Review Article

The prognostic value of testicular microlithiasis as an incidental finding for the risk of testicular malignancy in children and the adult population: A systematic review. On behalf of the EAU pediatric urology guidelines panel

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Summary

Introduction
The exact correlation of testicular microlithiasis (TM) with benign and malignant conditions remains unknown, especially in the paediatric population. The potential association of TM with testicular malignancy in adulthood has led to controversy regarding management and follow-up.

Objective
To determine the prognostic importance of TM in children in correlation to the risk of testicular malignancy or infertility and compare the differences between the paediatric and adult population.

Study design
We performed a literature review of the Medline, Embase and Cochrane controlled trials databases until November 2020 according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) Statement. Twenty-six publications were included in the analysis.

Results
During the follow-up of 595 children with TM only one patient with TM developed a testicular malignancy during puberty. In the other 594 no testicular malignancy was found, even in the presence of risk factors. In the adult population, an increased risk for testicular malignancy in the presence of TM was found in patients with history of cryptorchidism (6% vs 0%), testicular malignancy (22% vs 2%) or sub/infertility (11–23% vs 1.7%) compared to TM-free. The difference between paediatric and adult population might be explained by the short duration of follow-up, varying between six months and three years. With an average age at inclusion of 10 years and testicular malignancies are expected to develop from puberty on, testicular malignancies might not yet have developed.

Conclusion
TM is a common incidental finding that does not seem to be associated with testicular malignancy during childhood, but in the presence of risk factors is associated with testicular malignancy in the adult population. Routine monthly self-examination of the testes is recommended in children with contributing risk factors from puberty onwards. When TM is still present during transition to adulthood a more intensive follow-up could be considered.

Introduction
The clinical significance of testicular microlithiasis (TM) remains unclear, thus posing a strategic problem for clinicians. Despite an increased incidence due to improved sensitivity and availability of ultrasound equipment, the natural history of TM is unknown. TM is defined as hyperechogenic foci in the testicular parenchyma, in different degrees of presence and diffusely spread throughout the testes, often found bilaterally [1]. The echogenic shadow typically seen in renal lithiasis or calcifications is lacking in TM.

The size of TM found on ultrasound is generally 1–2 mm and has been associated with generalized testicular dysgenesis. When TM is associated with a testicular tumour it is...
mostly seen around or within the tumour [2–6]. TM associated with a testicular tumour on testicular biopsy is usually smaller in size, 25–75um [2,3]. Also, TM demonstrated on ultrasound is not always found in the biopsy specimen [2,6]. The discrepancy between radiological and histological TM makes the interpretation for future implications difficult.

Although the EAU/ESPU guidelines do not recommend routine ultrasound for undescended or non-palpable testis, there are various reasons why ultrasound of the testis is performed in children. TM is therefore often found as an incidental finding without any accompanying risk factors. TM can also be found in the presence of testicular pathology, such as a testicular tumor or undescended testes. This difference in presentation might be of significance when considering clinical consequences.

In the adult population, a routine ultrasound of the testes is indicated for infertility and suspicion of a testicular mass. In adults, testicular TM has been associated with a significantly increased risk for testicular malignancy compared to men in whom TM was absent (risk ratio of 8.5, 95%CI 4.5–16.1) [7]. In addition, the presence of TM is associated with impaired sperm parameters compared to adult men without TM [8]. However, no direct causative association between TM and malignancy or fertility has ever been found. The incidence of TM might be increased in benign conditions such as Klinefelter’s Syndrome, cryptorchidism, hypospadias and post trauma [1]. The question that arises therefore is; is there a higher incidence of TM in these patient groups, or is it because they undergo more frequent imaging studies? The exact correlation of TM with both benign and malignant conditions remains unknown, especially in the paediatric population. The potential association of TM with testicular malignancy and infertility in adulthood has led to controversy regarding management and follow-up. It is not clear if data on adults can simply be extrapolated to children and adolescents.

The first aim of this systematic review (SR) is to determine the prognostic importance of the diagnosis of TM in children and correlate this finding with the risk of testicular malignancy or infertility. Subsequently we compare the differences between the paediatric and adult population. This comparison is based on a literature review of the SRs and meta-analyses available in adults on the correlation between TM and testicular malignancy as well as infertility. Finally, we aim to provide a guideline for clinicians on the interpretation of the incidental finding of the diagnosis of TM and its clinical consequences in children.

Evidence acquisition

This systematic review was performed according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) Statement [9]. The a priori protocol is available at the PROSPERO database (CRD42020150898). The systematic review was structured into two sections: a systematic review about TM in the paediatric population and a literature search about TM in the adult population. The eligibility criteria and potential confounders (associated pathology such as cryptorchidism and testicular tumours) were identified by the European Association of Urology (EAU) Paediatric Urology guidelines panel.

Search strategy

For the first section we performed a literature search in the Medline, Embase and Cochrane controlled trials databases and clinicaltrial.gov for all relevant publications (no limitation for publication time and only English language) from 1946 until November 28, 2020. The patient group of interest were children under the age of 18 years who underwent a scrotal ultrasound for any indication and where TM was found in at least a proportion of the study population. Inclusion criteria included reporting of testicular tumours or infertility. Follow-up with any duration was included, but when no follow-up ultrasound was performed studies were excluded. Observational, interventional and prognostic studies were eligible for inclusion.

In the second part, we focussed on the available systematic reviews and meta-analyses about TM in the adult population. Again, a literature search was performed in the Medline, Embase and Cochrane controlled trials databases and clinicaltrial.gov for all relevant publications (no limitation for publication time and only English language) from 1946 until November 28, 2020. The patient group of interest were adults who underwent an ultrasound for any indication and where TM was found in at least part of the study population. The outcome of interest for the study was testicular malignancy or infertility. Systematic reviews and meta-analyses were eligible for inclusion.

For both sections two review authors have independently screened the titles and abstracts of identified records for eligibility. The full-text of all potentially eligible records were retrieved and screened independently by two review authors using a standardised form, linking together multiple records of the same study in the process. Any disagreements were resolved by discussion or by consulting a third review author.

Two review authors participated in the data extraction process. Study characteristics were extracted by one review author and a second review author checked data extractions for accuracy. Any disagreements have been resolved by discussion or by consulting a third review author.

Type of outcome measures

The primary outcome of the study was the prognostic value of TM (found on ultrasound) for testicular malignancy after 15 years of diagnosis. The secondary outcomes of interest were the prognostic value of TM for testicular malignancy after any follow-up, prognostic value of TM for infertility after any follow-up duration and presence of concurrent pathology, such as Down syndrome and McCune Albright Syndrome.

Risk of bias assessment

A risk of bias assessment was performed only for the included studies for the paediatric population. The risk of bias of each included study was assessed by two review authors working independently. Any disagreements were resolved by discussion or by consulting a third review author. Risk of bias was assessed by using the QUIPS tool as
recommended by the Cochrane Prognosis Methods Group [10]. This includes the assessment of risk of bias across six domains informed by corresponding prompting items: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding (associated pathology) and statistical analysis reporting. All domains consist of several criteria of which the combined rating produces a classification of high, moderate, or low risk. The overall risk of bias was considered low if \( \leq 2 \) domains were rated a moderate risk of bias and all others were rated a low risk of bias. The overall risk of bias was considered moderate if \( > 2 \) domains were rated a moderate risk of bias and all others were rated a low risk of bias. The overall risk of bias was considered high if \( \geq 1 \) domain was rated a high risk of bias, irrespective of all other domains. The risk of bias assessment for the studies for the adult population was already performed within the included systematic reviews and meta-analyses.

Data analysis

Because of the lack of high quality evidence, we were unable to perform a meta-analysis of the data to assess the association between TM and testicular malignancy. We constructed a narrative synthesis to assess the extracted data for the paediatric population. A narrative synthesis was also constructed for the adult population. The differences in results between the two populations are summarized in text and tabulations.

Evidence synthesis

Quantity of evidence identified

The PRISMA flow diagram demonstrates the study selection process (Fig. 1). For the paediatric population a total of 210 titles and abstracts were identified and 61 publications were retrieved for full-text screening. We found 15 studies eligible for inclusion with a total of 595 children for follow-up [11–25] and 4 studies for associated pathology [26–29].

For the adult population a total of 38 titles and abstracts were identified and 11 publications were retrieved for full-screening. We found 7 systematic reviews eligible for inclusion, which included a total of 168 studies [30–35].
Risk of bias for the included paediatric studies

Fig. 2 demonstrates the risk of bias for the paediatric studies which also includes the confounder associated pathology. An overall high risk of bias was found for all studies.

Characteristics of the included paediatric studies

The baseline characteristics of the included paediatric follow-up studies are summarized in Table 1. All of the included studies were observational studies, two prospective studies [11,12] and 13 retrospective studies [13–25]. The most reported mean age was an average of 10 years and the most reported duration of follow-up was an average of 36 months, see Table 1.

The definition for the diagnosis of TM varied between the studies. The most commonly used classifications were: Classic TM with $\geq 5$ microliths in 1 US image and Limited TM $< 5$ microliths in 1 image; Diffuse and Focal distribution; either bilateral or unilateral. TM was mostly found bilaterally and diffuse or classic distribution patterns were more common than limited or focal patterns.

Patients presented with different underlying pathology, including undescended testis, varicocele, inguinal hernias, scrotal pain or trauma, testicular masses or atrophy, Klinefelter Syndrome, Peutz-Jeghers Syndrome, McCune Albright Syndrome, Down Syndrome or no associated pathology.

Outcomes of the included studies

Paediatric population

The outcomes of the paediatric studies are presented in Table 2.

**Prognostic value of the diagnosis of TM for testicular malignancy and the correlation or risk of testicular malignancy.** Our primary outcome of interest was if the diagnosis of TM would be associated with testicular malignancy, post-pubertal, at 15 years follow-up, however, none of the studies had a follow-up exceeding 11 years.

Of the fifteen included studies with a total of 595 patients with TM only one study reported the development of 1 testicular malignancy during follow-up. This patient, aged 17 years, was diagnosed with a seminoma after 5 years of follow-up of bilateral TM. No other associated risk factors were reported in this patient.

From these 15 studies with 595 patients, only 20 testes demonstrated an increased TM pattern and 33 testes a decreased pattern or resolution of TM.

The presence of a concomitant testicular tumour and TM was reported in four studies [11,15,19,20]. This included seven germ cell tumours in boys all older than 13 years. In the five pre-adolescent boys only benign or premalignant tumours were reported, of these four had associated risk factors, i.e. cryptorchidism and Peutz-Jeghers Syndrome.

Four studies reported the evaluation of tumour markers [11,17,18,21] and four studies reported testicular biopsy results [11,15,17,21]. No abnormal outcomes were reported in association with the diagnosis of TM.

**Prognostic value of TM for infertility in children.** No studies were found looking specifically to the relationship between the diagnosis of TM in pre-pubertal boys and risk of infertility in adulthood.

**TM and associated pathology in children.** We found three studies reporting on the diagnosis of TM in association with Down Syndrome [26–28]. In children with Down Syndrome the prevalence of TM ranged from 22.8 to 36% vs 0–7% in children without Down Syndrome. During the follow-up one patient with Down Syndrome presented with a Leydig cell tumour, he also had concomitant cryptorchidism.
| Study (year), recruitment period | N of patients | Age (yr), mean ± SD, median (range) | Inclusion criteria | Exclusion criteria | Associated pathology | Definition used for testicular microlithiasis | Definition for change of TM | Duration of follow-up (mo), mean (SD), median (range) | Follow-up strategy |
|---------------------------------|--------------|-------------------------------------|--------------------|-------------------|----------------------|-----------------------------------------------|----------------------------|-----------------------------------------------|-------------------|
| Silveri et al (2011), 2002–2011 | 21           | Mean 10.5 yrs (range 8 mo–18 yrs)   | Incidentally discovered TM in asymptomatic patients | NR                | 6 UD; 4 varicocele; 1 hydrocele; 10 no associated pathology | Distribution of microliths inside the parenchyma (diffuse or focal) | NR | Mean 41.2 mo | Every six months clinical, US evaluation and AFP and HCG markers |
| Marte et al (2017), 2008–2014   | 81           | Mean 10.1 yrs (range 6 mo–17 yrs)   | Patients identified with TM | NR                | 7 no associated pathology; 19 UD; 18 varicocele; 14 painful testis; 6 hernia; 6 acute scrotum; 5 hydrocele; 2 epididymal cyst; 2 testicular malignancy; 1 severe hypoplasia; 1 benign tumour | Classic TM: >5 microliths in 1 US image; Limited TM: <5 microliths in 1 US image | Improvement: reduction of >50% microliths; Worsening: increase of >50% microliths | Median 4.7 yrs (range 1–7 yrs) | Urological examination and US at 12-month intervals |
| Lim et al (2015), 1997–2014     | Mean 11.3 ± 4.6 yrs | Patients diagnosed with TM and undergone at least twice scrotal US | NR | 6 UD; 3 testicular torsion; 3 epididymitis; 2 hydrocele; 2 varicocele; 2 epididymal cyst | Diffuse: TM in >3 sections; Focal: TM in <3 sections | Decreased: >20% decrease in TM; No change: <20% increase or decrease | Mean 79.1 mo (38.8 mo) | No standardized follow-up routine |
| Leenen et al (2002), 1996–1999  | 5            | Mean 10.5 yrs (range 6–18 yrs) | Sixteen consecutive patients with characteristic TM who underwent US examination at our institution | NR | 4 after orchiopexy; 3 Palpable scrotal mass; 2 Peutz-Jehgers Syndrome; 1 Trauma; 1 pulmonary metastases; 1 ALL | Quantification of NR calcifications: Few (5–50) or multiple (>50) in a single plane. | Distribution: focal clustering of foci in one-third only or in the periphery of the testicular parenchyma | Mean 19 mo | NR |

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| Study (year), recruitment period          | N of patients | Age (yr), mean ± SD, median (range) | Inclusion criteria                                                                 | Exclusion criteria                                                                 | Associated pathology                                                                 | Definition used for testicular microlithiasis | Definition for change of TM | Duration of follow-up (mo), mean (SD), median (range) | Follow-up strategy                                                                 |
|------------------------------------------|---------------|------------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Kocaoglu et al (2005), 1998–2004         | 9             | Mean 9.2 yrs (range 3–16 yrs)       | Children with TM at US between the recruitment period                                | NR                                                                                 | 2 scrotal pain; 2 varicoceles; 1 bilateral UDT; 1 unilateral UDT; 1 Klinefelter Syndrome with bilateral orchiopexia; 1 trauma; 1 insufficient growth and development | Diffuse or focal and bilateral or unilateral, with or without accompanying nodules | NR                          | Mean 31 mo (9–62 mo)                                                                                                          | Interval of 3–12 months in accordance with coexisting pathologies after the diagnosis of TM |
| Furness et al (1998), NR                 | 23            | Mean 12.3 yrs (range 6 months–21 yrs) | Incidentally discovered TM in childhood                                              | Children with previous or concurrent testicular malignancy at time of diagnosis of testicular microlithiasis | 6 orchialgia or acute pain; 5 hydrocele; 5 epididymitis-orchitis; 3 varicoceles; 3 scrotal trauma; testicular mass; testicular size discrepancy | Ultrasound findings include 1–3 mm, diffuse, punctate, nonshadowing, hyperechoic foci within testicular parenchyma | NR                          | Mean 27.6 mo (1mo-7yr)                                                                                                          | Usually consisted of yearly ultrasound and physical examination                   |
| Dutra et al (2011), 2005–2010            | 11            | Mean 7.5 yrs (range 1–15 yrs)       | Children with UDT, retractile testis, hypotrophy of the testis and inguinal hernia were submitted to US | NR                                                                                 | 5 UDT (3,93% of 127 pts); 4 retractile testis (14,8% of 27 pts); 1 testis hypotrophy (100% in 1 pt); 1 inguinal hernia (0,07% of 1349 pts). | Distributed hyperechogenic microliths                                                                 | NR                          | Range 6 mo −5 yrs                                                                                                               | Annual follow-up with physical examinations and ultrasound evaluations           |
| Dagash et al (2006), 1990–2004           | 7             | Mean 12 yrs (range 7–15 yrs)        | All patients referred for scrotal US                                                | Any children with coexistent testicular tumor                                         | 3 testicular pain; 2 UDT; 1 hydrocele, 1 asymptomatic scrotal swelling              | Multiple 1–3 mm NR                                                                                  | NR                          | Mean 35 mo (8–67 mo)                                                                                                               | Yearly US follow-up                                                             |
| Cooper et al                             | 83            | Mean 11.0 yrs                       | All patients <18 yrs of Patients with                                                 | Patients with scrotal pain                                                           | 40 scrotal pain; 9Classic TM > 5                                                   |                                                                                              | Mean 4.2 yr (1)                                                                                          |                                                                                     |
| Authors                  | Year(s)  | Mean Age | Diagnoses                                      | Staging Criteria                                                                 |
|-------------------------|----------|----------|-----------------------------------------------|----------------------------------------------------------------------------------|
| Volokhina et al         | 2014     | 10.6 yrs | Symptomatic children referred for US exams    | Symptomatic children referred for US exams for a very broad variety of reasons   |
|                         |          |          | with classic testicular microlithiasis       | with classic testicular microlithiasan for a very broad variety of reasons       |
| Yesil et al             | 2016     | 8.7 yrs  | Patients with TM who had undergone a scrotal  | Patients with TM who had undergone a scrotal US at least twice                   |
|                         |          |          | US twice                                     |                                                                                  |

### Testicular microlithiasis in children and adults

Testicular microlithiasis (TM) is a condition characterized by the presence of small calcified nodules within the testis. In children and adults, the condition is often asymptomatic and of uncertain significance. The diagnosis is typically made incidentally on scrotal ultrasound (US) imaging.

**Key Points**
- **Diagnosis**: US is the primary imaging modality for diagnosing TM. The presence of microliths within the testis is the key feature.
- **Epidemiology**: TM is more common in adults, but cases in children have been reported. The condition can be sporadic or familial.
- **Staging and Follow-up**: Staging is typically based on the number of microliths detected on US. Children with a high number of microliths may require more frequent follow-up to monitor for any progression to testicular cancer.
- **Management**: Treatment is generally not required for asymptomatic cases. However, high-risk patients (e.g., those with a large number of microliths) may benefit from closer surveillance or further testing.

### Table

| Study                  | Year(s) | Age Range | Diagnoses                          | Follow-up Protocol |
|------------------------|---------|-----------|------------------------------------|--------------------|
| Volokhina et al        | 2014    | 0.6-17.9 yrs | Classic TM > 5 microliths in 1 US image; Limited TM < 5 microliths in 1 US image and were grouped together with children without TM | Mean 265 days (9NR days-4yr) |
| Yesil et al            | 2016    | 8.7 yrs   | Diffuse TM: microliths in >3 sections; Focal TM: microliths in <3 sections | Mean 2.74 yrs (1.4yr) | Every 6 months, clinical and US evaluation + serum tumor markers (AFP and b-HCG) |

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| Study (year), recruitment period | N of patients | Age (yr), mean ± SD, median (range) | Inclusion criteria | Exclusion criteria | Associated pathology | Definition used for testicular microlithiasis | Definition for change of TM | Duration of follow-up (mo), mean (SD), median (range) | Follow-up strategy |
|---------------------------------|--------------|-----------------------------------|-------------------|-------------------|----------------------|-----------------------------------------------|--------------------------|-------------------------------------------------|------------------|
| Chiang et al (2011), 2002–2007  | 31           | Median 11 yrs (range 4.7–14.8 yrs) | Clinical indication for NR scrotal US and pts with TM were included | NR                | NR                  | Classic TM: >5 echogenic foci 1–3 mm in either or both testes; Limited TM: <5 foci. TM was differentiated as diffusely scattered throughout the parenchyma or segmented | NR                       | Mean 39.6 mo (0 NR –128.6 mo)                  |                   |
| Goede et al (2010), 1990–2009  | 9            | Mean 12.4 yrs (range 4.1–24.1 yrs) | Patients with acquired undescended (ascending) testis had follow-up | NR                | Acquired undescended (ascending) testis | Classic TM: >5 echogenic foci 1–3 mm in either or both testes; Limited TM: <5 foci. TM was differentiated as diffusely scattered throughout the parenchyma or segmented | NR                       | Median 1.36 yrs (0–3.2yrs)                    | Full physical examination, additionally US was repeated to confirm the diagnosis. |
| Nishimura et al (2017), 2009–2016 | 56          | Median age 11.3 mo (range 6.4–29.1 mo) | Patients with isolated congenital palpable UDT who underwent standard orchiopexy | Congenital undescended testis | Congenital undescended testis | Classic TM: >5 echogenic foci per field; Limited classification TM: <5 | Progression: change in echogenic foci per field; Limited classification from LTM to CTM | Median 24.9 mo (0.33–85.1 mo) | Serial US evaluations were performed before surgery, at 1 year |

**Table 1 (continued)**
Follow-up of patients without Down Syndrome was not performed.

One study described the prevalence of TM in patients with McCune Albright Syndrome [29]. A prevalence of 24% of TM was reported. Of the 54 patients 16 presented with concomitant testicular tumours, 11 Leydig cell hyperplasia, one Leydig cell and one Sertoli cell intraepithelial neoplasia, one seminoma and one embryonal carcinoma. During follow-up no testicular malignancies were described.

**Adult population**

The outcomes of the adult studies are presented in Table 3. For the adult population the included studies were four systematic reviews [7,30,31] and three meta-analyses [32–35].

The systematic reviews and meta-analyses sub-divided the adult population into seven groups: asymptomatic, symptomatic, cryptorchidism, sub/infertility, unspecified, with testicular tumour, with a positive family history and a specific prospective cohort.

Factors not associated with an increased risk for testicular malignancy in patients with TM. Patients who were asymptomatic (n = 3982) or who had a positive family history (n = 217) with TM did not show an increased risk for the development of testicular tumours [7,32,34,35]. The prevalence of TM was higher for the population with a positive family history compared to asymptomatic patients, however, these data are based on a single study.

Factors associated with an increased risk for testicular malignancy in patients with TM. In the symptomatic patient group (n = 22,763) an increased risk for testicular malignancy was found when TM was present [7,32,35]. Symptomatic was defined as testicular pain, testicular edema or increased testis volume. The risk was increased with a RR 14.2 for the group with TM in one systematic review and a significant difference of 11.2% with TM vs 1% TM-free in another systematic review. Prevalence of TM ranged from 0.6 to 18.1%.

In adult men with a history of cryptorchidism (n = 1455), an increased risk for testicular malignancy of 6% was found in patients presenting with the diagnosis of TM compared to 0% in the TM-free population [32,35]. The prevalence of TM was reported with a wide range from 2.8 to 36.5%.

The sub/infertility group (n = 9295) also demonstrated a higher risk for testicular tumour when TM was present on ultrasound [7,31,32,34,35]. The risk of tumour in the group with TM was reported to be RR 15.6, OR 18.6 and with significant differences of 10.9–22.6% in the TM group vs 1% TM-free in another systematic review. Prevalence of TM ranged from 0.6 to 18.1%.

In adult men with a history of cryptorchidism (n = 1455), an increased risk for testicular malignancy of 6% was found in patients presenting with the diagnosis of TM compared to 0% in the TM-free population [32,35]. The prevalence of TM was reported with a wide range from 2.8 to 36.5%.

The sub/infertility group (n = 9295) also demonstrated a higher risk for testicular tumour when TM was present on ultrasound [7,31,32,34,35]. The risk of tumour in the group with TM was reported to be RR 15.6, OR 18.6 and with significant differences of 10.9–22.6% in the TM group vs 1.6–1.7% in the TM-free group. Prevalence was reported to be between 0.9 and 20.1%.

Patients that had a history of testicular malignancy with TM (n = 156) showed an increased risk for testicular tumour of 22% vs 2% in the TM-free group [7,33,35]. A prevalence of TM of 15% was reported.

Three systematic reviews reported on the risk of testicular tumours in the presence of TM in specific prospective cohorts (n = 1487) [7,33,35]. The incidence of
| Study (year) | N of tumors during follow-up | Tumor characteristics | N of concomitant tumors and TM | Type and distribution of TM | Change in TM during follow-up | Tumor markers | Testicular biopsy results | Incidence of TM according to associated pathology |
|--------------|------------------------------|-----------------------|--------------------------------|-----------------------------|-----------------------------|---------------|--------------------------|-------------------------------------------------|
| Silveri et al (2011), 2002 –2011 | 0/21 | X | 0/21 | 7 diffuse/14 focal, 21 bilateral/0 unilateral | No change in TM pattern during FU | Normal | NR | NR |
| Marte et al (2017), 2008 –2014 | 1 malignant/1 benign | 1 seminoma (5yrs FU) in 17 year old/1 mature teratoma (3yrs FU) in 9 year old X | 0/21 | 30 CTM/14 LTM 54 bilateral/27 unilateral | 77/81 no change in TM pattern; 4/81 improved after surgery | 8/8 pts showed normal tumor markers | 12 biopsies (acute scrotum/varicocele) showed intratubular calcifications | NR |
| Lim et al (2015), 1997 –2014 | 0/23 | X | 0/23 | 20 diffuse/23 focal, 20 bilateral/2 unilateral/1 atrophic | Calcific density increased not significantly: 3.74%+6.0% vs 3.06%+-4.38%. 14 testis were increased, 18 testes decreased and in 11 testis no change. Half of the pts with diffuse TM 10/20 compared to focal TM 4/23 were increased p = 0.049 4 no change and 1 reduction in size | NR | 3 confirmed intratubular | NR |
| Leenen et al (2002), 1996 –1999 | 0/5 | X | 1 germ cell tumor in 13 year old; 2 Sertoli-cell tumors (associated with Peuts-Jehgers syndrome) | 15 diffuse/1 focal, 11 bilateral/5 unilateral | microcalcifications and 1 no detectable TM | NR | NR | NR |
| Kocaoglu et al (2005), 1998 –2004 | 0/9 | X | 0/9 | 7 diffuse/2 focal | NR | NR | NR | NR |
| Study                        | Sample Size | NR | Excluded | Biopsy Findings                                                                 | Other Findings                                                                 |
|------------------------------|-------------|----|----------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Furness et al (1998), NR     | 0/23        | X  |          | 1 benign Sertoli cell nodule                                                    | 25 bilateral/1 unilateral NR 15/15 showed normal tumour markers (AFP and b-HCG) |
| Dutra et al (2011), 2005–2010| 0/11        | X  |          | 9 bilateral/2 unilateral NR                                                      | 9 biopsies showed dystrophic calcifications without evidence of malignancy or abnormal seminiferous tubules. |
| Dagash et al (2006), 1990–2004| 0/7         | X  |          | Excluded                                                                        | 1 less prominent TM; 4 unchanged; 2 lost to follow up 1/1 showed normal tumour markers (AFP and b-HCG) |
| Cooper et al (2014), 2003–2012| 0/18        | X  |          | 6 pts had a premalignant or benign tumor (5 pts <11 yrs and 1 pt 14.5 yrs); with predisposing conditions in five (83%) (2 cryptorchidism and 3 Peuts-Jeghers syndrome). Four malignant tumors were found, all in adolescent boys (range 16.2–17.8 yrs). | 59 CTM/21 LTM 13 unchanged; 4 increased; 1 decreased 4 large cell Sertoli cell tumor; 3 immature teratoma; 2 juvenile granulosa cell tumor; 1 mature teratoma; 1 Leydig cell hyperplasia; 1 Leydig cell nodule; 3 intratubular germ cell neoplasia; 4 mixed germ cell tumors; 1 seminoma |

Testicular microlithiasis in children and adults (continued on next page)
| Study (year)                | N of tumors during follow-up | Tumor characteristics | N of concomitant tumors and TM | Type and distribution of TM | Change in TM during follow-up | Tumor markers | Testicular biopsy results | Incidence of TM according to associated pathology |
|----------------------------|------------------------------|-----------------------|--------------------------------|----------------------------|-------------------------------|---------------|--------------------------|------------------------------------------------|
| Volokhina et al (2014), 2000–2011 | 0/9                          | X                     | 1 mixed germ cell tumor in 16 year old 0/78 | 9 CTM                      | NR                            | NR            | NR                      | NR                                               |
| Yesil et al (2016), 2008–2015  | 0/78                         | X                     | 56 diffuse/22 focal 45 bilateral/33 unilateral | 2 decreased TM and 2 complete resolution of TM | NR                            | b-HCG were within normal limits for all patients; AFP was slightly elevated in 7 patients (8.97%), all patients exhibited normal AFP levels upon follow-up. NR | NR                      | 6 (7.7%) biopsies were performed: 1 dermoid cyst, others normal testicular tissue or fetal arrest. |
| Chiang et al (2011), 2002–2007 | 0/19                         | X                     | 0/31                           | 23 bilateral/8 unilateral | 27 unchanged, 2 increase and 4 resolution of TM | NR            | NR                      | NR                                               |
| Goede et al (2010), 1990–2009  | 0/204                        | X                     | 0/320                          | 6 CTM/3 LTM                | NR                            | NR            | NR                      | 9/320 (2.8%) acquired UDT                        |
| Nishimura et al (2017), 2009–2016 | 0/55                        | X                     | 0/55                           | Preoperative: 2 LTM Postoperative: 7 CTM/7 LTM 12 unilateral/2 bilateral | Unilateral UDT: 1 LTM unchanged; 1 LTM and 6 CTM developed. Bilateral UDT: 1 LTM progressed to CTM; 3 LTM developed. Contralateral descended testis: 2 LTM developed. | NR            | NR                      | 14/65 (21.5%) congenital UDT                      |
| Riebel et al (2000), 1986–1996 | 0/68                         | X                     | 0/68                           | NR                         | NR                            | NR            | NR                      | NR                                               |
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Table 3   Outcomes of the adult systematic reviews.

| Population  | Study            | N of studies | N of patients | Prevalence of TM | N of tumours with TM | N of tumours without TM | Risk of tumour | Contributing factors | Follow-up |
|-------------|------------------|--------------|---------------|------------------|---------------------|-------------------------|----------------|----------------------|-----------|
|             | Tan et al.       | 4            | 3982          | 3.7%             | 1/146               | 1/3836                  | NR            |                      |           |
|             | Leblanc et al.   | 2            | 3683          | 4%               | 0/137               | 1/4346                  | NR            |                      |           |
|             | Aoun et al.      | 2            | NR            | 2.4–5.6%         | NR                  | NR                     | NR            |                      |           |
| Asymptomatic|                 |              |               |                  |                     |                         |               |                      |           |
|             | Tan et al.       | 2            | 551           | 5.4%             | 6/30                | 7/521                   | RR 14.2 (95% CI 4.64–43.4) |                      | Symptomatic: testicular pain, testicular edema or increased testis volume |
|             | Leblanc et al.   | 12           | 22,212        | 5.3%             | 74/661              | 210/21,407              | NR            |                      |           |
|             | Aoun et al.      | 15           | NR            | 0.6–18.1%        | NR                  | NR                     | NR            |                      |           |
|             | Leblanc et al.   | 6            | 797           | 36.5%            | 3/50                | 0/766                   | RR 15.6 (95% CI 2.07–102.6) |                      |           |
|             | Aoun et al.      | 8            | NR            | 2.8–9.5%         | NR                  | NR                     | NR            |                      |           |
|             | Pedersen et al.  | 9            | 1455          | 2.3–100%         | 3/82                | 0/1373                  | NR            |                      |           |
| Symptomatic |                 |              |               |                  |                     |                         |               |                      |           |
|             | Aoun et al.      | 14           | NR            | 0.9–20.1%        | NR                  | NR                     | NR            |                      |           |
|             | Pedersen et al.  | 17           | 7981          | 10.9%            | 10/98               | 80/701                  | RR 15.6 (95% CI 2.07–102.6) |                      |           |
|             | Barbonetti et al.| 8            | 5268          | 3.5%             | 14/180              | 20/5088                 | OR 18.11 (95% CI 8.09–40.55) |                      |           |
|             | Tan et al., Leblanc et al., Aoun et al., Pedersen et al. | 2 | 217 | 36.7–48% | 0/23 (only reported in one study) | 0/25 (only reported in one study) | No difference between TM and TM-free |           |
| Cryptorchidism|                  |              |               |                  |                     |                         |               |                      |           |
|             | Leblanc et al.   | 6            | 797           | 36.5%            | 3/50                | 0/766                   | RR 15.6 (95% CI 2.07–102.6) |                      |           |
|             | Aoun et al.      | 8            | NR            | 2.8–9.5%         | NR                  | NR                     | NR            |                      |           |
|             | Pedersen et al.  | 9            | 1455          | 2.3–100%         | 3/82                | 0/1373                  | RR 15.6 (95% CI 2.07–102.6) |                      |           |
| Sub/Infertility|                |              |               |                  |                     |                         |               |                      |           |
|             | Tan et al.       | 2            | 3486          | 4.3%             | 1/151               | 3/3335                  | RR 15.6 (95% CI 2.07–102.6) |                      |           |
|             | Leblanc et al.   | 11           | 5228          | 8.3%             | 60/265              | 114/6594                | RR 15.6 (95% CI 2.07–102.6) |                      |           |
|             | Aoun et al.      | 14           | NR            | 0.9–20.1%        | NR                  | NR                     | NR            |                      |           |
|             | Pedersen et al.  | 17           | 7981          | 10.9%            | 10/98               | 80/701                  | RR 15.6 (95% CI 2.07–102.6) |                      |           |
|             | Barbonetti et al.| 8            | 5268          | 3.5%             | 14/180              | 20/5088                 | OR 18.11 (95% CI 8.09–40.55) |                      |           |
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(continued on next page)
| Population                      | Study                                                   | N of studies | N of patients | Prevalence of TM | N of tumours with TM | N of tumours without TM | Risk of tumour |
|---------------------------------|---------------------------------------------------------|--------------|---------------|------------------|----------------------|------------------------|----------------|
| TM and testicular tumour        | Tan et al., Leblanc et al., Aoun et al.                | 1            | 156           | 15%              | 5/23                 | 3/133                  | With TM 22% vs 2% |
|                                 |                                                        |              |               |                  |                      |                        | TM-free OR 12,0  |
|                                 |                                                        |              |               |                  |                      |                        | (p = 0.002)     |
| Prospective cohort              | Leblanc et al.                                          | 16           | 1465          | NR               | 16/1465              | NR                     | 35.4 mo        |
|                                 | Richenberg et al.                                       | 9            | 389           | NR               | 4/389                | NR                     | NR             |
| Unspecified patient cohort      | Tan et al.                                              | 14           | 30,169        | 3.4%             | 157/1030             | 492/29,139             | RR 10.06 (95% CI |
|                                 | Leblanc et al.                                          | 8            | 26,957        | 5%               | 121/1284             | 302/23,194             | With TM 9.4% vs  |
|                                 | Wang et al.                                             | 14           | 35,578        | 4.2%             | NR                   | NR                     | RR 12.7 With TM vs |
|                                 |                                                        |              |               |                  |                      |                        | TM-free (p < 0.001)|


testicular malignancy during follow-up in patients with TM ranged between 1 and 7%. Only two patients did not have known risk factors for testicular tumour, while the other patients had infertility, cryptorchidism, testicular tumour of testicular atrophy.

Discussion

Principal findings

With this systematic review we present the results of follow-up in the largest group of paediatric patients, 595 form 15 studies, with the diagnosis of TM. During follow-up only one patient with TM developed a testicular malignancy and this was during puberty. In the other 594 patients no testicular malignancy was found, even in the presence of other risk factors for testicular malignancy such as cryptorchidism. However, it is important to emphasize that the follow-up duration mostly varied between six months and three years, but never exceeded 11 years. Given that the average age was about 10 years and testicular malignancies are expected to develop from puberty on, it is very well conceivable that testicular malignancies had not yet developed.

It was also shown that there is no additional value to determine tumour markers or perform testicular biopsies in children with TM, since this did not have any clinical consequences.

TM was described according to different classifications; classic vs limited and diffuse vs focal. This did not correlate with change in TM during follow-up or association with testicular malignancy. There seems to be no preferred classification system.

In the adult population, an increased risk of testicular malignancy in the presence of TM was observed for the various subgroups, specifically patients with a history of cryptorchidism, sub/infertility and a history of testicular malignancy. While patients with TM that were asymptomatic or had a family history of testicular malignancy were not at risk.

The fact that patients with TM and additional risk factors show an increased risk for testicular malignancies during adulthood confirms the hypothesis that the follow-up of paediatric patients with TM might have been too short.

A systematic review and meta-analysis was published in 2019 by Yu et al. [36], also investigating the association between TM and testicular tumours in children. They included 10 follow-up studies with 296 children. They report four tumours during follow-up, however, they included benign tumours and concurrent testicular tumours at diagnosis of TM. In our analysis we have separated the concomitant diagnosis testicular tumour with TM, since this does not demonstrate what happens with TM as an incidental finding. In addition, we were able to include 5 more studies and include 199 more children to further strengthen the results. Also, a systematic comparison to the adult literature has now been performed.

Implications for clinical practice

Based on the current literature we would recommend that in asymptomatic children and without risk factors; where TM is incidentally found on ultrasound this warrants no further investigation or follow-up.

In children where TM is found in the presence of risk factors, such as cryptorchidism, monthly self-examination from puberty is advised without additional routine ultrasound follow-up. The available data do not support the need for earlier self-examination, which would be difficult in the paediatric population.

An important moment arises during the transition phase from paediatric to adult urology, especially for patients that present with sub/infertility issues and a history of TM and additional risk factors highlighted in this review. Based on the EAU guidelines Sexual and Reproductive Health this is a group of patients in whom the option of yearly US follow-up and even testicular biopsies has to be considered [37]. This specific group of patients might benefit from this more intensive follow-up and a referral to the adult urologist might be indicated for children with TM and additional risk factors when they reach the age of 18 years.

Further research

It is imperative that studies with a long-term follow-up of children diagnosed with TM with and without risk factors should be conducted, specifically follow-up exceeding puberty. One could propose a study were children with TM are called back for medical history and a current ultrasound investigation at age 25 or 30 years. This will hopefully answer the still remaining questions regarding TM:

- Is TM found during childhood the same entity as TM found in adults with a concomitant pathology?
- What is the origin of TM? Could it be the result of intratesticular trauma, obstruction or inflammation? Or is it indeed a precursor for testicular malignancy?
- Is there a correlation between TM and sub/infertility?

Future research should focus on prospective studies in which the role of possible contributing risk factors can be investigated and the clinical consequence of TM is more elucidated.

Limitations and strengths of the study

In this systematic review several strengths and limitations need to be addressed.

First, in the paediatric population only observational studies could be included and only two of these studies were prospectively conducted. Also, patients with various associated pathologies were grouped together and not controlled for, resulting in an increased risk of bias.

The second limitation of the systematic review is the heterogeneity of the data in the adults. The prevalence of TM is reported with a wide range for the different patient subgroups, indicating that the original studies included in the systematic reviews have a high risk of bias.

The third main limitation of the systematic review is that the reported follow-up did not exceed puberty in most studies looking at TM in children, even when risk factors were present. Testicular malignancies are expected to occur from puberty on and it is therefore feasible that
testicular malignancies may have occurred after completion of the study. Especially, if the data from the paediatric population are compared to the adult population where this increased risk for testicular malignancy has been shown for patients with additional risk factors.

This immediately highlights one of the strengths of this study. A systematic approach was followed to collect the data of both children and adults and a direct comparison could be made between these two populations.

One of the other strengths of this study is that it represents the largest collection of follow-up data in children and thereby best reflects the available evidence in the literature.

Conclusion

TM is a relatively common incidental finding at testicular ultrasound. In the paediatric population TM does not seem to be associated with testicular malignancy. In the adult population TM in combination with a history of cryptorchidism, sub/infertility or a previous history of testicular tumours is associated with an increased risk for testicular malignancy. Routine monthly self-examination of the testes is only recommended in children with contributing risk factors from puberty onwards. When TM is still present with accompanying risk factors during transition to adulthood a more intensive follow-up with ultrasound and even biopsy could be considered.

Conflict of interest

None.

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References

[1] J Clin Ultrasound 1996 Miller, et al. Testicular microlithiasis: a benign condition with a malignant association. J Clin Ultrasound 1996 May;24(4):197–202.
[2] Holm M, Hoei-Hansen CE, Rajpert-de Meyts E, Skakkebaek NE. Increased risk of carcinoma in situ in patients with testicular germ cell cancer with ultrasonic microlithiasis in the contralateral testicle. J Urol 2003;170(4 Pt 1):1163–7.
[3] Hoei-Hansen CE, Holm M, Rajpert-De Meyts E, Skakkebaek NE. Histological evidence of testicular dysgenesis in contralateral biopsies from 218 patients with testicular germ cell cancer. J Pathol 2003;200(3):370–4.
[4] Bedayat A, Chen BY, Hayim M, Zheng L, Gagne SM, McIntosh LJ, et al. A private investigation: radiologic-pathologic correlation of testicular tumors. Curr Prob Diagn Radiol 2017;46(3):242–56.
[5] Rocher L, Ramchandani P, Beifield J, Bertolotto M, Derchi LE, Correas JM, et al. Incidentally detected non-palpable testicular tumours in adults at scrotal ultrasound: impact of radiological findings on management Radiologic review and recommendations of the ESUR scrotal imaging subcommittee. Eur Radiol 2016;26(7):2268–79.
[6] de Gouveia Brazao CA, Pierik FH, Oosterhuis JW, Dohle GR, Looijenga LH, Weber RF. Bilateral testicular microlithiasis predicts the presence of the precursor of testicular germ cell tumors in subfertile men. J Urol 2004;171(1):158–60.
[7] Cancer 2010 Tan et al. 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 2010 Oct 1;116(19):4520–32.
[8] Urology 2014 Xu et al. The association between testicular microlithiasis and semen parameters in Chinese adult men with fertility intention: experience of 226 cases. Urology 2014 Oct;84(4):815–20.
[9] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7):e1000097.
[10] Hayden JA, van der Windt DA, Cartwright JL, Coët P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158(4):280–6.
[11] Marte A, Pintozzi L, Creti G, Chiesa PL, Renzo DD, Gasparella M, et al. Long-term follow-up of testicular microlithiasis in children and adolescents: multicenter prospective cohort study of the Italian Society of pediatric urology. Eur J Pediatr Surg 2017 Apr;27(2):155–60.
[12] Dutra RA, Perez-Boscillo AC, Melo EC, Crvinel JC. Clinical importance and prevalence of testicular microlithiasis in pediatric patients. Acta Cir Bras 2011 Oct;26(5):387–90.
[13] Silveri M, Bassani F, Cola Jacomo M, Orazi C, Adorisio O. Management and follow-up of pediatric asymptomatic testicular microlithiasis: are we doing it well? Urol J 2011 Fall;8(4):287–90.
[14] Lim B, Song SH, Song G, Kim KS. Changes of calcific density in pediatric patients with testicular microlithiasis. Korean J Urol 2015 Apr;56(4):318–23.
[15] Leenen AS, Riebel TW. Testicular microlithiasis in children: sonographic features and clinical implications. Pediatr Radiol 2002 Aug;32(8):575–9.
[16] Kocaoglu M, Bozlar U, Bulakbasi N, Saglam M, Uçöz T, Somuncu I. Testicular microlithiasis in pediatric age group: ultrasonography findings and literature review. Diagn Interv Radiol 2005 Mar;11(1):60–5.
[17] Furness 3rd PD, Husmann DA, Brock 3rd JW, Steinhardt GF, Bukowski TP, Freedman AL, et al. Multi-institutional study of testicular microlithiasis in childhood: a benign or premalignant condition? J Urol 1998 Sep;160(3 Pt 2):1151–4. discussion 1178.
[18] Kocaoğlu Y, Yucoy, Müller H. Ultrasound demonstration of testicular microlithiasis in pediatric patients: is there an association with testicular germ cell tumors? Pediatr Radiol 2014 Jan;44(1):50–5.
[19] Yesil S, Tanyildiz HG, Sahin G. How should we monitor boys with testicular microlithiasis? Pediatr Hematol Oncol 2016 Apr;33(3):171–7.
[20] Chiang LW, Yap TL, Asiri MM, Phalq Ong CC, Low Y, Jacobsen AS. Implications of incidental finding of testicular microlithiasis in paediatric patients. J Pediatr Urol 2012 Apr; 8(2):162–5.
[21] Goede J, Hack WW, van der Voort-Doedens LM, Pierik FH, Looijenga LH, Sijstermans K. Testicular microlithiasis in boys and young men with congenital or acquired descended (ascending) testis. J Urol 2010 Apr;183(4):1339–43.
[22] Nishimura Y, Moriya K, Nakamura M, Nishida M, Sato M, Kudo Y, et al. Prevalence and chronological changes of testicular microlithiasis in isolated congenital descended testes
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operated on at less than 3 Years of age. Urology 2017 Nov;109:159–64.

[26] Riebel T, Herrmann C, Wit J, Sellin S. Ultrasonographic late results after surgically treated cryptorchidism. Pediatr Radiol 2000 Mar;30(3):151–5.

[27] Vachon L, Fareau GE, Wilson MG, Chan LS. Testicular microlithiasis in patients with Down syndrome. J Pediatr 2006 Aug;149(2):233–6.

[28] Cebeci AN, Aslanger A, Ozdemir M. Should patients with Down syndrome be screened for testicular microlithiasis? Eur J Pediatr Surg 2015 Apr;25(2):177–80.

[29] Goede J, Weijerman ME, Broers CJ, de Winter JP, van der Voort-Doodens LM, Hack WW. Testicular volume and testicular microlithiasis in boys with Down syndrome. J Urol 2012 Mar;187(3):1012–7.

[30] Boyce AM, Chong WH, Shawker TH, Pinto PA, Linehan WM, Bhattacharryya N, et al. Characterization and management of testicular pathology in McCune-Albright syndrome. J Clin Endocrinol Metab 2012 Sep;97(9):E1782–90.

[31] Wang T, Liu L, Luo J, Liu T, Wei A. A meta-analysis of the relationship between testicular microlithiasis and incidence of testicular cancer. Urol J 2015 Apr 29;12(2):2057–64.

[32] Barbonetti A, Martorella A, Minaldi E, D’Andrea S, Bardhi D, Castellini C, et al. Testicular cancer in infertile men with and without testicular microlithiasis: a systematic review and meta-analysis of case-control studies. Front Endocrinol 2019 Mar 21;10:164.

[33] Aoun F, Slaoui A, Naoum E, Hassan T, Albisinni S, Azzo JM, et al. Testicular microlithiasis: systematic review and Clinical guidelines. Prog Urol 2019 Sep;29(10):465–73.

[34] Richenberg J, Brejt N. Testicular microlithiasis: is there a need for surveillance in the absence of other risk factors? Eur Radiol 2012 Nov;22(11):2540–6.

[35] Pedersen MR, Rafaelsen SR, Møller H, Vedsted P, Østher PJ. Testicular microlithiasis and testicular cancer: review of the literature. Int Urol Nephrol 2016 Jul;48(7):1079–86.

[36] Leblanc L, Lagrange F, Lecoanet P, Marçon B, Eschwege P, Hubert J. Testicular microlithiasis and testicular tumor: a review of the literature. Basic Clin Androl 2018 Jul 9;28:8.

[37] Yu CJ, Lu JD, Zhao J, Wei Y, Zhao TX, Lin T, et al. Incidence characteristics of testicular microlithiasis and its association with risk of primary testicular tumors in children: a systematic review and meta-analysis. World J Pediatr 2020 Dec;16(6):585–97.

[38] Salonia A, Bettocchi C, Carvalho J, Corona G, Jones TH, Kadioglu A, et al. EAU guidelines on sexual and reproductive Health. The Netherlands: Publisher: EAU Guidelines Office. Place published: Arnhem; 2020. p. 978–94. 92671-07-3.