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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

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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 is 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

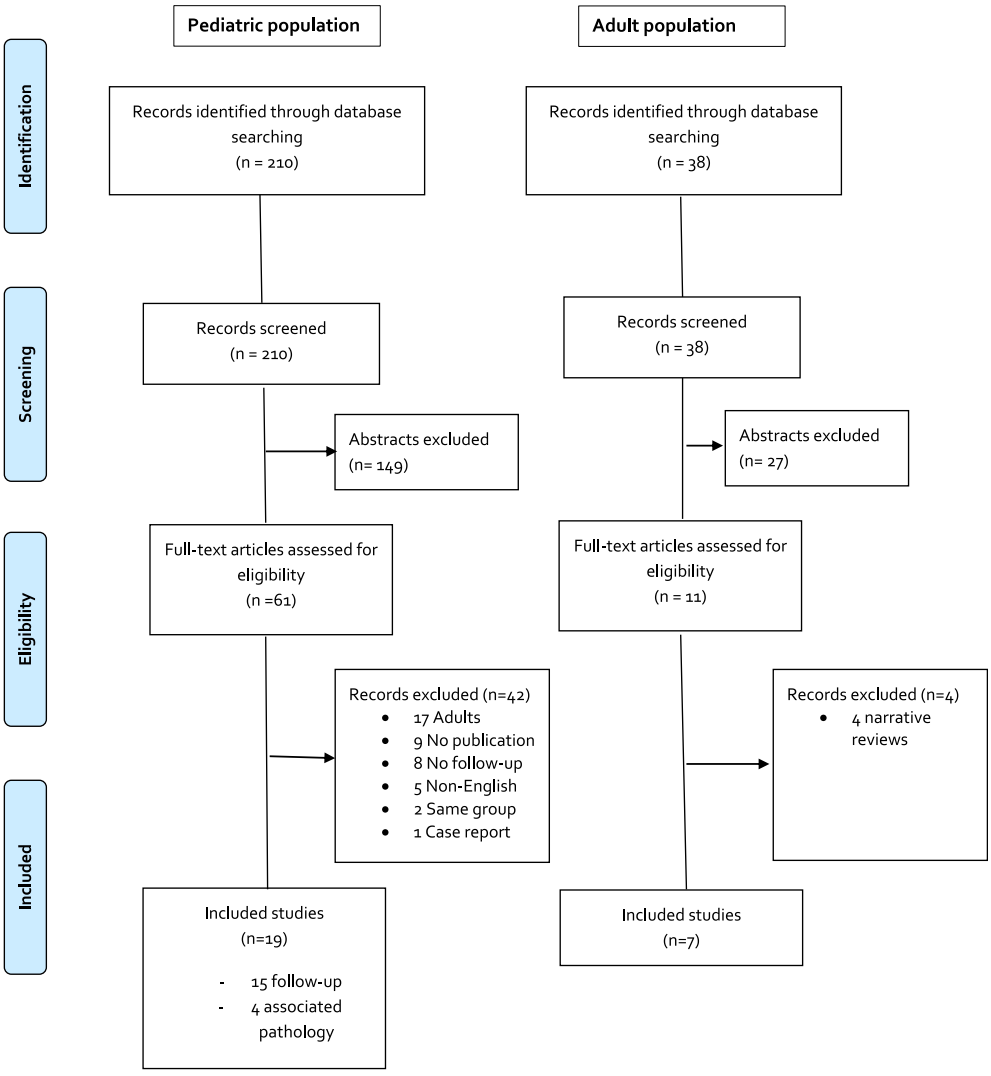

Fig 1 PRISMA flow diagram.

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 ≤ 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 ≥ 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 abstract 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].

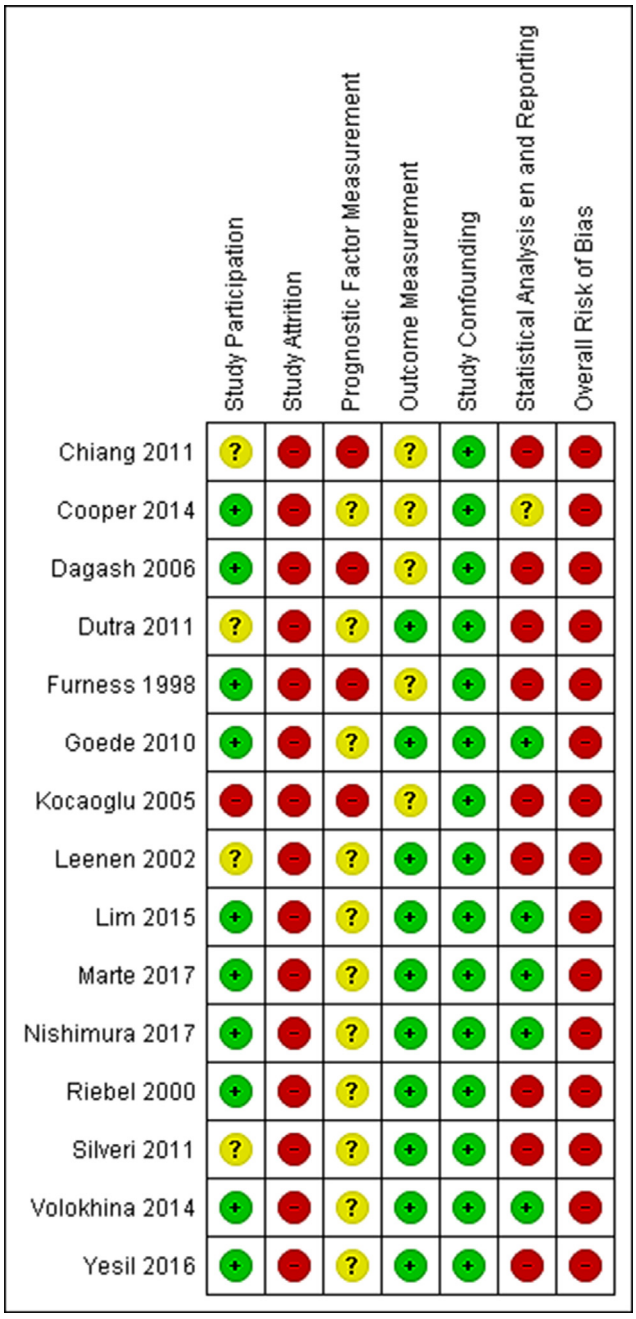

Fig 2 Risk of bias summary of the 15 included paediatric follow-up studies.

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 $<$ 5microliths 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-Jehgers 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.

Table 1 Study characteristics of the paediatric follow-up studies.

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 UDT; 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 UDT; 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	23	Mean 11.3 ± 4.6 yrs	Patients diagnosed with TM and undergone at least twice scrotal US	NR	6 UDT; 3 testicular torsion; 3 epididymitis; 2 hydrocele; 2 varicocele; 2 epididymal cyst	Diffuse: TM in >3 sections; Focal: TM in<3 sections	Increased: >20% increase in TM; 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; 4 UDT; 3 Palpable scrotal mass; 2 Peutz-Jehgers Syndrome; 1 Trauma; 1 pulmonary metastases; 1 ALL	Quantification of 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	NR	Mean 19 mo	NR

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Table 1 (*continued*)

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
Kocaoğlu 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 orchalgia or acute pain; 5 hydrocele; 5 epididymitis-orchitis; 3 varicocele; 3 scrotal trauma; 2 testicular mass; 2 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 <3 mm seen in a single ultrasound scan. The distribution of calcifications was diffuse or focal, uni or bilateral	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 echogenic foci within the parenchyma of the testis on US	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	40 scrotal pain; 9	Classic TM >5	NR	Mean 4.2 yr (1	NR

(2014), 2003 −2012	(range 0.6 −17.9 yrs)	age who had a scrotal US study and included the keywords "microlithiasis", "microcalcifications" and "punctate calcifications". At least one year follow-up.	testicular tumors who were diagnosed with TM only at retrospective review of the US studies not to bias the results	UDT; 7 testicular mass; 5 varicocele; 5 hydrocele; 4 hernia; 3 scrotal swelling; 3 follow-up of known TM; 3 Peutz-Jeghers syndrome; 1 scrotal trauma; 1 gynecomastia; 1 non-palpable testis; 1 asymmetric size of testicle; 1 McCune Albright Syndrome; 1 mixed gonadal dysgenesis; 1 Klinefelter syndrome; 1 leukemia	microliths in 1 US image; Limited TM $<$ 5 microliths in 1 US image. In CTM distribution was diffuse or clustered (localized in 1 area, patchy or nodular)		−14.5yr)	
Volokhina et al (2014), 2000 −2011	87	Mean 10.6 yrs	Symptomatic children referred for US exams for a very broad variety of reasons with classic testicular microlithiasis	NR	NR	Classic TM $>$ 5 microliths in 1 US image; Limited TM $<$ 5 microliths in 1 US image and were grouped together with children without TM	NR	Mean 265 days (9 days-4yr)	NR
Yesil et al (2016), 2008−2015	81	Mean 8.7 $\pm$ 4.1 yrs	Patients with TM who had undergone a scrotal US at least twice	NR	31 UDT; 11 hydrocele; 5 scrotal pain; 5 scrotal swelling; 4 asymmetric size of testicle; 4 non palpable testis; 4 varicocele; 3 precocious puberty; 2 gynaecomastia; 2	Diffuse TM: microliths in $>$3 sections; Focal TM: microliths in $<$3 sections	NR	Mean 2.74 yrs (1.4yr)	Every 6 months, clinical and US evaluation + serum tumor markers (AFP and b-HCG)

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Table 1 (*continued*)

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
					down syndrome; 2 hernia; 2 scrotal trauma; 1 testicular mass; 1 congenital adrenal hyperplasia; 1 Klinefelter syndrome				
Chiang et al (2011), 2002 −2007	31	Median 11 yrs (range 4.7 −14.8 yrs)	Clinical indication for scrotal US and pts with TM were included	NR	17 scrotal swelling or enlargement; 12 UDT; 10 hydrocele; 9 orchidalgia; 8 varicocele; 7 inguinal hernia; 7 torsion of hydatid cyst of Morgagni; 4 evaluation of testis size; 1 non-palpable testis	NR	NR	Mean 39.6 mo (0 −128.6 mo)	NR
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	Patients with concomitant congenital anomalies, such	Congenital undescended testis	Classic TM: >5 echogenic foci per field; Limited TM: <5	Progression: change in classification from LTM to CTM	Median 24.9 mo (0.33−85.1 mo)	Serial US evaluations were performed before surgery, at 1 year

		and preoperative testicular US evaluations	as hypospadias, chromosomal anomaly, disorders of sexual development, endocrine disorders, and other symptoms related to UDT. Also patients who had failed orchiopexy, acquired UDT or >3 yrs at orchiopexy	echogenic foci per field.	or when new TM was identified during follow-up in patients without TM on previous examination Improvement: change from CTM to LTM or disappearance of all TM on subsequent US		after surgery, and different times at 2 years or later after surgery depending on the physicians preference
Riebel et al (2000), 1986–1996	68	Average 8 yrs 6 mo (range 3 yrs–13 yrs 6 mo)	Boys who had undergone surgical correction of UDT and who received a US examination	NR	All UDT	NR	NR	Average 5 yrs 2mo (2–11 yrs)	NR

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 RR14.2 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 1.6–1.7% 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

Table 2 Outcomes of the paediatric follow-up studies.

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	1 seminoma in 17 year old	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	NR	NR	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	4 no change and 1 reduction in size	NR	3 confirmed intratubular	
					microcalcifications and 1 no detectable TM	NR		
Kocaoğlu et al (2005), 1998 −2004	0/9	X	0/9	7 diffuse/2 focal	NR	NR	NR	NR

Furness et al (1998), NR	0/23	X	Excluded; 1 benign Sertoli cell nodule	25 bilateral/1 unilateral	NR	15/15 showed normal tumour markers (AFP and b-HCG)	9 biopsies showed dystrophic calcifications without evidence of malignancy or abnormal seminiferous tubules.	NR
Dutra et al (2011), 2005 −2010	0/11	X	0/11	9 bilateral/2 unilateral	NR	NR	NR	5/127 (3,93%) UDT RR 9,88; 4/27 (14.8%) retractile testis RR 36,58; 1/1 (100%) hypotrophic testis RR 79,1%; 1/1349 (0,07%) inguinal hernia RR 0,01
Dagash et al (2006), 1990 −2004	0/7	X	Excluded	5 bilateral/2 unilateral	1 less prominent TM; 4 unchanged; 2 lost to follow up	1/1 showed normal tumour markers (AFP and b-HCG)	NR	NR
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 62 bilateral/21 unilateral	13 unchanged; 4 increased; 1 decreased	NR	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 tumor with TM 10/83 (12%) vs. TM-free 10/3370 (0.3%)

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Table 2 (*continued*)

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	9 CTM	NR	NR	NR	NR
Yesil et al (2016), 2008 −2015	0/78	X	0/78	56 diffuse/22 focal 45 bilateral/33 unilateral	2 decreased TM and 2 complete resolution of TM	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.	6 (7,7%) biopsies were performed: 1 dermoid cyst, others normal testicular tissue or fetal arrest.	NR
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	5/68 (7.4%) UDT

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
Asymptomatic									
	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		
Symptomatic									
	Tan et al.	2	551	5.4%	6/30	7/521	RR 14,2 (95% CI 4,64—43,4)		
	Leblanc et al.	12	22,212	5.3%	74/661	210/21,407	With TM 11,2% vs TM-free 1% ($p < 0,0001$)	Symptomatic: testicular pain, testicular edema or increased testis volume	
	Aoun et al.	15	NR	0.6—18.1%	NR	NR	NR		
Cryptorchidism									
	Leblanc et al.	6	797	36.5%	3/50	0/766			
	Aoun et al.	8	NR	2.8—9.5%	NR	NR	NR		
	Pedersen et al.	9	1455	2.3—100%	3/82	0/1373			
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	With TM 22,6% vs TM-free 1,7% ($p < 0,0001$)		
	Aoun et al.	14	NR	0.9—20.1%	NR	NR	NR		
	Pedersen et al.	17	7981	Infertile 6,0% vs Fertile 4,8% ($p < 0,05$)	10.9%	1.6%	Infertility with TM 10,9% vs TM-free 1,6% ($p < 0.001$)		
	Barbonetti et al.	8	5268	3.5%	14/180	20/5088	OR 18.11 (95% CI 8,09—40,55)		
TM and family history									
	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		

(*continued on next page*)

Table 3 (*continued*)

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
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									
	Tan et al.	2	1029	4.2%	3/43	NR	NR	NR	19.5—24 mo
	Leblanc et al.	16	1465	NR	16/1465	NR	NR	4 infertility, 4 cryptorchidism, 3 testicular tumour, 2 testicular atrophy	35.4 mo
	Richenberg et al.	9	389	NR	4/389	NR	1% (95% CI 0,4 —2,6%)	2 testicular tumour, 1 testicular atrophy	NR
Unspecified patient cohort									
	Tan et al.	14	30,169	3.4%	157/1030	492/29,139	RR 10,06 (95% CI 6,92—14,64)		
	Leblanc et al.	8	26,957	5%	121/1284	302/23,194	With TM 9,4% vs TM-free 1,3% ($p < 0,0001$)		
	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, or 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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