Review Article

# Partial orchiectomy and testis intratubular germ cell neoplasia: World literature review

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## Abstract

Approximately 5% of all patients diagnosed with testicular cancer may have contralateral intratubular germ cell neoplasia (ITGCN) and may develop contralateral germ cell tumor. Here, we present a historical review and current literature regarding ITGCN and partial orchiectomy. The PubMed world literature search was performed for articles written in the English language. Search terms used were: Partial orchiectomy and ITGCN, with a return of 322 articles. Articles obtained were from the United States, Germany, Denmark and the Netherlands as well as a few case reports from Australia, France, Turkey and Spain. A critical review of the literature was performed. Partial orchiectomy is an option for the management of testicular malignancy in a select group of patients in whom radical orchiectomy is not desirable, including those with a solitary testicle, bilateral concurrent malignancies and a desire for paternity or being independent from androgen supplementation. Reports have demonstrated the feasibility of partial orchiectomy, but there are strict surgical criteria; tumor less than 2 cm in size, maintenance of cold ischemia, meticulous dissection to maintain testicular blood supply and biopsying of adjacent testicular parenchyma to ensure negative margins and absence of concurrent ITGCN. Partial orchiectomy is followed by testicular irradiation of 18-20 Gy; this radiation dose reduces fertility but maintains leydig cell function with androgen independence. Patients with a history of testicular carcinoma have a 5% chance of developing a metachronous contralateral tumor. Partial orchiectomy is a technically challenging procedure that requires close follow-up, but may represent a reasonable management option in selected patients.

**Key Words:** Intratubular germ cell neoplasia, partial orchiectomy, testicular carcinoma *in situ*

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## INTRODUCTION

According to the American Cancer Society statistics, in 2010, approximately 8480 new cases of testicular cancer will be diagnosed and close to 350 men will die of testicular cancer in the United States.[1] Historically, testicular cancer has been associated with either synchronous or metachronous testicular cancer in up to 5% of the cases.[2-5] Even higher rates of concomitant intratubular germ cell neoplasia (ITGCN) or testicular carcinoma *in situ* (CIS) have been reported. As treatments for retroperitoneal disease have dramatically changed the management landscape in these patients, more and more patients may be found with concerning lesions in their remaining testicle. Patients who undergo bilateral orchiectomies are faced with significant psychologic distress.[6] The increasing prevalence of "at risk" men represents a growing number of testicular cancer patients that may be candidates for testicular-preserving therapies.

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Partial orchiectomy aims to preserve some degree of testicular tissue in the setting of a localized testicular cancer. Testicular-preserving strategies have been advocated in particular instances, including the solitary testicle with malignancy in whom paternity or avoidance of exogenous androgen supplementation is desired, in concurrent bilateral testicular malignancies and in those concerned about cosmesis.[7-10] The first reported partial orchiectomy was performed by Richie in the US in 1984.[11] Since then, most of the world literature has been published by groups in Germany, the Netherlands and Denmark, with few case reports of success from Turkey, France and Australia.[12-14] As the incidence of testis cancer increases, a larger group of men may be confronted with this dilemma and may be candidates for testicular-preserving treatments. Here, we present a historical review and current literature regarding partial orchiectomy.

A PubMed (www.pubmed.gov) world literature search was performed for articles written in the English language. Search terms used were partial orchiectomy, with a return of 322 articles. Most of the world literature is from the US, Germany, Denmark and the Netherlands. There are a few case reports from Australia, France, Turkey and Spain. Articles from centers with large experience with CIS of testicle, infertility, bilateral germ cell neoplasia and partial orchiectomy were carefully reviewed.

## SURGICAL TECHNIQUE

Weissbach described the details of the inguinal approach for partial orchiectomy.[7] Through an inguinal incision approach, simulating the traditional open orchiectomy inguinal approach, the external oblique fascia is identified and incised with care taken to avoid the ilioinguinal nerve if possible. Next, the spermatic cord is isolated with a Penrose drain. The testicle within the tunica vaginalis is then separated from the scrotal skin by dividing the gubernaculum with care taken to avoid violation of the scrotal skin. Wound towels are placed around the skin incision to protect it from inadvertent tumor exposure, and then the testicle and cord are delivered into the operative field. Intraoperative Doppler and ultrasound can be helpful for planning the excision strategy in order to preserve the vessels and assist with tunical closure. Under cold ischemia, the tunica albuginea is incised and the tumor is isolated and excised. After tumor excision, biopsies of the resection bed are performed [Figure 1] because of the high incidence of surrounding ITGCN (80-90%). After assuring negative tumor margins, the tunica is closed with an absorbable suture and the testicle delivered back to the scrotum.[7,8] Partial orchiectomy can be a challenging surgical procedure with needed pre- and intraoperative planning to avoid testis vasculature, maintaining cold ischemia and coordinated efforts to biopsy-surrounding areas for ITGCN.[7]

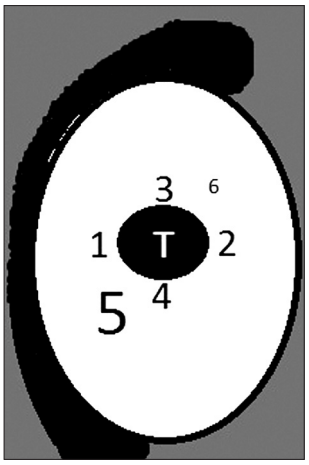


**Figure 1:** Biopsying scheme after tumor enucleation (T = tumor, numbers represent tri-planar biopsies)

## OUTCOMES

Weissbach and colleagues reported success in their initial series of 10 of 14 patients treated with partial orchiectomy and local radiotherapy.[7] This was followed by the Heidenreich and colleagues series, with no reported local recurrences in 72 of 73 patients after a mean-follow up 91 months.[8-10]

## INTRATESTICULAR GERM CELL NEOPLASIA OR CARCINOMA *IN SITU*

Also known as ITGCN or testicular intraepithelial neoplasia (TIN), it is the precursor of testicular germ cell tumors (GCTs), except for spermatocytic seminomas in elderly men, yolk sac tumors and mature teratomas in infants. ITGCN is non-invasive because the neoplastic cells are confined within the seminiferous tubules. This entity was first described by Skakkebaek in 1972 who, after noticing abnormal spermatogonia pathologic changes on testicular biopsies in two patients who were referred for infertility work-up, was initially unable to characterize these findings but eventually one of the two patients developed embryonal carcinoma in that testicle, the other patient underwent prophylactic orchiectomy with final pathology showing persistent ITGCN.[15] ITGCN is a precursor for GCTs and consists of large, intratubular, gonocyte-like cells with large nuclei and abundant glycogen, having a "fried egg" appearance. ITGCN diagnosis can be further confirmed with placental alkaline phosphatase (PlAP) staining of the testicular biopsy tissue.[2] ITGCN is abundant in tissue surrounding a primary GCT up to 82% of cases after the Heidenreich and colleagues specimen review in their 73 patients' series.[10]

The incidence of ITGCN varies from 1 to 5% in the reviewed literature.[2,16] Numerous factors have been associated with an increased incidence of ITGCN; cryptorchidism (2-4%),[17,18] infertility (2.2%),[3,18] ambiguous genitalia (25%), contralateral

testis in patients with history of testicular cancer (5%) and <1% in the general population, which is similar to the life-time risk of developing testicular carcinoma.[2,3,5] The estimated risk of ITGCN progressing to invasive growth is 40, 50 and 70%, with 3, 5 and 7 years, respectively,[19] and the overall progression is 50%.[20]

## RADIOTHERAPY FOR INTRATUBULAR GERM CELL NEOPLASIA

Radiotherapy for testicular ITGCN was first described in 1986 by Von der Maase and colleagues.[21] After partial orchiectomy, the testicle is typically treated with a 20 Gy dose if one of the adjacent six quadrant biopsies demonstrates ITGCN unless the patient desires paternity.[7,8] A lower radiation dose can compromise oncologic control and, therefore, most studies have advocated 18-20 Gy, which sustains androgen but not sperm production,[21-23] with few case reports of radiation therapy failure in the literature.[24,25]

## CONTRALATERAL INTRAEPITHELIAL GERM CELL NEOPLASIA

The Dieckmann and colleagues review of 1954 patients with a unilateral GCT who underwent a contralateral testicular biopsy concurrently showed a prevalence of 4.9%, with testicular atrophy having a 4.3-fold increased risk of having contralateral ITGCN.[26] Patients with ITGCN were significantly younger, and only three patients with negative ITGCN on biopsying went on to develop frank carcinoma. Because of similar incidence rates, their data suggest that ITGCN can be a precursor for testicular carcinoma.

## TESTICULAR BIOPSYING

Contralateral testicular biopsying is performed in Europe, with data showing a concomitant contralateral ITGCN rate of 4-6%,[2] a false-negative biopsying rate close to 0.5% and a decrease in the needed follow-up length from 25 years to 5 years after negative biopsying.[27] Von der Maase and colleagues estimated the risk of developing invasive growth after ITGCN to be 40% within 3 years and 50% within 5 years.[19] None of their biopsied 473 patients without ITGCN developed contralateral testicular cancer after 12-96 months follow-up and no serious complications arose from their biopsies.[19]

Biopsying the contralateral testicle to look for ITGCN is not practiced in the US. Herr and colleagues[28] did not recommend routine biopsying because of the low incidence of contralateral ITGCN and the emotional distress on a patient with a positive finding.[20] Another argument against routine biopsying is the markedly improved survival since the introduction of platinum-based chemotherapy.[29] Their consensus in the literature on biopsying high-risk patients; prior infertility, cryptorchidism and atrophic testicle-sentence is unclear.[20] The European germ cell cancer consensus group (EGCCCG) has outlined specific characteristics of high-risk patients who might be considered for contralateral testis biopsy; testicular volume <12 ml, history of cryptorchidism or age <30 years.[30-31] This approach allows intervention, generally with radiation, before an invasive tumor is evident thus sparing the testis.[31]

## BILATERAL TESTICULAR CANCER

The reviewed literature shows that most bilateral testicular GCTs are seminomas and occur metachronously on an average after 4 years.[32,33] In the Klatte and colleagues review,[32] bilateral tumors are of similar histologies in more than 50% of the cases, and 74% were seminomas. More important is the observation that having a history of testicular GCT increases the risk of having a contralateral tumor by 26-fold.

The Memorial Sloan-Kettering Cancer Center (MSKCC) reported an overall incidence of bilateral testicular cancer of 1.5% in a review of patients spanning 50 years and a decrease in the incidence of contralateral cancer with time. This is consistent with the hypothesis that treatment with cisplatin chemotherapy decreased the risk of developing a contralateral testicular tumor.[33] Similar findings in the Sonneveld and colleagues review[16] showed that the overall prevalence of bilateral testicular cancer in stage I patients was 3.6%, and has slightly decreased over the past three decades, attributed to intensive follow-up, improvement of radiodiagnostic techniques, serum tumor markers and patient education, which have resulted in earlier lower-stage diagnosis of contralateral tumors and hence improved prognosis.

## CHEMOTHERAPY

Whether cisplatin-based chemotherapy may eradicate testicular ITGCN is a matter of debate in the reviewed literature. Kleinschmidt and colleagues recently investigated the eradication of ITGCN after receiving carboplatin or a combination of platinum, etoposide and bleomycin (PEB).[34] Overall, seven of 11 patients failed either of these chemotherapeutic regimens after undergoing biopsying at a mean of 8.8 months post-treatment. Reasons that may keep platinum-based chemotherapies from completely eradicating ITGCN include the blood-testes barrier and the possibility that ITGCN is resistant to chemotherapies, with increasing success for the treatment of initial testicular carcinoma and all reports recommending close follow-up for contralateral tumor occurrence.[33]

On the other hand, some reports have attributed the decreased incidence of contralateral testicular tumors to platinum-based chemotherapy.[29,33] Van Basten and colleagues, in their review of testicular cancer in Dutch men, noted that a three-times lower

incidence rate of a contralateral testicular tumor was found in the chemotherapy subgroup compared with those on surveillance.[35] Fossa and colleagues[29] in their review of the surveillance, epidemiology and end results database (SEER) showed a decreased incidence of contralateral testicular cancer that they hypothesized could be related to platinum-based chemotherapy.

## CONCLUSIONS

Partial orchiectomy for testicular carcinoma is more commonly practiced in Europe than in the US. It is suitable for patients with a solitary testicle who seek paternity and for those who seek independence from androgen supplementation. For the patient to be a candidate for partial orchiectomy, the recommended tumor size is less than 2 cm, tumor location needs to be far from the testicular vasculature and the protocol described by Weissbach includes six biopsies of tumor surroundings to rule out residual ITGCN. Because of the high concurrence of ITGCN (80-90%), those patients will be referred for radiotherapy, and the recommended dose is 18-20 Gy. Because of the excellent response of testicular GCTs to platinum-based chemotherapy, patients' will continue to live longer and will need to be routinely followed-up with physical examination and/or imaging of the contralateral testicle.

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