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Risk Factors and Treatment Outcomes of 1,375 Patients with Testicular Leydig Cell Tumors: Analysis of Published Case Series Data

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Abstract: AIMS Leydig cell tumors (LCTs) are rare but the most common non-germ cell testicular tumors. Only limited evidence exists for reliably differentiating between benign and malignant LCTs and for optimally managing the different types and stages of this rare disease. This review aims to synthesize the available evidence regarding the clinical presentation and clinicopathological characteristics associated with LCT malignancy and management. **METHODS** We analyzed published case series with LCTs patients. The association between clinicopathological variables and the presence of metastatic disease was assessed using regression analyses. **RESULTS** We included 357 reports, reviewing available data from 1,375 patients (median age: 34y). Testis-sparing surgery (TSS) was performed in 463 patients. Local recurrence after TSS occurred in 8 of 121 (7%) patients with available follow-up information. Metastases were found in 101 patients and were most often located in the retroperitoneal lymph nodes (60%), lungs (38%), and/or liver (29%). The multivariable models with or without multiple imputation predicting metastatic disease included older age, larger tumor size, the presence of any adverse factor (larger tumor diameter, necrosis, angiolymphatic invasion, pleomorphism, high mitotic index, atypia), and any protective factor (Reinke crystals, lipofuscin pigments, gynecomastia) with model AUCs of 0.93. Durable remission after resection of metastases or platinum-based chemotherapy was rarely seen. **CONCLUSION** Our risk tables using clinicopathological parameters can help identify patients harboring malignant tumors. These patients should undergo staging and either be followed or receive further treatment. In metastatic disease surgical and systemic treatment might result in disease control in some patients.

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Risk factors and Treatment Outcomes of 1,375 Patients with Testicular Leydig Cell Tumors: Analysis of Published Case Series Data

Running head: Analysis of published case series data of patients with testicular Leydig cell tumors

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27 **Aims:** Leydig cell tumors (LCTs) are rare but the most common non-germ cell testicular tumors. Only
28 limited evidence exists for reliably differentiating between benign and malignant LCTs and for opti-
29 mally managing the different types and stages of this rare disease. This review aims to synthesize the
30 available evidence regarding the clinical presentation and clinicopathological characteristics associated
31 with LCT malignancy and management.

32 **Methods:** We analyzed published case series with LCTs patients. The association between clinico-
33 pathological variables and the presence of metastatic disease was assessed using regression analyses.

34 **Results:** We included 357 reports, reviewing available data from 1,375 patients (median age: 34y).
35 Testis-sparing surgery (TSS) was performed in 463 patients. Local recurrence after TSS occurred in 8
36 of 121 (7%) patients with available follow-up information. Metastases were found in 101 patients and
37 were most often located in the retroperitoneal lymph nodes (60%), lungs (38%), and/or liver (29%).
38 The multivariable models with or without multiple imputation predicting metastatic disease included
39 older age, larger tumor size, the presence of any adverse factor (larger tumor diameter, necrosis, angio-
40 lymphatic invasion, pleomorphism, high mitotic index, atypia), and any protective factor (Reinke crys-
41 tals, lipofuscin pigments, gynecomastia) with model AUCs of 0.93. Durable remission after resection
42 of metastases or platinum-based chemotherapy was rarely seen.

43 **Conclusion:** Our risk tables using clinicopathological parameters can help identify patients harboring
44 malignant tumors. These patients should undergo staging and either be followed or receive further treat-
45 ment. In metastatic disease surgical and systemic treatment might result in disease control in in some
46 patients.

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Introduction

50 Leydig cell tumors (LCTs) are rare but are the most common non-germ cell testicular
51 tumors. LCTs usually present with a painless testicular mass and/or endocrine activity leading
52 to gynecomastia or infertility¹. As the majority of LCTs are benign, most patients are cured by
53 local excision alone. The identification of an LCT with malignant potential is important for
54 detecting malignant disease at an early stage because metastatic disease is often rapidly pro-
55 gressive and usually associated with an unfavorable prognosis.

56 Given that LCTs are extremely rare, there are several unanswered questions regarding
57 the optimal management of patients with localized and metastatic disease. The aim of this study
58 was to synthesize the available information from LCT patients, including the clinical presenta-
59 tion, the clinicopathological factors associated with metastatic disease, the treatment options
60 for benign and malignant LCTs, and the outcomes of patients with metastatic spread.

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Methods

Search Methods and Study Selection

A literature search up to September 17, 2015, was conducted using the electronic databases MEDLINE, EMBASE, Scopus, the Cochrane Database of Systematic Reviews, and Web of Science as described in supplementary file 1.

Statistical analysis

Univariable logistic regression analyses were performed to identify variables potentially associated with metastatic disease. For continuous variables, receiver operating curve (ROC) analyses were performed to identify the optimal cut-off points of metastatic disease risk factors (Supplementary file 1). Due to a significant shortfall in recording of pathological variables (Supplementary Figure 1), we created two consolidated variables. One consolidated variable was defined by the presence of any of the identified adverse pathological risk factors. A second variable was defined by the presence of any protective pathological factor. We performed a first multivariable regression analysis with the consolidated variables for pathological risk factors using the original dataset without multiple imputations; the second analysis was performed after multiple imputations using chained random forests (Supplementary file 1). The multivariable models were used to calculate prediction intervals for the presence or absence of metastatic disease at initial diagnosis or during follow-up. All statistical tests were two-sided. All p-values <0.05 were considered statistically significant and all analyses are considered exploratory and hypothesis generating.

Results

Studies

After deduplication, 3,274 publications met the initial search criteria, of which 796 publications were eligible for full-text review after the title and abstract had been screened. After full-text screening of 534 manuscripts, 357 studies remained, with available data from 1,355

patients (Figure 1). We also included 20 patients from our own institution, giving a total cohort of 1,375 patients of which individual patient data was available for 488 patients (Supplementary Table 1) with a median age 34 years (IQR 26–42) (Table 1).

Clinical presentation

Clinical signs and symptoms were reported in 1,056 patients: these included testicular enlargement (22%), gynecomastia (23%), infertility (17%), scrotal pain (7%), and precocious puberty (7%). Palpable tumors were reported in 298 patients (26%). Twenty-three percent were diagnosed incidentally during testicular ultrasonography performed for the evaluation of other conditions (e.g., infertility assessment). Serum tumor markers of germ cell cancers including alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH) were elevated in 1%, 2%, and 3% patients, respectively. The included 76 children and young adults <18 years mostly presented with precocious puberty (62%) and/or testicular enlargement (46%).

Local treatment and recurrences

The type of local treatment was mentioned in 1,342 of 1,375 patients (97%). Radical orchiectomy was performed in 879 (65%) patients, while 463 (35%) underwent TSS. Nine of the latter (2%) went on to have a completion orchiectomy due to positive surgical margins at the first operation. Follow-up information on local recurrences after TSS was available in 121/463 patients (26%). Eight recurrences (7%) were observed after a median of 17.5 months (range 4–34 months). Five of these patients underwent further TSS, one patient had a radical orchiectomy and, for two patients, the exact local recurrence treatment was not described. One of those eight patients developed liver metastases after 107 months of follow-up, was treated with Mitotane, and showed stable disease during treatment². Contralateral LCTs were diagnosed in a total of 17 patients (3%) after a median of 27 months (range 1–168 months).

Adjuvant therapies

Adjuvant retroperitoneal lymphnode dissection (RPLND) was performed in 15 patients, of which 12 patients with negative lymph nodes (LN) remained disease-free after a median of 95 months (Supplementary Table 2). In three cases, the histopathologic examination of the removed LN revealed micro metastatic disease. All of those three patients with micro metastatic disease additionally received chemotherapy: One patient remained disease-free at 164 months after treatment with Vincristine, Actinomycin, Cyclophosphamide, and Adriblastin (VACAD), whereas two patients showed progressive disease despite Cisplatin, Vinblastine, and Bleomycin (PVB), and passed away after 51 and 31 months, respectively.

Metastatic spread and primary landing zone

Any metastatic disease at any time point was reported in 101/1040 (10%) patients, of whom 28 were described with only one metastatic disease site. In 6/101 the exact timing of metastatic disease in relation to diagnosis was not described whereas in 95/101 metastatic spread at initial diagnosis or at disease recurrence during follow-up could be explored. At initial staging, metastases were present in 30/95 patients, including the retroperitoneal LN (n=19), lung (n=15), liver (n=5), mediastinal LN (n=4), kidney (n=4), and brain (n=3) (Figure 2). A total of 65 patients developed metastases during follow-up (retroperitoneal LN (n=35), liver (n=24), lung (n=23), bones (n=10), and inguinal LN (n=8). Metastases during follow-up were diagnosed after a median of 24 months (range 1–204 months). Of note, 82% of all metastases were diagnosed during the first 5 years. To determine the primary LCT landing zone, we analyzed the subgroup of the 28 patients with a single metastatic site. Retroperitoneal LN represented the most common primary landing zone, including 17 patients (61%). Other locations of single metastases were the visceral organs in 5 patients (18%), lungs in 4 patients (14%), and bones and inguinal LN each in 1 patient (4%).

Risk factors for metastatic disease

Univariable analyses identified a significant association between metastatic disease and the following clinicopathological variables: age, tumor size, presence of necrosis, angiolymphatic invasion, pleomorphism, high mitotic index, atypias, Reinke crystals, lipofuscin pigment, and gynecomastia (Table 2). To discriminate between patients with localized and metastatic diseases, ROC analyses revealed ideal cut-off points for the age of 42 years and for a tumor diameter of 30mm.

Both multivariable models with or without multiple imputation predicting metastatic disease included tumor size, the presence of any adverse factor (larger tumor diameter, necrosis, angiolymphatic invasion, pleomorphism, high mitotic index, atypia), and any protective factor (Reinke crystals, lipofuscin pigments, gynecomastia). This combination analysis resulted in AUCs of 0.93 for both models. Age was an independent predictor of metastatic disease only in the multivariable analysis using the imputed data set. All remaining variables were independent predictors of metastatic disease in both models (Table 3). All potential combinations of the four variables (largest tumor diameter, age, presence of any adverse factor and any protective factor) and the associated risk for metastatic disease are shown in Figure 3 for the imputed and in Supplementary Figure 2 for the original data set.

Treatment of metastatic disease and outcome

Due to the lack of therapy guidelines, many different treatment modalities have been described in the literature. Data regarding chemotherapy was available for 48 patients. The response to chemotherapy was usually poor (Supplementary Table 3). Only 3/48 (6%) patients experienced a complete response after either Bleomycin, Etoposide, Cisplatin (BEP) or PVB, but follow-up data was not provided. A partial response was described in 15/48 (31%) patients, including 5 who received Mitotane and 10 who received platinum-based chemotherapy.

Surgery was performed in 40 patients, of whom 6 showed a complete response: unfortunately, follow-up data was not provided (Supplementary Table 4). The most commonly performed procedure was RPLND (n=28). Information regarding clear template boundaries or completeness of resection of those 28 patients was not described in most reports.

Data regarding radiotherapy was available for 16 patients (Supplementary Table 5). The effect of radiotherapy on Leydig cell tumor metastases was reported as limited, with only one published case report describing a partial response when used to treat supraclavicular metastases² and only two reports documented pain relief after palliative radiotherapy^{2, 3}. One other case report described a favorable outcome after spinal decompression surgery and adjuvant radiotherapy⁴.

Discussion

Our analysis of published case series represents the most comprehensive summary of the available literature regarding testicular LCTs. The local recurrence rate of 7% supports the use of TSS in men with LCTs but only after appropriate counselling of the patients about the risk of recurrence and the requirement for a subsequent completion orchiectomy in case of histological risk factors. If TSS is to be used, regular testicular ultrasound should be considered for at least 3 years after surgery. To differentiate between benign and malignant LCTs, pathological workup should provide information about the presence of risk factors or protective factors for metastatic disease. We identified a range of these and have created a risk table based on our multivariable models to predict the presence of metastasis. Due to significant missingness of individual prognostic/pathological factors in our dataset, we refrained from applying multiple imputations for each risk factor but decided, in the univariable analyses, to create consolidated variables of variables that were significantly associated with metastatic disease. Given this limitation, our model should be used with caution. However, in the absence of a

clear definition of LCT malignancy, we hope that our risk table provides a clinically useful tool based on the best currently available evidence and we believe that this should replace the previously used definition from 1985, which was based on only 14 benign and 5 malignant cases⁵.

Figure 3 supports clinicians in decision-making e.g., whether further imaging or adjuvant therapy should be considered. Risk assessment can be helpful in several clinical scenarios: (1) In patients with a low risk for metastatic disease (lower age, smaller tumors, absence of pathological risk factors), staging and follow-up with imaging could be omitted, and patients after TSS may only undergo ultrasound surveillance of the testis. (2) In patients with high risk for metastatic disease (older age, larger tumors, presence of pathological risk factors), one should consider staging and regular follow-up for at least 5 years with cross-sectional imaging of the chest, abdomen, and pelvis.

The available data does not support the regular use of adjuvant therapy for localized disease even with a high risk for metastatic disease. The fact that in two-thirds of the cases, the primary metastatic LCT landing site was the retroperitoneum adjuvant RPLND might have the potential to cure some patients with micro-metastatic disease as recently suggested⁶. However, as our data does not provide evidence that LCTs have a discreet step wise progression involving a specific primary landing site not clear recommendation regarding adjuvant RPLND can be given. Furthermore, chemotherapy and radiotherapy has not been shown to have curative potential in patients with metastatic LCTs. Thus, we believe that neither adjuvant chemotherapy nor radiotherapy can be recommended in patients with localized LCTs.

Patients with metastatic disease have poor prognoses, and standard treatment recommendations do not exist. Surgical resection of metastases and/or chemotherapy with BEP or PVB should be discussed with the patient, as some patients were reported to have complete remission after RPLND and/or chemotherapy. Mitotane and radiotherapy represent palliative treatment options only.

Strength and limitations

LCTs are rare, and the published literature consists only of retrospective studies, so this meta-analysis is prone to bias. Moreover, clinicopathological risk factors were often not completely reported. Thus, we had to use consolidated variables and/or imputations for multivariable analyses with obvious limitations. Our search criteria were designed and reviewed both by clinicians and librarians and were predefined in a peer-reviewed protocol. However, it is possible that not all potentially relevant studies were identified due to undetected imprecision of our search strategy, which would have to be classified as another potential source of bias. Give the rarity of LCT and lack of coded individual risk factors in large cancer registries more conclusive answers can't be expected as shown in a recent analyses of the SEER database producing only 76 LCTs ⁷. Moreover, the chosen cut-offs represent statistically derived cut-offs, which may not represent the clinically most useful cut-offs. However, in absence of efficacy data and decision analyses comparing surveillance versus adjuvant therapies we had to apply the used methodology. Due to the absence of available retrospective or ongoing prospective trials and to evaluate our model, we recently opened the OrphAn Testis Histologies (OATH) Registry and encourage collaborators to contribute data of patients with rare testis cancer histologies (<http://bit.ly/OATH-registry>). Although we agree that our current recommendations are based on a very limited level of evidence the current comprehensive analysis of the published LCTs is unique and might support clinicians and patients in clinical decision making.

Conclusion

This analysis defines clinicopathological variables associated with malignancy and suggests management options in patients with testicular LCT. The presented methodology is applicable in any rare cancer and may increase the knowledge in rare diseases.

235 **Declarations**

236 **Ethics approval and consent to participate**

237 This analysis of published case series does not require a formal ethics approval.

238 **Consent for publication**

239 All authors consented to this publication.

240 **Availability of data and material**

241 The datasets used and/or analyzed during the current study are available from the correspond-
242 ing author on reasonable request.

243 **Competing interests**

244 The authors have nothing to disclose.

245 **Funding**

246 None

247 **Authors' contributions**

248 Conception and design: CDF, NWC, JB, TH

249 Data acquisition: JBG, CDF, PKB

250 Data analysis and interpretation: SH, MSW, KPD, TS

251

252 Drafting the manuscript: CDF, JBG, SH, JB, TH, PKB

253 Critical revision of the manuscript for scientific and factual content: MSW, KPD, TS, NWC

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255 Statistical analysis CDF, JBG, SH, MSW

256 Supervision NWC, PKB, JB, KPD, TS, TH

CDF and JG selected abstracts, extracted data and created figures. CDF and JG drafted the search strategy. CDF, SH, MSW performed the statistical analysis and CDF, JB and TH drafted the first manuscript draft. PKB provided histopathology support. NWC, JB, KPD, TS reviewed the manuscript. All authors read and approved the final manuscript.

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none

Figure legends

Figure 1 Flow chart of the study selection process

Figure 2 Anatomical locations of metastases in 101 patients of which the exact timing of metastatic disease in relation to diagnosis was described in 95/101 patients. Whereas 30/95 patients had metastatic disease at initial staging, 65/95 patients developed metastatic disease during follow-up.

Figure 3 Point estimates and 95% Confidence interval probabilities for metastatic disease according to different clinical scenarios within the imputed data set. Adverse factor is defined by the presence of any of the following variables: larger tumor diameter, necrosis, angiolymphatic invasion, pleomorphism, high mitotic index, atypia). Protective factors is defined by presence of any of the following variables: Reinke crystals, lipofuscin pigments, gynecomastia.

Table legends

Table 1 Patient characteristics of cases with individual patient data

Table 2 Univariable logistic regression analysis identifying clinicopathological predictors of metastatic disease

Table 3 Multivariable regression analyses of clinicopathological variables predicting metastatic disease

Supplementary material legends

Supplementary Table 1 Summary of included reports

Supplementary Table 2 Patients with adjuvant retroperitoneal lymph node dissection

Supplementary Table 3 Chemotherapy regimens and response in patients with metastatic Leydig cell tumors

Supplementary Table 4 Surgical resection for metastatic Leydig cell tumors

Supplementary Table 5 Patients with metastatic Leydig cell tumors treated with radiotherapy

Supplementary Figure 1 Bar chart diagram describing the completeness of variable reporting

Supplementary Figure 2 Point estimates and 95% Confidence interval probabilities for metastatic disease according to different clinical scenarios within the original dataset. Adverse factor is defined by the presence of any of the following variables: larger tumor diameter, necrosis, angiolymphatic invasion, pleomorphism, high mitotic index, atypia). Protective factors is defined by presence of any of the following variables: Reinke crystals, lipofuscin pigments, gynecomastia.

Supplementary File 1 Supplementary methods

Supplementary File 2 Detailed search strategy

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