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

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Abstract

Objectives: Searching for testicular intraepithelial neoplasia (TIN; carcinoma in situ) in the contralateral testis of patients with germ cell tumour (GCT) may early disclose contralateral GCT. A single biopsy of the testis is thought to accurately detect TIN. Reports on false-negative biopsies have challenged this view. We investigated whether systematic two-site biopsies are more sensitive than single biopsies. We also studied the prevalence of contralateral TIN in a large patient sample.

Methods: A total of 2318 patients with testicular GCT underwent contralateral double biopsy. All of the biopsy pairs were examined histologically for spermatogenesis and for presence of TIN. Statistical analysis involved first, overall prevalence of contralateral TIN; second, associations of clinical factors with TIN; third, frequency of discordant findings regarding TIN among biopsy pairs; and finally, associations of discordance with clinical factors.

Results: A total of 119 patients (5.13%; 95% confidence interval [CI], 4.27–6.11) had contralateral TIN. TIN is associated with poor spermatogenesis (relative risk [RR] 15.74; 95%CI, 10.38–23.86) and with testicular atrophy (RR 3.78). According to TIN, 31.1% of biopsy pairs were discordant. Discordance was significantly less frequent in atrophic testes and in patients with poor spermatogenesis.

Conclusions: We confirmed the prevalence of contralateral TIN to be about 5%. TIN is significantly associated with poor spermatogenesis and with testicular atrophy. The diagnostic extra yield imparted by double biopsies is 18%. Discordant results regarding TIN are predominantly encountered in normal-sized testicles. The new standard in diagnosing TIN is two-site biopsy.
1. **Introduction**

Testicular germ cell tumours (GCTs) in the adult are preceded by a noninvasive lesion called testicular intraepithelial neoplasia (TIN) or carcinoma in situ [1,2]. This precursor can be detected immunohisto-logically in testicular tissue [3]. Searching for TIN by testicular biopsy may facilitate early detection of GCT. This method appears feasible because TIN is believed to be dispersed within the testicle, and a single random biopsy of the testis is thought to be accurate [4].

Consensus groups considered searching for TIN useful in select patients with testicular GCT to look for contralateral cancer [5–9]. However, the clinical significance of testicular biopsies has remained controversial [10]. The prevalence of contralateral TIN is around 5% in central and northern Europe [11]. This figure is well compatible with the frequency of bilateral tumours [12]. However, the database on contralateral TIN is substantiated by only two studies involving >1000 patients [11,13]. The usefulness of biopsies has further been challenged by the experi-ence of GCT arising in testicles despite a previous biopsy negative for TIN [12,14]. The calculated biopsy failure rate is around 0.5% [15]. Missing the diagnosis had been attributed to a nonrandom distribution of TIN within the testicle, and this finding is clearly in conflict with the original theory of TIN being a dispersed lesion. Accordingly, topographic mapping studies in testicular parenchyma had demonstrated that TIN was arranged focally rather than in a random fashion [16,17]. It was thus rational to attempt improving the sensitivity of testicular biopsy by multiple sampling. We used the principle of double biopsies. There were two end points to our investigation: first, to corroborate the overall knowledge of contralateral TIN by studying its prevalence in a large patient sample, and second, to explore the frequency of discordant findings according to TIN among biopsy pairs and to see if discordant results were associated with clinical parameters.

2. **Patients and methods**

A total of 2318 patients with histologically proven testicular GCT (Table 1) were enrolled in a prospective study conducted in 114 hospitals in Germany and Austria from May 2000 through July 2003 (see the Appendix A). The trial was approved by an ethical committee. All patients had signed informed consent. All of the patients underwent contralateral two-site biopsy. Operative technique involved standard open surgery with excision of a specimen from the cranial and caudal pole of the testis, respectively [18]. Specimens were fixed in Steive solution and sent for central histologic review (V.L.). Histologic work-up consisted of standard microscopy (hematoxylin and eosin staining) and immunohistology after staining of placental alkaline phosphatase as reported previously (Fig. 1) [9,11,17]. Morphologically, the presence of TIN was assessed in each specimen of the biopsy pairs. Discordant results were noted when TIN was detected in only one specimen. Spermatogenesis was rated according to a modified Johnsen score as detailed previously [15]. This score ranged from score 10 (normal spermatogenesis) to score 1 (Sertoli cells only). To facilitate statistical evaluation, the score was condensed to three categories, with score points 1–3, 4–7, and 8–10 representing poor, moderate, and good spermatogenesis, respectively. The following parameters were registered: histology (seminoma or non-seminoma), age, clinical stage (Lugano classification), laterality of GCT, history of undes-cended testis (UDT), history of infertility, and testicular atrophy (side of biopsy) as assessed by the surgeon.

The first end point was the overall prevalence of contralateral TIN. Statistical analysis involved descriptive tabulation of proportions with calculating 95% confidence intervals (CIs). To look for significant associations of TIN with clinical factors univariate analysis was done by calculating odds ratios with corresponding Blyth Still Casella CIs [19] and by using the \( \chi^2 \) test or the Fisher exact test (for small patient samples). Then, multivariate analysis was accomplished using classification and regression tree (CART) analysis [20]. This is a nonparametric tree modeling technique for analysing high-dimensional interactions and for detecting homogenous subgroups in a data set (SC software, Mole Software, Belfast, Northern Ireland). Bipartition of the entire sample is generated by selecting the

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**Table 1 – Patient characteristics**

<table>
<thead>
<tr>
<th>Total no.</th>
<th>2318</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>35 yr</td>
</tr>
<tr>
<td>Age range</td>
<td>16–70 yr</td>
</tr>
<tr>
<td>Mean age</td>
<td>35.8 yr (SD ± 9.3 yr)</td>
</tr>
<tr>
<td>Pure seminoma</td>
<td>n = 1360</td>
</tr>
<tr>
<td>Non-seminoma</td>
<td>n = 958</td>
</tr>
</tbody>
</table>

SD = standard deviation.

**Fig. 1 – Testicular biopsy specimen, immunohistologic examination. Staining of placental alkaline phosphatase. Note: Testicular intraepithelial neoplasia cells with uptake of red stain. These cells are arranged along the basement membrane. Original ×300.**
minimal \( p \) value of the associated exact permutation test for all bipartitions considered. The subsets of patients are then further partitioned. The results are displayed as a regression tree. This analysis represents an explorative tool for detecting systematic structures in a data set. In addition, multivariate logistic regression analysis was performed to validate results of CART analysis. Multivariate analysis was performed in two different versions: first, by omitting the spermatogenesis score (model 1) and second by including the score (model 2). This dual approach appeared meaningful from both a clinical and a biologic viewpoint, respectively. Clinically, information regarding spermatogenesis is available only as a result of the biopsy and thus the score is rather useful in preoperative decision-making. Biologically, however, associations of TIN with spermatogenesis need to be explored for a better understanding of TIN, and so the score is indispensable for our analysis.

The second end point was the frequency of discordant biopsy pairs regarding TIN. Statistical analysis involved descriptive tabulation of proportions with 95%CI. Association of discordance with clinical factors was assessed in an identical manner as done for the prevalence of TIN. Statistical examination involved univariate analysis and multivariate CART analysis as well as logistic regression analysis.

3. Results

3.1. Prevalence of contralateral TIN

Contralateral TIN was present in 119 patients (5.13%; 95%CI, 4.27–6.11). Significant associations of TIN with clinical factors as found by univariate statistical analysis are shown in Table 2. No associations were found with clinical stage (\( p = 0.153 \)), histology of GCT (\( p = 0.876 \)), and laterality (\( p = 0.441 \)).

Multivariate CART analysis (model 1) demonstrated testicular atrophy and patient age below 40 yr to be independently associated with contralateral TIN (Fig. 2). Risk of having TIN was highest (18%) in men younger than 40 yr who had testicular atrophy at the same time. Testicular atrophy is the strongest indicator for the presence of TIN. However, about two thirds of the patients with TIN were lacking this factor. Multivariate logistic regression analysis confirmed testicular atrophy was significantly associated with TIN involving a relative risk (RR) of 3.78 (95%CI, 2.55–5.60). Age older than 40 yr confers a significantly reduced risk of 0.30 (95%CI, 0.17–0.54) in this model.

If spermatogenesis score is included into analysis (model 2), then poor spermatogenesis is the strongest indicator (\( p < 0.001 \)) for the presence of TIN (Fig. 3). Associations with testicular atrophy and age are only present in second-line subgroups. Surprisingly, clinical stage and histology of GCT represent significant risk indicators in third-line and fourth-line subgroups. Using logistic regression analysis, “poor spermatogenesis score” confers a risk of 15.74 (95%CI, 10.38–23.86) of having TIN. Testicular atrophy and age above 40 yr represent significant

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>TIN positive</th>
<th>( p )</th>
<th>OR, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>578</td>
<td>40 (6.92%)</td>
<td>( p &lt; 0.001 )</td>
<td>1.0</td>
</tr>
<tr>
<td>30 to &lt;35</td>
<td>481</td>
<td>30 (6.24%)</td>
<td>0.90 (0.57–1.41)</td>
<td>0.86 (0.55–1.34)</td>
</tr>
<tr>
<td>35 to &lt;40</td>
<td>556</td>
<td>33 (5.94%)</td>
<td>0.86 (0.55–1.34)</td>
<td>0.42 (0.24–0.74)</td>
</tr>
<tr>
<td>40 to &lt;50</td>
<td>520</td>
<td>15 (2.88%)</td>
<td>0.42 (0.24–0.74)</td>
<td>0.08 (0.003–0.41)</td>
</tr>
<tr>
<td>≥50</td>
<td>183</td>
<td>1 (0.55%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UDT (non–tumour-bearing testis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2259</td>
<td>111 (4.91%)</td>
<td>( p = 0.003 )</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>59</td>
<td>8 (13.56%)</td>
<td>2.76 (1.40–5.14)</td>
<td></td>
</tr>
<tr>
<td>UDT (any side)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2187</td>
<td>107 (4.89%)</td>
<td>( p = 0.032 )</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>131</td>
<td>12 (9.16%)</td>
<td>1.87 (1.06–3.24)</td>
<td></td>
</tr>
<tr>
<td>Infertility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2294</td>
<td>113 (4.93%)</td>
<td>( p &lt; 0.001 )</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
<td>6 (25.0%)</td>
<td>5.08 (2.39–9.42)</td>
<td></td>
</tr>
<tr>
<td>Testicular atrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2038</td>
<td>78 (3.83%)</td>
<td>( p &lt; 0.001 )</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>280</td>
<td>41 (14.64%)</td>
<td>3.83 (2.67–5.44)</td>
<td></td>
</tr>
<tr>
<td>Spermatogenesis score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>2075</td>
<td>61 (2.94%)</td>
<td>( p &lt; 0.001 )</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>114</td>
<td>5 (4.39%)</td>
<td>1.49 (0.62–3.48)</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>129</td>
<td>53 (41.1%)</td>
<td>13.98 (10.08–19.17)</td>
<td></td>
</tr>
</tbody>
</table>

The \( p \) value was determined according to the \( \chi^2 \) test or Fisher exact test (in small sub-samples).

TIN = testicular intraepithelial neoplasia; OR = odds ratio; CI = confidence interval; UDT = undescended testis.
indicators, too, with odds ratios (ORs) of 1.80 (95%CI, 1.16–2.79), and 0.30 (95%CI 0.17–0.54), respectively.

### 3.2. Discordant results among biopsy pairs

Discordant results among biopsy pairs were found in 31.1% of the patients positive for TIN (Table 3). By univariate analysis, discordance is inversely associated with testicular atrophy and poor spermatogenesis score (Table 4). No associations were found with age (\(p = 0.602\)), clinical stage (\(p = 0.525\)), histology (\(p = 0.307\)), laterality (\(p = 0.536\)), UDT (\(p = 0.752\)), and infertility (\(p = 0.37\)). In multivariate CART analysis, only testicular atrophy proved to be inversely associated with discordant findings when the spermatogenesis score was excluded. Multivariate logistic regression analysis demonstrated that the odds of discordant findings was only 0.25 (95%CI, 0.09–0.71) in atrophic testicles when compared to normal testes (\(p = 0.0093\)). If spermatogenesis score is included in CART analysis, then “good spermatogenesis” is significantly associated with discordant findings (\(p = 0.0022\)). In this model, atrophy, too, is significantly inversely associated

![Fig. 2](image-url) - Association of contralateral testicular intraepithelial neoplasia with clinical factors (spermatogenesis score not included). Multivariate classification and regression tree analysis.

![Fig. 3](image-url) - Association of clinical and histologic parameters with contralateral testicular intraepithelial neoplasia (spermatogenesis score included). Multivariate classification and regression tree analysis. SG = spermatogenesis; CS = clinical stage.
with discordance but this applies to the subgroup of patients with “good score,” only (Fig. 4). Logistic regression analysis reveals that patients with “moderate” or “poor” spermatogenesis score involve a significantly decreased risk of discordant results with an OR of 0.33 (95%CI, 0.16–0.71). Likewise, testicular atrophy “protects” against discordant results (OR 0.30; 95%CI, 0.10–0.87).

4. Discussion

4.1. Prevalence of TIN

The prevalence of contralateral TIN of 5.13% as found in this study does agree with previous investigations [3,21]. Some smaller studies found higher rates, but their wide CIs broadly overlap with the confidence limits of our study [22,23]. Although statistically, there is no significant difference among the reports regarding contralateral TIN, variation might yet be generated biologically. Young age is significantly associated with contralateral TIN [11,24]. So, younger age in the recent Danish study (median 33.6 yr vs. 35 yr in our study) may partly account for the higher prevalence of TIN (8.7%) observed in that study. Another determinant is probably the higher overall incidence of GCT in Denmark when compared to Germany.

Bilateral testicular tumours develop in 3%–4% of the cases in northern Europe [12,25].

Table 3 – Discordance rate according to TIN among double biopsies

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>% (of total population)</th>
<th>% (of TIN-positive patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concordant</td>
<td>82</td>
<td>3.54% (95%CI, 2.68–4.56%)</td>
<td>68.9% (95%CI, 59.2–76.5%)</td>
</tr>
<tr>
<td>Discordant</td>
<td>37</td>
<td>1.60% (95%CI, 1.04–2.31%)</td>
<td>31.1% (95%CI, 23.2–39.9%)</td>
</tr>
</tbody>
</table>

TIN = testicular intraepithelial neoplasia.

Table 4 – Association of clinical and histologic factors with discordant results according to TIN among 119 biopsy pairs by univariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Discordant results</th>
<th>p</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular atrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>78</td>
<td>30 (38%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>41</td>
<td>7 (17%)</td>
<td>0.44 (0.18–0.88)</td>
</tr>
<tr>
<td>Spermatogenesis score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>61</td>
<td>27 (44%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>0 (0%)</td>
<td>0.0 (0.0–1.23)</td>
</tr>
<tr>
<td>Poor</td>
<td>53</td>
<td>10 (19%)</td>
<td>0.43 (0.21–0.77)</td>
</tr>
</tbody>
</table>

TIN = testicular intraepithelial neoplasia; RR = relative risk; CI = confidence interval.

Fig. 4 – Discordance rate of biopsy pairs in regard to testicular intraepithelial neoplasia. Association with histologic and clinical factors. Multivariate classification and regression tree analysis. SG = spermatogenesis.
consistent with the prevalence of 5.1% of contralateral TIN. The slightly higher figure of contralateral TIN when compared to bilateral tumours (5.1% vs. 3%-4%) mainly results from different investigation methodologies. Bilateral tumours are assessed retrospectively; thus, second tumours may escape detection because of long latency intervals, the patient's death, or treatment-related eradication of precursors. Conversely, contralateral TIN is considered to be present in all cases since puberty and it is assessed prospectively without loss of any case.

4.2. Clinical factors associated with contralateral TIN

Poor spermatogenesis involves a 15-fold elevated risk of having TIN. Age below 40 yr is a second-line indicator. Testicular atrophy is another second-line indicator only in cases with good or moderate spermatogenesis. Surprisingly, clinical stage and histology (non-seminoma) are further subordinate risk factors for TIN in the subgroups of young patients with poor spermatogenesis. The hierarchal structure of risk indicators is novel information to date and this constitutes a notable refinement of knowledge about the biology of TIN. Poor spermatogenesis was found in alliance with TIN already in 1978 [26] and this relationship has repeatedly been confirmed [1,24,27]. The very strong association of TIN with poor spermatogenesis found in the present study is in line with the hypothesis that both TIN and testicular cancer are features of the "testicular dysgenesis syndrome" [28]. Nonetheless, at present it is not clear whether poor spermatogenesis constitutes the soil for TIN or vice versa if sperm production is rendered deficient as a result of spreading TIN. The fact that half of the TIN cases in this study (61 of 119) were found in conjunction with normal spermatogenesis lends support to the assumption that poor spermatogenesis is the sequel of TIN.

From a clinical viewpoint, histologic information on spermatogenesis is available postoperatively only. Thus, in attempting to offer contralateral biopsy exclusively to particular high-risk patients the clinician is dependent on surrogate parameters for poor spermatogenesis. Testicular atrophy and poor spermatogenesis are closely interrelated. Accordingly, atrophy is the strongest predictor of TIN involving a 3.7-fold increased risk of TIN when compared to normal-sized testes. Age below 40 yr is the only significant second-line predictor of TIN. The highest risk of having TIN (18%) is encountered in patients with testicular atrophy being younger than 40 yr. But those with testicular atrophy being older than 40 yr and those without atrophy but who are younger than 40 yr are still bearing risks of 7.0% and 4.8%, respectively. Only patients without atrophy being older than 40 yr have low risk (1.6%). In tailoring contralateral biopsy to patients at particular risk it appears feasible to withhold biopsies in this latter subgroup. Of note, scrotal sonography may also uncover testicles at risk for malignancy. However, due to methodologic concerns this factor had not been addressed in the present multicentric study. Interestingly, we found age below the threshold of 40 yr to be associated with TIN, whereas previous studies had defined a limit of 30 yr [11,24]. TIN prevalence is highest in patients younger than 30 yr (6.9%), and there is a continuous decline with increasing age (Table 2). Even in the age category of 35–40 yr the prevalence of TIN is as high as 5.9%. So, the ceiling age for searching for TIN is probably 40 rather than 30 yr.

4.3. Discordant biopsies

Thirty-one percent of the patients with contralateral TIN had discordant results among the biopsy pairs. This key finding is clearly conflicting with the theory of TIN being dispersed throughout the testis [4]. However, this result is in accord with TIN-mapping studies that reported a focal rather than random distribution of TIN in testicular tissue adjacent to GCTs [16,17,29]. Consequently, false-negative results had been found in 0.5% of biopsies [15]. This figure roughly implies that 10% of the TIN-positive patients will be overlooked. It was thus rational to attempt improving diagnostics of TIN by increasing the number of biopsies, which is a principle that had borne fruit in prostatic cancer. Multiple sampling was first explored in a histopathologic workbench study of testes removed for TIN. Four-site biopsies had concordant findings in only one of five cases [27]. In a clinical pilot study contralateral three-site biopsies were performed in 295 patients with GCT [30]. Overall the prevalence of TIN was 8.1% (95%CI, 5.2%–11.8%). Six of the 24 patients (25%; 95%CI, 9.77%–46.71%) with TIN had discordant findings among the biopsy sets. The conclusion was that multiple sampling is more sensitive than single biopsy. The present nationwide investigation does fully endorse that approach. The discordance rate reported by Kliesch et al. is somewhat lower than that found in our study (25% vs. 31%). Although this difference is not significant statistically there might exist a biologic clue to account for the variation. In the Kliesch study the biopsies had been performed through a single incision of the tunica albuginea. Thus, two regions of the testis lying in close vicinity to each other had been probed. In our study, two
independent incisions lying about 2 cm apart had been performed, thus exploring two topographically different parts of the testis. Clearly, given the nonrandom distribution of TIN, the rate of discordance is expected to increase with growing distance between the biopsy sites. In all, discordance among biopsy sets is considerable. The extra yield afforded by double biopsies is around 18% as follows from the calculation: This study comprised 119 cases with contralateral TIN. If current diagnostic standard (i.e., single biopsy) had been applied, then all of the 82 patients with concordant findings would have been correctly diagnosed. Of the 37 patients with discordant results, certainly half of them (n = 18) would have been uncovered by single biopsy leaving 18 cases undetected. In total, by current standard 100 patients would have been identified. Eighteen remain undiagnosed; all can be detected with the new method. Thus, the extra yield of two-site versus one-site biopsy, respectively, is 18% (18 cases in excess to 100 cases diagnosed by current standard). Two-site biopsies should be the new standard in searching for TIN.

4.4. Association of discordant biopsy results with clinicopathologic factors

Discordant results regarding TIN are significantly more frequent among patients with good spermatogenesis than among those with poor spermatogenesis. Also, dissimilar findings are more likely among normal-sized than in small testicles. In the subgroup of patients with normal-sized testes and normal spermatogenesis, the discordance rate is as high as 53%. This is novel information, and there are probably two reasons for this finding, one statistical and one biologic. Basically, the accuracy of statistical analysis depends on sample size. Applying this rule to testicular biopsies, it is evident that a standard biopsy of 3 mm size taken from a small (atrophic) testis represents a much larger sample than does a biopsy taken from a normal-sized testis. Consequently, sampling error will be lower in small testes, and accordingly, discordant findings are less frequent. Secondly, TIN cells populating a seminiferous tubule usually force out spermatogenic cells. Further, if there is widespread TIN within the testis, then spermatogenic arrest will prevail in large areas resulting in tubular shrinkage and testicular size decrease. Thus, it becomes probable that in atrophic (small) testes two-site biopsies will usually yield identical results because typically in these testicles there is widespread TIN with consequentially impaired spermatogenesis. If there is TIN in a normal-sized testis, then it is usually present in localised areas only and spermatogenesis has not yet deteriorated secondary to spreading TIN. In this setting double biopsies may easily disclose discordant results regarding TIN. Practically speaking, the diagnostic benefit of double biopsies over single biopsies is significant in normal-sized testicles, but it is minor in atrophic gonads. So, small testicles might still be explored by single biopsy. All other testicles should be subjected to the new standard of two-site biopsies.

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A study of the German Testicular Cancer Study Group (GTCSG), project no. AH/07/00/xx.

Appendix A

List of participating institutions (ranked by number of cases contributed)

1. Vivantes-Klinikum Am Urban, Berlin
2. Albertinen-Krankenhaus, Hamburg
3. Zeisigwaldkliniken Bethanien, Chemnitz
4. Klinikum Barmen, Wuppertal
5. Zentralkrankenhaus St. Jürgen-Str., Bremen
6. Krankenhaus Friedrichshain, Berlin
7. Evangelisches und Johanniter Klinikum, Oberhausen
8. Hannover Krankenhäuser
9. Klinikum der Stadt Villingen-Schwenningen
10. Evangelisches Jung-Stilling-Krankenhaus, Siegen
11. Charité Universitätsklinikum, Berlin
12. Universitätsklinikum Essen
13. Evangelisches Johannes-Krankenhaus, Bielefeld
14. St.-Elisabeth-Krankenhaus, Köln
15. Paracelsus Klinik Golzheim, Düsseldorf
16. Julius-Maximilian-Universität, Würzburg
17. St.-Agnes-Hospital, Bocholt
18. Evangelisches Krankenhaus Göttingen-Weende
19. Carl-Thiem-Klinikum, Cottbus
20. Städtisches Klinikum Solingen
21. Städtisches Klinikum Braunschweig
22. Evangelisches Krankenhaus Bad Godesberg, Bonn
23. Klinikum Minden
24. Kreiskrankenhaus Riesa
25. Städtisches Krankenhaus Sindelfingen
26. Städtisches Krankenhaus Martha-Maria, Halle/Saale
27. Vogtland Klinikum Plauen
28. Kreiskrankenhaus Reutlingen
29. St.-Hildegarids-Krankenhaus, Köln-Lindenthal
30. St.-Josefs-Hospital Uerdingen, Krefeld
31. Krankenhaus der Anhaltischen Diakonissenanstalt, Dessau
32. St.-Marien-Krankenhaus Ahaus
33. Borromäus-Hospital, Leer
34. Johanniter-Krankenhaus Stendal
35. Elisabeth-Krankenhaus Rheydt, Mönchengladbach
36. Klinikum der Friedrich-Schiller-Universität, Jena
37. Kreiskrankenhaus Freiberg
38. Georg-August-Universität Göttingen
39. Klinikum Deggendorf
40. Bundesknappschaftskrankenhaus, Würselen
41. Städtisches Krankenhaus Salzgitter
42. Virngrund-Klinik Ellwangen
43. Augusta-Kranken-Anstalt, Bochum
44. Allgemeines Krankenhaus Viersen
45. Elbe-Klinikum Stade
46. Klinikum der Philipps-Universität, Marburg
47. Wartburg-Klinikum Eisenach
48. St.-Franziskus-Hospital Lohne
49. Universitäts-Krankenhaus Hamburg-Eppendorf
50. Dr. med. Telle, Wolfsburg
51. Marienhospital Herne
52. Dr.-Horst-Schmidt-Kliniken, Wiesbaden
53. Städtisches Klinikum Wolfburg
54. St.-Bonifatius-Hospital Lingen
55. Marienhospital Gelsenkirchen
56. Westpfalz-Klinikum, Kaiserslautern
57. Marienhospital Altenessen, Essen
58. Diakonissenkrankenhaus Dresden
59. Allgemeines Krankenhaus Hagen
60. Reinhard-Nieter-Krankenhaus, Wilhelmshaven
61. Marien-Krankenhaus Bergisch-Gladbach
62. Klinikum Hoyerswerda
63. Klinikum Hof
64. Klinikum Coburg
65. Ruppiner Kliniken, Neuruppin
66. Paracelsusklinik, Osnabrück
67. Universitätsklinikum Benjamin-Franklin, Berlin
68. Klinikum Osnabrück
69. Albert-Schweitzer-Krankenhaus, Northeim
70. Universitätsklinik Innsbruck, Austria
71. Humaine-Klinikum Bad Saarow, Bad Saarow-Pieskow
72. St.-Josefs-Hospital Lennestadt
73. Theresienkrankenhaus Mannheim
74. Landeskrankenhaus Leoben, Austria
75. Humboldt-Krankenhaus Berlin
76. Herz-Jesu-Krankenhaus, Münster-Hiltrup
77. St.-Barbara-Klinik Hamm
78. Klinikum Wetzlar-Braunfels
79. Dr. med. Brüggeboes, Baden-Baden
80. EN-Süd-Klinikum Schwelm
81. Knappschafts-Krankenhaus Dortmund
82. Krankenhaus-Seypark, Langen-Destriedt
83. St.-Elisabethen-Krankenhaus, Katharina-Kasper-Kliniken, Frankfurt/Main
84. Nephrologisches Zentrum Niedersachsen, Hannoversch Münden
85. St.-Vinzenz-Krankenhaus Datteln
86. Kliniken des Main-Taunus-Kreises, Bad Sooden
87. Urologische Klinik am Leberberg, Wiesbaden
88. Kreiskrankenhaus Bad Hersfeld
89. Kreiskrankenhaus Hameln
90. St.-Barbara-Hospital Gladbeck
91. Bundeswehr-Zentralkrankenhaus Koblenz
92. St.-Petri-Hospital Warburg
93. Allgemeines Krankenhaus Celle
94. Wald-Klinikum Gera
95. Krankenhaus Hetzelstift, Neustadt/Wien/Austria
96. Klinikum Ernst-von-Bergmann, Potsdam
97. Evangelisches Krankenhaus Luckau
98. Marienkrankenhaus Hamburg
99. Sädtkrankenhaus Rüsselsheim
100. Stadtkrankenhaus Worms
101. Franziskus-Krankenhaus Berlin
102. Klinikum Memmingen
103. Städtisches Klinikum Kemperhof, Koblenz
104. Klinikum Essen-Mitte
105. Klinikum Hannover-Siloah, Hannover
106. Vivantes-Klinikum Neukölln, Berlin
107. Diakonissenkrankenhaus Stuttgart
108. St.-Elisabeth-Krankenhaus Zweibrücken
109. Allgemeines Krankenhaus Linz, Austria
110. Städtisches Klinikum Görlitz
111. Kliniken Sigmaringen
112. Dr. med. Friedrich, Püttlingen
113. Evangelisches Krankenhaus Ruhr, Witten
114. Dres. med. Beckerling/Rembrink, Gelsenkirchen

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Editorial Comment
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The German Testicular Cancer Study Group are to be congratulated on yet another comprehensive and well designed prospective study of this disease. This trial of 2318 patients provides new insights regarding the presence of Testicular Intraepithelial Neoplasia (TIN) in men with testicular germ cell tumours, but how will this new information help to inform clinical practice in this area of urological oncology?

The issue of contra-lateral testicular biopsy to diagnose TIN at the time of orchidectomy in men with testicular germ cell tumour is a controversial
one. In the European Consensus paper on the treatment of germ cell cancer [1], in relation to TIN, there is a clear recommendation that “contra-lateral (testicular) biopsy should be discussed with the patient, in particular those at high risk”. This is an uncontentious statement, particularly given the reported risk of TIN in young men with testicular atrophy, history of maldescent and familial tendency, [2,3], data which is supported by this report. The study by Dieckmann et al. confirms that the incidence of TIN in men with testicular atrophy and age <40 is 18% and that the diagnosis can be made reliably in men with testicular atrophy using a single biopsy. Although this incident figure is lower than the 34% rate of TIN reported previously in high risk cases [2–4] it illustrates the importance of focussing on the high risk group. The chance of developing a second malignancy in the presence of TIN in has been reported to be as high as 70% at seven years [5] and despite careful follow-up, most second tumours are not diagnosed early enough: a high proportion have metastatic disease at second presentation [6] and up to 50% of patients will require aggressive therapy with cytotoxic drugs or radiation [7]. TIN is a condition which, when detected, needs treatment. The data in this study by Dieckman et al. confirms that this group of men clearly should have a contra-lateral testicular biopsy at the time of their primary orchidectomy and that sampling is required only from a single site when there is testicular atrophy. Individuals found to have TIN should then receive treatment in an expert centre.

The second statement in relation to TIN, by the European Consensus group, that “contra-lateral biopsy should be performed, preferably at the time of orchiectomy” in all patients, is rather more contentious. This is an area of clinical controversy [8] and the practice has not been adopted widely by urologists [9]. Does the information provided by the German Testis cancer group help in this controversy? The information provided does confirm that in the normal testis there is a significant discrepancy in the correlation of biopsies from different sites, confirming previous reports [10,7] that TIN in the testis at risk has a heterogenous distribution and that there is a significant false negative rate from a single biopsy. A second biopsy in another area of the testis will increase the diagnostic yield by 18% and for clinicians who see this issue as important, consideration should be given to taking two samples rather than one to minimise the false negative rate. However, the question remains as to whether this procedure should be carried out routinely in all men who have normal sized contra-lateral testes with no risk factors. The reported literature shows that in terms of testicular loss, second biopsy is a low risk procedure [11,12], although the information available in the literature to date is insufficiently detailed to show accurately what the true complication rate of this procedure is in terms of post operative haematoma, infection and testicular pain. Furthermore, there is the added issue of cost in some health care systems. It is also important to consider the fact that large numbers of men would undergo a biopsy for no individual benefit and that the small number of men who would actually develop second malignancy in this group (<1% of the total), can be treated effectively in the event that they develop a second cancer. Armed with this knowledge, many clinicians have taken the view that patient counselling and observation is better than universal intervention in this situation. But for those clinicians who are still unsure as to how to proceed, the information regarding sperm count provided in this study may help. In patients with a low sperm count the data shows that there was a 16 fold increase in the risk of associated TIN in the contra-lateral testis in men undergoing orchidectomy for testis cancer. Unfortunately, the data do not show how many of these men had normal sized testes and what the relative risk was in this particular sub-group. Notwithstanding, it might be reasonable to carry out an urgent sperm count before going ahead with a radical orchidectomy in men with testis cancer. After all, this might help to facilitate a risk stratified approach to contra-lateral biopsy of the palpably normal testis, continuing the risk stratified approach pioneered by clinician researchers over many years in this condition.

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