell tumours." Histopathology 47(1): 48-56.

Hoei-Hansen, C. E., Nielsen, J. E., Almstrup, K., Hansen, M. A., Skakkebaek, N. E., Rajpert-DeMeyts, E. & Leffers, H. (2004a). "Identification of genes differentially expressed in testes containing carcinoma in situ." Mol Hum Reprod 10(6): 423-431.

Hoei-Hansen, C. E., Nielsen, J. E., Almstrup, K., Sonne, S. B., Graem, N., Skakkebaek, N. E., Leffers, H. & Rajpert-De Meyts, E. (2004b). "Transcription factor AP-2gamma is a developmentally regulated marker of testicular carcinoma in situ and germ cell tumors." Clin Cancer Res 10(24): 8521-8530.

Hoei-Hansen, C. E., Rajpert-De Meyts, E., Daugaard, G. & Skakkebaek, N. E. (2005b). "Carcinoma in situ testis, the progenitor of testicular germ cell tumours: a clinical review." Ann Oncol 16(6): 863-868.

Holm, M., Hoei-Hansen, C. E., Rajpert-De Meyts, E. & Skakkebaek, N. E. (2003). "Increased risk of carcinoma in situ in patients with testicular germ cell cancer with ultrasonic microlithiasis in the contralateral testicle." J Urol 170(4 Pt 1): 1163-1167.

Holstein, A. F. & Korner, F. (1974). "Light and electron microscopical analysis of cell types in human seminoma." Virchows Arch A Pathol Anat Histol 363(2): 97-112.

Holstein, A. F. & Lauke, H. (1996). "Histologic diagnostics of early testicular germ-cell tumor." Int J Urol 3(3): 165-172.

Holzbeierlein, J. M., Sogani, P. C. & Sheinfeld, J. (2003). "Histology and clinical outcomes in patients with bilateral testicular germ cell tumors: the Memorial Sloan Kettering Cancer Center experience 1950 to 2001." J Urol 169(6): 2122-2125.

Howlader, N., Noone, A. M., Krapcho, M., Neyman, N., Aminou, R., Waldron, W., Altekruse, S. F., Kosary, C. L., Ruhl, J., Tatalovich, Z., Cho, H., Mariotto, A., Eisner, M. P., Lewis, D. R., Chen, H. S., Feuer, E. J., Cronin, K. A. & Edwards, B. K. (2011). "SEER Cancer Statistics Review, 1975-2008." National Cancer Institute. Bethesda, MD.

Huyghe, E., Matsuda, T. & Thonneau, P. (2003). "Increasing incidence of testicular cancer worldwide: a review." J Urol 170(1): 5-11.

Huyghe, E., Muller, A., Mieusset, R., Bujan, L., Bachaud, J. M., Chevreau, C., Plante, P. & Thonneau, P. (2007). "Impact of diagnostic delay in testis cancer: results of a large population-based study." Eur Urol 52(6): 1710-1716.

Ikinger, U., Wurster, K., Terwey, B. & Mohring, K. (1982). "Microcalcifications in testicular malignancy: diagnostic tool in occult tumor?" Urology 19(5): 525-528.

Jacobsen, G. K., Henriksen, O. B. & von der Maase, H. (1981). "Carcinoma in situ of testicular tissue adjacent to malignant germ-cell tumors: a study of 105 cases." Cancer 47(11): 2660-2662.

Jacobsen, G. K. & Norgaard-Pedersen, B. (1984). "Placental alkaline phosphatase in testicular germ cell tumours and in carcinoma-in-situ of the testis. An immunohistochemical study." Acta Pathol Microbiol Immunol Scand A 92(5): 323-329.

Jones, T. D., MacLennan, G. T., Bonnin, J. M., Varsegi, M. F., Blair, J. E. & Cheng, L. (2006). "Screening for intratubular germ cell neoplasia of the testis using OCT4 immunohistochemistry." Am J Surg Pathol 30(11): 1427-1431.

Jones, T. D., Ulbright, T. M., Eble, J. N. & Cheng, L. (2004). "OCT4: A sensitive and specific biomarker for intratubular germ cell neoplasia of the testis." Clin Cancer Res 10(24): 8544-8547.

Jorgensen, N., Giwercman, A., Muller, J. & Skakkebaek, N. E. (1993). "Immunohistochemical markers of carcinoma in situ of the testis also expressed in normal infantile germ cells." Histopathology 22(4): 373-378.

Kleinschmidt, K., Dieckmann, K. P., Georgiew, A., Loy, V. & Weissbach, L. (2009). "Chemotherapy is of limited efficacy in the control of contralateral testicular intraepithelial neoplasia in patients with testicular germ cell cancer." Oncology 77(1): 33-39.

Kliesch, S., Thomaidis, T., Schutte, B., Puhse, G., Kater, B., Roth, S. & Bergmann, M. (2003). "Update on the diagnostic safety for detection of testicular intraepithelial neoplasia (TIN)." APMIS 111(1): 70-74; discussion 75.

Krabbe, S., Skakkebaek, N. E., Berthelsen, J. G., Eyben, F. V., Volsted, P., Mauritzen, K., Eldrup, J. & Nielsen, A. H. (1979). "High incidence of undetected neoplasia in maldescended testes." Lancet 1(8124): 999-1000.

Lacerda, H. M., Akre, O., Merletti, F. & Richiardi, L. (2009). "Time trends in the incidence of testicular cancer in childhood and young adulthood." Cancer Epidemiol Biomarkers Prev 18(7): 2042-2045.

Lauke, H. (1997). "Rapid method to detect CIS-cells." Adv Exp Med Biol 424: 69-70.

Lenz, S., Skakkebaek, N. E. & Hertel, N. T. (1996). "Abnormal ultrasonic pattern in contralateral testes in patients with unilateral testicular cancer." World J Urol 14 Suppl 1: S55-58.

Linke, J., Loy, V. & Dieckmann, K. P. (2005). "Prevalence of testicular intraepithelial neoplasia in healthy males." J Urol 173(5): 1577-1579.

Looijenga, L. H., Zafarana, G., Grygalewicz, B., Summersgill, B., Debiec-Rychter, M., Veltman, J., Schoenmakers, E. F., Rodriguez, S., Jafer, O., Clark, J., van Kessel, A. G., Shipley, J., van Gurp, R. J., Gillis, A. J. & Oosterhuis, J. W. (2003). "Role of gain of 12p in germ cell tumour development." APMIS 111(1): 161-171; discussion 172-163.

Loy, V., Wigand, I. & Dieckmann, K. P. (1990). "Incidence and distribution of carcinoma in situ in testes removed for germ cell tumour: possible inadequacy of random testicular biopsy in detecting the condition." Histopathology 16(2): 198-200.

Manivel, J. C., Jessurun, J., Wick, M. R. & Dehner, L. P. (1987). "Placental alkaline phosphatase immunoreactivity in testicular germ-cell neoplasms." Am J Surg Pathol 11(1): 21-29.

Manning, M., Junemann, K. P. & Alken, P. (1998). "Decrease in testosterone blood concentrations after testicular sperm extraction for intracytoplasmic sperm injection in azoospermic men." Lancet 352(9121): 37.

Mark, G. J. & Hedinger, C. (1965). "Changes in remaining tumor-free testicular tissue in cases of seminoma and teratoma." Virchows Arch Pathol Anat Physiol Klin Med 340(1): 84-92.

Moller, H. (1989). "Decreased testicular cancer risk in men born in wartime." J Natl Cancer Inst 81(21): 1668-1669.

Moller, H. (1993). "Clues to the aetiology of testicular germ cell tumours from descriptive epidemiology." Eur Urol 23(1): 8-13; discussion 14-15.

Mortensen, M. S., Gundgaard, M. G. & Daugaard, G. (2011). "Treatment options for carcinoma in situ testis." Int J Androl 34(4 Pt 2): e32-36.

Muller, J., Skakkebaek, N. E., Nielsen, O. H. & Graem, N. (1984). "Cryptorchidism and testis cancer. Atypical infantile germ cells followed by carcinoma in situ and invasive carcinoma in adulthood." Cancer 54(4): 629-634.

Myrup, C., Westergaard, T., Schnack, T., Oudin, A., Ritz, C., Wohlfahrt, J. & Melbye, M. (2008). "Testicular cancer risk in first- and second-generation immigrants to Denmark." J Natl Cancer Inst 100(1): 41-47.

Myrup, C., Wohlfahrt, J., Oudin, A., Schnack, T. & Melbye, M. (2010). "Risk of testicular cancer according to birthplace and birth cohort in Denmark." Int J Cancer 126(1): 217-223.

Olesen, I. A., Hoei-Hansen, C. E., Skakkebaek, N. E., Petersen, J. H., Rajpert-De Meyts, E. & Jorgensen, N. (2007). "Testicular carcinoma in situ in subfertile Danish men." Int J Androl 30(4): 406-411; discussion 412.

Pamenter, B., De Bono, J. S., Brown, I. L., Nandini, M., Kaye, S. B., Russell, J. M., Yates, A. J. & Kirk, D. (2003). "Bilateral testicular cancer: a preventable problem? Experience from a large cancer centre." BJU Int 92(1): 43-46.

Petersen, P. M., Giwercman, A., Daugaard, G., Rorth, M., Petersen, J. H., Skakkeaek, N. E., Hansen, S. W. & von der Maase, H. (2002). "Effect of graded testicular doses of radiotherapy in patients treated for carcinoma-in-situ in the testis." J Clin Oncol 20(6): 1537-1543.

Petersen, P. M., Giwercman, A., Hansen, S. W., Berthelsen, J. G., Daugaard, G., Rorth, M. & Skakkebaek, N. E. (1999). "Impaired testicular function in patients with carcinoma-in-situ of the testis." J Clin Oncol 17(1): 173-179.

Ploen, L. & Setchell, B. P. (1992). "Blood-testis barriers revisited. A homage to Lennart Nicander." Int J Androl 15(1): 1-4.

Prym, C. & Lauke, H. (1994). "Carcinoma-in situ of the human testis: tumour cells are distributed focally in the seminiferous tubules." Andrologia 26(4): 231-234.

Pryor, J. P., Cameron, K. M., Chilton, C. P., Ford, T. F., Parkinson, M. C., Sinokrot, J. & Westwood, C. A. (1983). "Carcinoma in situ in testicular biopsies from men presenting with infertility." Br J Urol 55(6): 780-784.

Rajpert-De Meyts, E. (2006). "Developmental model for the pathogenesis of testicular carcinoma in situ: genetic and environmental aspects." Hum Reprod Update 12(3): 303-323.

Rajpert-De Meyts, E. & Skakkebaek, N. E. (1994). "Expression of the c-kit protein product in carcinoma-in-situ and invasive testicular germ cell tumours." Int J Androl 17(2): 85-92.

Sanli, O., Kadioglu, A., Atar, M., Acar, O. & Nane, I. (2008). "Grading of classical testicular microlithiasis has no effect on the prevalence of associated testicular tumors." Urol Int 80(3): 310-316.

Sedlmayer, F., Holtl, W., Kozak, W., Hawliczek, R., Gebhart, F., Gerber, E., Joos, H., Albrecht, W., Pummer, K. & Kogelnik, H. D. (2001). "Radiotherapy of testicular intraepithelial neoplasia (TIN): a novel treatment regimen for a rare disease." Int J Radiat Oncol Biol Phys 50(4): 909-913.

Skakkebaek, N. E. (1972). "Possible carcinoma-in-situ of the testis." Lancet 2(7776): 516-517.

Skakkebaek, N. E. (1975). "Atypical germ cells in the adjacent "normal" tissue of testicular tumours." Acta Pathol Microbiol Scand A 83(1): 127-130.

Skakkebaek, N. E. (1978). "Carcinoma in situ of the testis: frequency and relationship to invasive germ cell tumours in infertile men." Histopathology 2(3): 157-170.

Skakkebaek, N. E. (1979). "Carcinoma-in-situ of testis in testicular feminization syndrome." Acta Pathol Microbiol Scand A 87(1): 87-89.

Skakkebaek, N. E., Berthelsen, J. G., Giwercman, A. & Muller, J. (1987). "Carcinoma-in-situ of the testis: possible origin from gonocytes and precursor of all types of germ cell tumours except spermatocytoma." Int J Androl 10(1): 19-28.

Slowikowska-Hilczer, J., Szarras-Czapnik, M. & Kula, K. (2001). "Testicular pathology in 46,XY dysgenetic male pseudohermaphroditism: an approach to pathogenesis of testis cancer." J Androl 22(5): 781-792.

Sonne, S. B., Almstrup, K., Dalgaard, M., Juncker, A. S., Edsgard, D., Ruban, L., Harrison, N. J., Schwager, C., Abdollahi, A., Huber, P. E., Brunak, S., Gjerdrum, L. M., Moore, H. D., Andrews, P. W., Skakkebaek, N. E., Rajpert-De Meyts, E. & Leffers, H. (2009). "Analysis of gene expression profiles of microdissected cell populations indicates that testicular carcinoma in situ is an arrested gonocyte." Cancer Res 69(12): 5241-5250.

Souchon, R., Gertenbach, U., Dieckmann, K. P., Hahn, E., Ruwe, M., Stambolis, C., Loy, V. & Classen, J. (2006). "Contralateral testicular cancer in spite of TIN-negative double biopsies and interval cisplatin chemotherapy." Strahlenther Onkol 182(5): 289-292.

Summersgill, B., Osin, P., Lu, Y. J., Huddart, R. & Shipley, J. (2001). "Chromosomal imbalances associated with carcinoma in situ and associated testicular germ cell tumours of adolescents and adults." Br J Cancer 85(2): 213-220.

Tan, I. B., Ang, K. K., Ching, B. C., Mohan, C., Toh, C. K. & Tan, M. H. (2010). "Testicular microlithiasis predicts concurrent testicular germ cell tumors and intratubular germ cell neoplasia of unclassified type in adults: a meta-analysis and systematic review." Cancer 116(19): 4520-4532.

van Casteren, N. J., de Jong, J., Stoop, H., Steyerberg, E. W., de Bekker-Grob, E. W., Dohle, G. R., Oosterhuis, J. W. & Looijenga, L. H. (2009). "Evaluation of testicular biopsies for carcinoma in situ: immunohistochemistry is mandatory." Int J Androl 32(6): 666-674.

von der Maase, H., Berthelsen, J. G., Jacobsen, G. K., Hald, T., Rorth, M., Christophersen, I. S., Sorensen, B. L., Walbom-Jorgensen, S. & Skakkebaek, N. E. (1985). "Carcinoma-in-situ of testis eradicated by chemotherapy." Lancet 1(8420): 98.

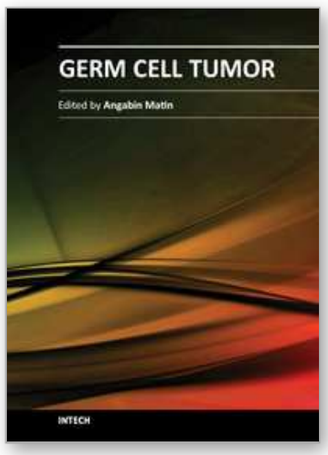
von der Maase, H., Meinecke, B. & Skakkebaek, N. E. (1988). "Residual carcinoma-in-situ of contralateral testis after chemotherapy." Lancet 1(8583): 477-478.

von der Maase, H., Rorth, M., Walbom-Jorgensen, S., Sorensen, B. L., Christophersen, I. S., Hald, T., Jacobsen, G. K., Berthelsen, J. G. & Skakkebaek, N. E. (1986). "Carcinoma in situ of contralateral testis in patients with testicular germ cell cancer: study of 27 cases in 500 patients." Br Med J (Clin Res Ed) 293(6559): 1398-1401.

von Eckardstein, S., Tsakmakidis, G., Kamischke, A., Rolf, C. & Nieschlag, E. (2001). "Sonographic testicular microlithiasis as an indicator of premalignant conditions in normal and infertile men." J Androl 22(5): 818-824.

Walsh, T. J., Croughan, M. S., Schembri, M., Chan, J. M. & Turek, P. J. (2009). "Increased risk of testicular germ cell cancer among infertile men." Arch Intern Med 169(4): 351-356.

Wood, H. M. & Elder, J. S. (2009). "Cryptorchidism and testicular cancer: separating fact from fiction." J Urol 181(2): 452-461.



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The book aims to provide an overview of current knowledge regarding germ cell tumors. It deals with the clinical presentations, treatment modalities, the biology and genetics of germ cell tumors in children and adults. Most chapters are focused on testicular germ cell tumors whose incidence has been increasing in young males. Included are reviews on the pathogenesis, risk factors, diagnosis and treatment regimens applied to precursor, pre-invasive lesions as well as to seminomatous and non-seminomatous germ cell tumors of the testes. In addition, a review is included on the diagnosis and current management options for intracranial germ cell tumors in children. Authors have also contributed articles on the genetics and epigenetics of germ cell tumor development in humans and in the mouse model system. This book will be of interest to scientists, physicians and lay readers wishing to review recent developments in the field of germ cell cancers.

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