



University of Southern Denmark

Testicular microlithiasis and testicular cancer

review of the literature

Pedersen, Malene Roland; Rafaelsen, Søren Rafael; Møller, Henrik; Vedsted, Peter; Osther, Palle Jörn

Published in:

International Urology and Nephrology

DOI:

10.1007/s11255-016-1267-2

Publication date:

2016

Document version:

Proof

Document license:

Unspecified

Citation for published version (APA):

Pedersen, M. R., Rafaelsen, S. R., Møller, H., Vedsted, P., & Osther, P. J. (2016). Testicular microlithiasis and testicular cancer: review of the literature. *International Urology and Nephrology*, 48(7), 1079-1086.
<https://doi.org/10.1007/s11255-016-1267-2>

Go to publication entry in University of Southern Denmark's Research Portal


Terms of use

This work is brought to you by the University of Southern Denmark.
Unless otherwise specified it has been shared according to the terms for self-archiving.
If no other license is stated, these terms apply:

- You may download this work for personal use only.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim.
Please direct all enquiries to puresupport@bib.sdu.dk

2 **Testicular microlithiasis and testicular cancer:**
3 **review of the literature**

4 **Malene Roland Pedersen**^{1,2,3}  · **Søren Rafael Rafaelsen**^{1,3} · **Henrik Møller**^{4,5} ·
5 **Peter Vedsted**⁵ · **Palle Jörn Ooster**^{2,3}

6 Received: 6 November 2015 / Accepted: 11 March 2016
7 © Springer Science+Business Media Dordrecht 2016

8 **Abstract**

9 *Purpose* To perform a systematic literature review to
10 assess whether the occurrence of testicular microlithiasis
11 (TML) in conjunction with other risk factors is associated
12 with testicular cancer.

13 *Methods* A systematic literature search was performed of
14 original articles in English published 1998 to 2015. Rele-
15 vant studies were selected by reading the title and abstract
16 by two of the authors. Studies were included if TML was
17 diagnosed by ultrasonography and a risk condition was
18 reported. Studies were only eligible if the particular risk
19 condition was reported in more than one article.

20 *Results* In total, 282 abstracts in were identified. Based
21 on title and abstract the eligibility was assessed and 31
22 studies were included. Five conditions in relation to TML
23 and testicular cancer emerged: Down syndrome, McCune–
24 Albright syndrome, cryptorchidism, infertility and familial
25 disposition of testicular cancer.

26 *Conclusion* Data support the conclusion that TML is not
27 an independent risk factor for testicular cancer but associ-
28 ated with testicular cancer through other conditions. In

male infertility, TML appears to be related to an increased 29
risk of testicular cancer possibly as part of a testicular dys- 30
genesis syndrome. 31

Keywords Testicular dysgenesis syndrome · Testicular 32
microlithiasis · Testicular cancer · Ultrasonography 33

Introduction 34

Modern ultrasonography (US) gives more detailed infor- 35
mation than previously. As a consequence, testicular micro- 36
lithiasis (TML) is diagnosed more frequently. The origin of 37
TML is unknown. Typically, TML is diagnosed by scrotal 38
US performed for a variety of indications. Recently, it was 39
demonstrated that both inter- and intraobserver agreement 40
with regard to detecting TML with US is high [1]. TML is 41
characterised by the presence of multiple microintra- 42
tubular calcifications without any acoustic shadow in the testicle 43
and is often an incidental finding in US examinations of the 44
scrotum. The size of TML typically has a range of 1–3 mm 45
[2]. 46

Several studies deal with prevalence of TML in both 47
asymptomatic and symptomatic men. Peterson et al. [3] 48
reported a prevalence of 5.6 % in 1504 asymptomatic 49
males (18–35 years old) from the US army reserve officer 50
training corps. In another study of a 2179 asymptomatic 51
males from a similar population, the prevalence was found 52
to be 2.4 % [4]. Goede et al. [5] investigated 670 asymp- 53
tomatic boys in the age range 0–19 years and found a 54
prevalence of 4.2 %. The reported prevalence in healthy 55
populations in other series varies from 0.6 to 9.0 % [6–9]. 56
In symptomatic males, the prevalence in general is higher 57
than in asymptomatic males ranging from 8.7 to 18.1 % 58
[10–12]. 59

A1 ✉ Malene Roland Pedersen
A2 malene.roland.vils.pedersen@rsyd.dk
A3 ¹ Department of Radiology, Vejle Hospital, Part of Lillebaelt
A4 Hospital, Kabbeltoft 25, 7100 Vejle, Denmark
A5 ² Department of Urology, Urological Research Center,
A6 Lillebaelt Hospital, Fredericia, Denmark
A7 ³ Institute of Regional Health Research, University of Southern
A8 Denmark, Odense, Denmark
A9 ⁴ Cancer Epidemiology and Population Health, King's College
A10 London, London, UK
A11 ⁵ Research Unit for General Practice, Department of Public
A12 Health, Aarhus University, Aarhus, Denmark

60 TML has consistently been associated with carcinoma
61 in situ (CIS) and testicular cancer; however, the relation is
62 still controversial. In the literature, several independent con-
63 ditions have been reported to have very high frequencies of
64 TML. If TML, as suggested by some authors, is the visible
65 sign of a premalignant condition, one would expect that these
66 disease states also would be associated with testicular cancer.

67 The aim of this paper was through a systematic literature
68 review to evaluate whether TML, alone or in conjunction
69 with other risk factors, is related to occurrence of testicular
70 cancer.

71 Materials and methods

72 Search strategy

73 A literature search of original articles reporting on the rela-
74 tion between TML and specific conditions was performed
75 using MEDLINE/PubMed starting January 2013 until
76 January 2015. The included articles were published in the
77 period from 1998 to 2015. The following keywords were
78 used in the search strategy: testicular microlithiasis, micro-
79 lithiasis calcification. Review articles were used to iden-
80 tify other relevant studies through the snowball method.
81 All abstracts were read though and only English-language
82 articles were included. Relevant studies were selected

by reading the title and the abstract by two of the authors
(MRP and PJO).

Inclusion and exclusion criteria

85 Studies were included if TML was diagnosed by US and
86 a risk condition was reported. Studies were only eligible
87 if the particular risk condition was reported in more than
88 one article. There were no criteria on number of patients
89 enrolled in each study.
90

Included studies

91 The search strategy identified 344 abstracts, of which 282
92 were in English. Of these, a total of 31 studies met the
93 inclusion criteria. Two studies (Yee et al. [13] and Negri
94 et al. [14]) had data on more than one risk condition (cryp-
95 torchidism and infertility). Seven studies investigated only
96 children or adolescents and seven both men and boys and
97 17 studies investigated men only. Tables 1, 2, 3, 4, 5 and 6
98 present characteristics of the different studies.
99

Data extraction from the papers

100 Data were collected on study design, patient characteris-
101 tics, prevalence of TML, *p* value if available; country, num-
102 ber of patients enrolled and reported cancer cases.
103

Table 1 Characteristics of studies evaluating TML in Down syndrome

Author	Year	Country	Mean age (range)	<i>N</i> = DS	<i>N</i> = TML and DS (prevalence)	<i>N</i> = total TC ^{DS} /TC ^{DS} with TML
Cebeci et al. <i>N</i> = 50	2015	Turkey	2.4 (1–22)	25	9 (36.0 %)	0/0
Goede et al. <i>N</i> = 79	2012	Netherlands	8.8 (0–18)	79	18 (22.8 %)	0/0
Vachon et al. <i>N</i> = 92	2006	USA	10.7 (0–30)	92	27 (29.3 %)	1/1 ^a

DS Down syndrome, TC^{DS} testicular cancer in males with Down syndrome, TML testicular microlithiasis

^a Ninety-two patients with Down syndrome, and 200 healthy controls. In the healthy controls, 14 men had TML; no TCs were found in control cases. One Leydig cell tumour was found in a male with Down syndrome with TML after 4-year follow-up

Table 2 Characteristics of studies evaluating TML in McCune–Albright syndrome

Author	Year	Country	Mean age (range)	<i>N</i> = MAS	<i>N</i> = TML and MAS (prevalence)	<i>N</i> = total TC ^{MAS} /TC ^{MAS} with TML
Boyce et al. <i>N</i> = 54	2012	USA	NR (3–59)	54	13 (24.1 %)	1/0 ^a
Wasniewska et al. <i>N</i> = 40	2004	Italy	13.9 (5–21)	8	5 (62.5 %)	0/0

MAS McCune–Albright syndrome, TC^{MAS} testicular cancer in males with McCune–Albright syndrome, TML testicular microlithiasis

NR Not reported

^a One male with MAS was reported with an embryonal cell tumour, and 5 years later with a seminoma in the contralateral testis. There was no information on TML in this case

Table 3 Characteristics of studies evaluating TML in cryptorchidism

Author	Year	Country	Mean age (range)	N = C	N = TML and C (prevalence)	N = total TC ^C /TC ^C with TML
Cooper et al. N = 3370	2014	USA	11 (1–18)	9	9 (100 %)	10/3
Chiang et al. N = 31	2012	Singapore	NR (5–15)	12	12 (100 %)	0/0
Dutra et al. N = 1504	2011	Brazil	7.5 (1–5)	127	5 (3.9 %)	0/0
Yee et al. N = 1439	2011	Korea	19.1 (0–87)	310	7 (2.3 %)	NR
Goede et al. N = 501	2010	Netherlands	12.5 (3–29)	501	14 (2.8 %)	0/0
Negri et al. N = 2172	2008	Italy	37 (20–62)	232	23 (9.9 %)	NR
Kosan et al. N = 197	2007	Turkey	28.3 (NR)	8	2 (25 %)	NR
Konstantinos et al. N = 391	2006	Greece	37 (15–76)	36	2 (5.5 %)	0/0
Patel et al. N = 112	2005	USA	19.6 (18–29)	112	8 (7.1 %)	0/0

C cryptorchidism, NR not reported, TC^C testicular cancer in males with cryptorchidism, TML testicular microlithiasis

104 Statistics

105 Z-test was used to evaluate differences in proportions
106 between groups.

107 Results

108 In analysing the association between TML and possible
109 conditions, five conditions had been studied. Three stud-
110 ies referred to *Down syndrome*, two referred to *McCune–*
111 *Albright syndrome*, nine referred to *cryptorchidism*, seven-
112 teen referred to *infertility*, and two studies dealt with *familial*
113 *disposure to testicular cancer* (Tables 1, 2, 3, 4, 6). In the
114 following section, we discuss the relationship between TML
115 and malignancy in relation to these conditions (Fig. 1).

116 Down syndrome

117 The three studies concerning TML and Down syndrome
118 (DS) were conducted in children (Table 1). The boys with
119 Down syndrome had higher prevalence of TML than the
120 general healthy population. The prevalence of TML was
121 reported between 22.8 and 36.0 %, compared to 0–7 % in
122 healthy controls [15–17]. The overall prevalence of TML in
123 DS was 27.6 %. No case of testicular cancer was recorded
124 among 142 DS men with TML. Only one study found a tes-
125 ticular cancer (Leydig Cell tumour) in an individual with
126 DS and TML (1/54 = 1.9 %), and the cancer was diag-
127 nosed during the fourth year of follow-up.

McCune–Albright syndrome

McCune–Albright Syndrome (MAS) is a congenital dis-
ease characterised by polyostotic fibrous dysplasia, café-
au-lait pigmentation and early puberty. Two studies were
included concerning TML and MAS. Both studies included
boys and men (Table 2). The prevalence of TML in MAS
males was 24.1 % [18] and 62.5 % [19]. Combining both
studies, the prevalence was 29.0 %. One testicular cancer
(embryonal cell tumour) was reported among 62 cases of
MAS [18], with no known risk factors or TML.

Cryptorchidism

Our search resulted in nine studies of cryptorchidism and
TML (Table 3). In four series of cryptorchidism reported
the frequencies of TML were 100 % [20], 3.9 % [21],
2.8 % [22] and 7.1 % [23]. No testicular malignancy was
reported. One series [14] found an association of the previ-
ous cryptorchidism and an increased risk of testicular can-
cer (odds ratio 7.5), but there was no information linking
TML to the cancer cases (Table 3). In the study of Cooper
et al., nine patients with cryptorchidism and TML were
found, and three of these were diagnosed with intratubular
germ cell neoplasia [24].

Infertility

We included seventeen studies concerning infertility
(Table 4). The prevalence of TML in infertile men varied

Table 4 Characteristics of studies evaluating TML and male infertility

Author	Year	Country	Mean age (range)	N = infertile	N = TML in infertile (prevalence)	N = total TC ^I /TC ^I with TML
Jiang et al. N = 22	2012	China	31.6 (25–40)	22	22 (100 %)	0
La Vignera et al. N = 1056	2012	Italy	43.3 (0.3–87)	320	60 (18.8 %)	15/10 ^a
Yee et al. N = 1429	2011	Korea	19.1 (0–87)	60	10 (16.6 %)	47/10
Zhang et al. N = 34	2010	China	31.1 (NR)	34	17 (50 %)	0/0
Negri et al. N = 2172	2008	Italy	37 (19.8–61.9)	415	17 (4.1 %)	14/NR
Ou et al. N = 1978	2007	Taiwan	32 (1–88)	12	4 (33.3 %)	17/9 ^a
Parenti et al. N = 14	2007	Italy	NR (19–43)	2	0 (0 %)	11/2
Qublan et al. N = 384	2006	Jordan	31 (21–63)	234	23 (9.8 %)	0/0
Sakamoto et al. N = 969	2006	Japan	40.9 (20–97)	550	31 (5.6 %)	0/0
Sakamoto et al. N = 545	2006	Japan	35.8 (22–56)	545	30 (5–5 %)	1/0
Mazzilli et al. N = 303	2005	Italy	NR (29–51)	281	13 (4.6 %)	0/0
Brazao et al. N = 263	2004	Netherlands	NR (NR)	263	53 (20 %)	7 CIS/6 CIS ^a
Von Eckardstein et al. N = 1701	2001	Germany	NR (NR)	1399	32 (2.3 %)	NR/2 CIS ^a
Thomas et al. N = 159	2000	UK	NR (NR)	159	10 (6.3 %)	0/0
Pierik et al. N = 1372	1999	Netherlands	NR (20–58)	1372	12 (0.9 %)	7/0
Ganem et al. N = 22	1999	USA	29 (8–63)	5	5 (100 %)	8/2 ^a
Aizenstein et al. N = 180	1998	USA	37 (31–49)	180	5 (2.8 %)	0/0

NR not reported, CIS carcinoma in situ, TC^I testicular cancer, TML testicular microlithiasis

^a For cancer subtypes please refer to Table 5

Table 5 Cancer subtypes reported in patients with testicular tumours and TML

Cancer subtype	Risk factor				Total (%)
	Down syndrome	McCune–Albright syndrome	Cryptorchidism	Infertility	
Seminoma	–	–	6	24	30 (36)
Mixed germ cell tumour	–	–	6	11	17 (20)
Leydig cell tumour	1	–	–	8	9 (11)
Teratoma	–	–	2	4	6 (7)
Yolk sac tumour	–	–	1	1	2 (3)
Embryonal carcinoma	–	–	–	1	1 (1)
IGCN/CIS	–	–	3	15	18 (22)
Total	1	–	18	64	83

IGCN/CIS intratubular germ cell neoplasia/carcinoma in situ

Table 6 Characteristics of studies evaluating TML in males with familial disposition to testicular malignancy

Author	Year	Country	Mean age (range)	N = Cancer cases	N = TML (prevalence)	N = TC ^F /TC ^F with TML
Korde et al. N = 81	2008	UK	39 (NR)	48	23 (48 %)	0/0 ^a
Coffey et al. N = 328	2007	UK	47 (25–78)	169	62 (36.7 %)	NR ^b

NR not reported, TC^F testicular cancer in males with familial disposition, TML testicular microlithiasis

^a Forty-eight affected males and 33 unaffected male blood relatives from 31 multiple-case testicular germ cell tumour families. TML was found in 8 of 33 unaffected males and in 23 of 48 affected males

^b A total of 169 cancer cases found (76 seminoma, 92 non-seminoma and one of unknown origin) and four developed a second tumour (two seminoma and two CIS), but no information if any had TML. No cancers found in the 58 relatives, and 1 cancer was diagnosed in the 101 control cases, but no information if TML or not

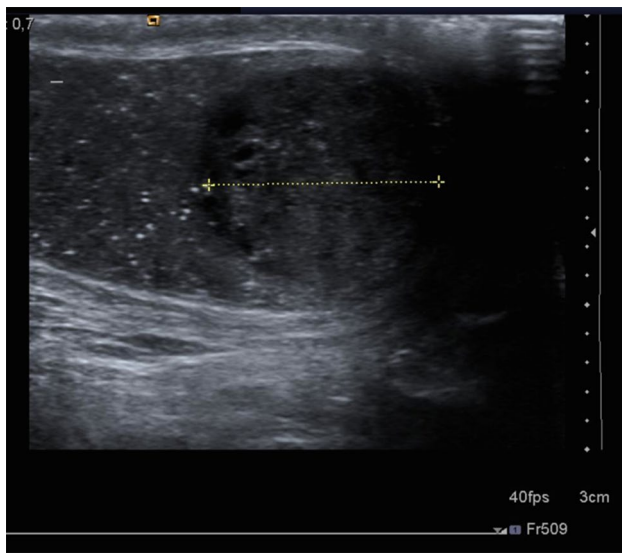


Fig. 1 An ultrasonography of a 16-year-old male with testicular cancer and multiple TML diagnosed in 2014 in our Department of Radiology. The longitudinal size of the tumour was 1.6 cm

153 between 0.9 and 18.8 %, compared to 2.3–9.8 % in studies
 154 who also included fertile men [14, 25–29]. By pooling the
 155 data, the overall prevalence of TML was 6.0 and 4.8 % in
 156 infertile and fertile men, respectively ($p < 0.05$). The rela-
 157 tion between testicular cancer and TML was inconsistently
 158 reported. In the following analysis, only studies reporting
 159 both cancer cases and TML are considered. In total, 44 can-
 160 cers were reported in 5092 infertile males (0.90 %) com-
 161 pared to 52 cancers in 2889 fertile men (1.8 %) ($p < 0.01$)
 162 [13, 14, 25–35]. Analysing the relation between TML
 163 and testicular cancer (including CIS) in infertile men, the
 164 pooled data revealed that the cancer prevalence of infertili-
 165 ty plus TML was 10.9 and 1.6 % in case of infertility with-
 166 out TML ($p < 0.001$). Correspondingly, the cancer preva-
 167 lence of fertility plus TML was 6.1 % compared to 2.6 %
 168 in fertile men without TML (NS). Comparing cancer preva-
 169 lence between infertility plus TML and fertility plus TML,

there was only a weak trend towards a higher cancer rate
 among the infertile TML men. Cancer subtypes in infertile
 men with TML are presented in Table 5.

Familial disposition to testicular cancer

Two studies concerning TML and family history of tes-
 ticular cancer were identified (Table 6). Both studies were
 conducted prospectively in adults with TML prevalence
 between 48.0 to 36.7 %. Korde et al. [36] found that TML
 was more frequent in the contralateral testis of men with a
 history of testicular germ cell tumours and that TML was
 more prevalent among family members than previously
 described in the general population. Eighty-one men (48
 with testicular cancer and their 33 unaffected relatives)
 from 31 families were investigated; 14 had brothers with
 testicular cancer; 6 had fathers with testicular cancer; 3
 cousins with testicular cancer; and 8 had more than two
 affected family members with testicular cancer. The preva-
 lence of TML was significantly higher among cases than
 among unaffected men (48 vs. 24 %; $p = 0.04$). No can-
 cer was found in the group of relatives with TML (8 of 33
 relatives).

Coffey et al. [37] analysed ultrasound data of 328 men
 (169 testicular cancer cases; 58 relatives to the cases; 101
 controls). A greater concordance for TML in relatives of
 testicular cancer cases than would be expected was dem-
 onstrated. No testicular cancer case was found in the group
 of relatives, whereas one testicular cancer was found in the
 control group and three in the remaining testis of the case
 group (Table 5). Overall TML was present with a higher
 frequency in cases with prior testicular cancer (36.7 %)
 compared to controls (17.8 %).

Discussion

Males with Down syndrome and McCune–Albright syn-
 drome appear to have the highest frequencies of TML,



204 ranging from 23 to 63 %. The present analysis revealed that
 205 in these conditions there seemed to be no relation between
 206 TML and development of testicular cancer. This observa-
 207 tion questions TML as an independent risk factor for tes-
 208 ticular malignancy. Males with Down syndrome had higher
 209 risk of testicular cancer [38, 39], and possibly decreased
 210 spermatogenesis [40], but from the present analysis TML
 211 does not seem to be related to higher risk of malignancy.
 212 Individuals with MAS are often affected by hormonal dis-
 213 orders such as early puberty, which also is the case among
 214 males with Down syndrome. This association between
 215 TML and chromosomal abnormalities may indicate TML
 216 as part of a degenerative process of the testis.

217 Cryptorchidism is associated with increased risk of tes-
 218 ticular cancer [41–44]. As seen from the present analysis,
 219 there is, however, no clear evidence whether TML and
 220 cryptorchidism or TML and testicular cancer are inter-
 221 linked. However, as TML-related cancer risk in cryptor-
 222 chidism was inconsistently reported, further studies are
 223 warranted.

224 Infertility is a risk factor for testicular cancer [45–47].
 225 Numerous studies have suggested the association between
 226 testicular malignancy, TML and infertility [7, 36, 37, 48].
 227 The prevalence of TML in infertile men is generally higher
 228 than in fertile men [6–9, 13, 30]. Our analysis showed
 229 that TML was associated with an approximated sevenfold
 230 higher cancer risk compared to infertile men without TML
 231 (10.9 vs. 1.6 %), confirming that TML, infertility and tes-
 232 ticular cancer seem to be interlinked. Thus, TML may be
 233 an indicator of a “testicular dysgenesis syndrome”, consist-
 234 ing of infertility, cryptorchidism, CIS and testicular cancer
 235 [49].

236 Families with both TML and testicular malignancy have
 237 been reported [36, 37], as well as TML in siblings [50].
 238 In the two included studies, 28 relatives with TML were
 239 found, but no cancer cases reported. The relative risk of
 240 developing testicular cancer if ones brother is diagnosed
 241 with testicular germ cell tumour is 8–10 times higher [51,
 242 52]. A higher TML frequency among family members
 243 may be due to both genetics and shared exposures. Preva-
 244 lence of TML in male blood relatives has been reported as
 245 high as 48 % [37]. The high prevalence may be an indica-
 246 tor of a genetic factor rather than exposure due to the high
 247 prevalence in TML families. Also, TML cluster in certain
 248 families has been suggested to be linked to development of
 249 testicular germ cell tumours [36, 37]. The present analysis
 250 questions this, since no testicular cancers were reported
 251 among TML blood relatives. Further studies are needed
 252 to clarify whether a family relation with regard to TML
 253 increases risk of testicular cancer.

254 Our review highlights that TML cannot be viewed
 255 isolated, as current clinical practice has tended to do.
 256 Decisions on clinical management should be based on

257 associated risk factors, a point of view that has been sup-
 258 ported by recent papers [53, 54]

259 With regard to cancer subtypes, data in the literature
 260 are sparse, and as evident from our analysis, cancer sub-
 261 types were inconsistently reported (Table 5). Recently, it
 262 was suggested that there might be a positive association
 263 between TML and seminoma, and a negative association
 264 between TML and embryonal cell carcinoma. This was
 265 confirmed in our review, in which seminoma accounted
 266 for 36 % of cancer cases reported with TML compared
 267 to 1 % for embryonal carcinoma (Table 5). There appears
 268 to be no association between TML, age and tumour size
 269 [55].

270 Holm et al. [56] compared clinical and histological data
 271 regarding the contralateral testicle in a population of men
 272 diagnosed with testicular germ cell cancer to find features
 273 associated with an increased risk of bilateral neoplasia.
 274 Ultrasound examination of the contralateral testicle was
 275 performed in 64 cases. They found that the frequency of
 276 TML seen on ultrasound was significantly higher among
 277 patients with CIS compared to those with a normal echo
 278 pattern. They concluded that the finding of contralateral
 279 TML on ultrasound in a patient with testicular germ cell
 280 cancer increases the risk of harbouring CIS in that testicle
 281 (odds ratio 28.6; CI 4.8–170.4). On the other hand, a nor-
 282 mal ultrasound pattern does not exclude the risk of CIS and
 283 as evident from the present analysis, whether sonographic
 284 TML found in other subgroups of patients or in men from
 285 the general population also implies an increased risk of
 286 testicular CIS remains questionable. In the present review
 287 CIS/Intratubular Germ Cell Neoplasia accounted for 22 %
 288 of reported tumours with TML.

289 The main limitation of the present analysis is that the
 290 included studies had different objectives, which may have
 291 resulted in selection bias and misrepresentation of the rela-
 292 tion between TML and testicular cancer. Furthermore,
 293 results in adults and boys may not be comparable.

294 Data in the literature seem to support the conclusion that
 295 TML is not an independent risk factor for testicular can-
 296 cer. In male infertility, TML appears to be related to an
 297 increased risk possibly as part of a testicular dysgenesis
 298 syndrome. Many of the findings may simply be due to sur-
 299 veillance bias as some groups are further examined.

300 Further longitudinal clinical studies are required to
 301 evaluate the true relationship between TML and testicular
 302 cancer. Evaluation of other imaging modalities, for instance
 303 MRI, may help in defining subgroups of TML patients at
 304 special risk of malignant development.

306 Compliance with ethical standards

307 **Conflict of interest** The authors declare that they have no conflicts
 308 of interest.

309 **References**

- 310 1. Pedersen MR, Graumann O, Horlyck A et al (2015) Inter- and intraobserver agreement in detection of testicular microlithiasis with ultrasonography. *Acta Radiol*. doi:10.1177/0284185115604516
- 311
- 312 2. Backus ML, Mack LA, Middleton WD et al (1994) Testicular microlithiasis: imaging appearances and pathologic correlation. *Radiology* 192:781–785
- 313
- 314 3. Peterson AC, Bauman JM, Light DE et al (2001) The prevalence of testicular microlithiasis in an asymptomatic population of men 18 to 35 years old. *J Urol* 166:2061–2064
- 315
- 316 4. Serter S, Gümüş B, Unlü M et al (2006) Prevalence of testicular microlithiasis in an asymptomatic population. *Scand J Urol Nephrol* 40:212–214
- 317
- 318 5. Goede J, Hack WWM, van der Voort-Doedens LM et al (2009) Prevalence of testicular microlithiasis in asymptomatic males 0 to 19 years old. *J Urol* 182:1516–1520
- 319
- 320 6. Derogee M, Bevers RFM, Prins HJ et al (2001) Testicular microlithiasis, a premalignant condition: prevalence, histopathologic findings, and relation to testicular tumor. *Urology* 57:1133–1137
- 321
- 322 7. Costabile RA (2007) How worrisome is testicular microlithiasis? *Curr Opin Urol* 17:419–423
- 323
- 324 8. Miller FNAC, Sidhu PS (2002) Does testicular microlithiasis matter? A review. *Clin Radiol* 57:883–890
- 325
- 326 9. Kim B, Winter TC 3rd, Ryu JA (2003) Testicular microlithiasis: clinical significance and review of the literature. *Eur Radiol* 13:2567–2576
- 327
- 328 10. Bach AM, Hann LE, Hadar O et al (2001) Testicular microlithiasis: what is its association with testicular cancer? *Radiology* 220:70–75
- 329
- 330 11. Deganello A, Svasti-Salee D, Allen P et al (2012) Scrotal calcification in a symptomatic paediatric population: prevalence, location, and appearance in a cohort of 516 patients. *Clin Radiol* 67:862–867
- 331
- 332 12. Middleton WD, Teefey SA, Santillan CS (2002) Testicular microlithiasis: prospective analysis of prevalence and associated tumor. *Radiology* 224:425–428
- 333
- 334 13. Yee WS, Kim YS, Kim SJ et al (2011) Testicular microlithiasis: prevalence and clinical significance in a population referred for scrotal ultrasonography. *Korean J Urol* 52:172–177
- 335
- 336 14. Negri L, Benaglia R, Fiamengo B et al (2008) Cancer risk in male factor-infertility. *Placenta* 29(Suppl B):178–183
- 337
- 338 15. Cebeci AN, Aslanger A, Ozdemir M (2015) Should patients with Down syndrome be screened for testicular microlithiasis? *Eur J Pediatr Surg* 25:177–180
- 339
- 340 16. Vachon L, Fareau GE, Wilson MG, Chan LS (2006) Testicular microlithiasis in patients with down syndrome. *J Pediatr* 149:233–236
- 341
- 342 17. Goede J, Weijerman ME, Broers CJ et al (2012) Testicular volume and testicular microlithiasis in boys with Down syndrome. *J Urol* 187:1012–1017
- 343
- 344 18. Boyce AM, Chong WH, Shawker TH et al (2012) Characterization and management of testicular pathology in McCune–Albright syndrome. *J Clin Endocrinol Metab* 97:E1782–E1790
- 345
- 346 19. Wasniewska M, De Luca F, Bertelloni S et al (2004) Testicular microlithiasis: an unreported feature of McCune–Albright syndrome in males. *J Pediatr* 145:670–672
- 347
- 348 20. Chiang L, Yap T, Asiri M et al (2012) Implications of incidental finding of testicular microlithiasis in paediatric patients. *J Pediatr Urol* 8:162–165
- 349
- 350 21. Dutra RA, Perez-bóscollo AC, Melo EC, Cruvinel JC (2011) Clinical importance and prevalence of testicular microlithiasis in pediatric patients. *Acta Cir Bras* 26:387–390
- 351
- 352 22. Goede J, Hack WWM, van der Voort-Doedens LM et al (2010) Testicular microlithiasis in boys and young men with congenital or acquired undescended (ascending) testis. *J Urol* 183:1539–1544
- 353
- 354 23. Patel RP, Kolon TF, Huff DS et al (2005) Testicular microlithiasis and antisperm antibodies following testicular biopsy in boys with cryptorchidism. *J Urol* 174:2008–2010
- 355
- 356 24. Cooper ML, Kaefer M, Fan R et al (2014) Testicular microlithiasis in children and associated testicular cancer. *Radiology* 270:857–863
- 357
- 358 25. Qublan HS, Al-Okoor K, Al-Ghoweri AS, Abu-Qamar A (2007) Sonographic spectrum of scrotal abnormalities in infertile men. *J Clin Ultrasound* 35:437–441
- 359
- 360 26. Mazzilli F, Delfino M, Imbrogno N et al (2005) Seminal profile of subjects with testicular microlithiasis and testicular calcifications. *Fertil Steril* 84:243–245
- 361
- 362 27. de Gouveia Brazao CA, Pierik FH, Oosterhuis JW et al (2004) Bilateral testicular microlithiasis predicts the presence of the precursor of testicular germ cell tumors in subfertile men. *J Urol* 171:158–160
- 363
- 364 28. Sakamoto H, Shichizyou T, Saito K et al (2006) Testicular microlithiasis identified ultrasonographically in Japanese adult patients: prevalence and associated conditions. *Urology* 68:636–641
- 365
- 366 29. von Eckardstein S, Tsakmakidis G, Kamischke A et al (2001) Sonographic testicular microlithiasis as an Indicator of premalignant conditions in normal and infertile men. *J Androl* 22:818–824
- 367
- 368 30. La Vignera S, Condorelli R, Vicari E et al (2012) Testicular microlithiasis: analysis of prevalence and associated testicular cancer in central-eastern Sicilian andrological patients. *Andrologia* 44(Suppl 1):295–299
- 369
- 370 31. Sakamoto H, Saito K, Shichizyo T et al (2006) Color Doppler ultrasonography as a routine clinical examination in male infertility. *Int J Urol* 13:1073–1078
- 371
- 372 32. Ou SM, Lee SS, Tang SH (2007) Testicular microlithiasis in Taiwanese men. *Arch Androl* 53:339–344
- 373
- 374 33. Parenti GC, Zago S, Lusa M et al (2007) Association between testicular microlithiasis and primary malignancy of the testis: our experience and review of the literature. *Radiol Med* 112:588–596
- 375
- 376 34. Ganem JP, Workman KR, Shaban SF (1999) Testicular microlithiasis is associated with testicular pathology. *Urology* 53:209–213
- 377
- 378 35. Pierik FH, Dohle GR, Van Muiswinkel JM et al (1999) Is routine scrotal ultrasound advantageous in infertile men? *J Urol* 162:1618–1620
- 379
- 380 36. Korde LA, Premkumar A, Mueller C et al (2008) Increased prevalence of testicular microlithiasis in men with familial testicular cancer and their relatives. *Br J Cancer* 99:1748–1753
- 381
- 382 37. Coffey J, Huddart RA, Elliott F et al (2007) Testicular microlithiasis as a familial risk factor for testicular germ cell tumour. *Br J Cancer* 97:1701–1706
- 383
- 384 38. Patja K, Pukkala E, Sund R et al (2006) Cancer incidence of persons with Down syndrome in Finland: a population-based study. *Int J Cancer* 118:1769–1772
- 385
- 386 39. Kuroda N, Amano S, Shiotsu T et al (2007) Mixed testicular germ cell tumor in an adult with cryptorchidism and Down's syndrome. *APMIS* 115:1292–1295
- 387
- 388 40. Pradhan M, Dalal A, Khan F, Agrawal S (2006) Fertility in men with Down syndrome: a case report. *Fertil Steril* 86(1765):e1–e3
- 389
- 390 41. Ferguson L, Agoulnik AI (2013) Testicular cancer and cryptorchidism. *Front Endocrinol (Lausanne)*. doi:10.3389/fendo.2013.00032
- 391
- 392 42. Hutson JM, Balic A, Nation T, Southwell B (2010) Cryptorchidism. *Semin Pediatr Surg* 19:215–224
- 393
- 394
- 395
- 396
- 397
- 398
- 399
- 400
- 401
- 402
- 403
- 404
- 405
- 406
- 407
- 408
- 409
- 410
- 411
- 412
- 413
- 414
- 415
- 416
- 417
- 418
- 419
- 420
- 421
- 422
- 423
- 424
- 425
- 426
- 427
- 428
- 429
- 430
- 431
- 432
- 433
- 434
- 435

- 436 43. Husmann DA (2005) Cryptorchidism and its relationship to tes- 459
 437 ticular neoplasia and microlithiasis. *Urology* 66:424–426 460
 438 44. Giwercman A, Grindsted J, Hansen B et al (1987) Testicular can- 461
 439 cer risk in boys with maldescended testis: a cohort study. *J Urol* 462
 440 138:1214–1216 463
 441 45. Walsh TJ, Croughan MS, Schembri M et al (2009) Increased risk 464
 442 of testicular germ cell cancer among infertile men. *Arch Intern* 465
 443 *Med* 169:351–356 466
 444 46. Møller H, Skakkebaek NE (1999) Risk of testicular cancer in 467
 445 subfertile men: case-control study. *BMJ* 318:559–562 468
 446 47. Doria-Rose VP, Biggs ML, Weiss NS (2005) Subfertility and 469
 447 the risk of testicular germ cell tumors (United States). *Cancer* 470
 448 *Causes Control* 16:651–656 471
 449 48. van Casteren NJ, Looijenga LH, Dohle GR (2009) Testicular 472
 450 microlithiasis and carcinoma in situ overview and proposed clinical 473
 451 guideline. *Int J Androl* 32:279–287 474
 452 49. Hoei-Hansen CE, Sommer P, Meyts ER, Skakkebaek NE 475
 453 (2005) A rare diagnosis: testicular dysgenesis with carcinoma 476
 454 in situ detected in a patient with microlithiasis. *Asian J Androl* 477
 455 7:445–447 478
 456 50. Thomas D, Vlachopapadopoulou E, Papadakis V et al (2008) 479
 457 Testicular microlithiasis in siblings: clinical implications. *Pediatr*
 458 *Radiol* 38:688–690
51. Heimdal K, Olsson H, Tretli S et al (1997) A segregation analy- 459
 52. sis of testicular cancer based on Norwegian and Swedish fami- 460
 53. lies. *Br J Cancer* 75:1084–1087 461
 54. Hemminki K, Li X (2004) Familial risk in testicular cancer as 462
 55. a clue to a heritable and environmental aetiology. *Br J Cancer* 463
 90:1765–1770 464
 56. Patel KV, Navaratne S, Bartlett E et al (2016) Testicular Micro- 465
 lithiasis: is sonographic surveillance necessary? Single centre 466
 14 year experience in 442 patients with testicular microlithiasis. 467
Ultraschall Med 37:68–73 468
 Richenberg J, Belfield J, Ramchandani P et al (2015) Testicular 469
 microlithiasis imaging and follow-up: guidelines of the ESUR 470
 scrotal imaging subcommittee. *Eur Radiol* 25:323–330 471
 Sharmeen F, Rosenthal MH, Wood MJ et al (2015) Relation- 472
 ship between the pathologic subtype/initial stage and microliths 473
 in testicular germ cell tumors. *J Ultrasound Med* 34:1977–1982. 474
 doi:10.7863/ultra.14.09031 475
 Holm M, Hoei-Hansen CE, Rajpert-De Meyts E, Skakkebaek 476
 NE (2003) Increased risk of carcinoma in situ in patients with 477
 testicular germ cell cancer with ultrasonic microlithiasis in the 478
 contralateral testicle. *J Urol* 170:1163–1167 479