

Testicular microlithiasis imaging and follow-up: guidelines of the ESUR scrotal imaging subcommittee

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Abstract

Objectives The subcommittee on scrotal imaging, appointed by the board of the European Society of Urogenital Radiology (ESUR), have produced guidelines on imaging and follow-up in testicular microlithiasis (TML).

Methods The authors and a superintendent university librarian independently performed a computer-assisted literature search of medical databases: MEDLINE and EMBASE. A further parallel literature search was made for the genetic conditions Klinefelter's syndrome and McCune-Albright syndrome.

Results Proposed guidelines are: follow-up is not advised in patients with isolated TML in the absence of risk factors (see Key Points below); annual ultrasound (US) is advised for patients with risk factors, up to the age of 55; if TML is found with a testicular mass, urgent referral to a specialist centre is advised. **Conclusion** Consensus opinion of the scrotal subcommittee of the ESUR is that the presence of TML alone in the absence of other risk factors is not an indication for regular scrotal US, further US screening or biopsy. US is recommended in the follow-up of patients at risk, where risk factors other than microlithiasis are present. Risk factors are discussed and the

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literature and recommended guidelines are presented in this article.

Key Points

- *Follow up advised only in patients with TML and additional risk factors.*
- *Annual US advised for patients with risk factors up to age 55.*
- *If TML is found with testicular mass, urgent specialist referral advised.*
- *Risk factors – personal/ family history of GCT, maldescent, orchidopexy, testicular atrophy.*

Keywords Testicular microlithiasis · Testis microcalcification · Germ cell tumour · Ultrasound

Introduction

Testicular microlithiasis (TML) is a common finding on scrotal ultrasound (US), but its significance remains controversial. In September 2012, the board of the European Society of Urogenital Radiology (ESUR) established a subcommittee on scrotal imaging which was asked to produce guidelines on imaging and follow-up in TML.

Process

The guidelines were written by consensus, based on expert opinion from members of the Scrotal Imaging Working Group of the ESUR, and following review of the literature. This consensus was reached after three face-to-face meetings of the subcommittee, communication amongst the subcommittee members by email and sharing of research findings and papers. Preliminary findings were discussed at committee meetings and all members agreed on the guidelines proposed below.

The authors and a superintendent university librarian independently performed a computer-assisted literature search of medical databases: MEDLINE (January 1951 to date) and EMBASE (January 1974 to date). The search parameters are summarised in Table 1. A further, parallel literature search was

made for the genetic conditions Klinefelter's syndrome and McCune-Albright syndrome, summarised in Table 2. All the references were imported into Endnote Professional Edition Version 7 © 1988–2013 Thompson Reuters and each study reviewed.

Results

The presence of TML alone in the absence of other risk factors is not an indication for regular scrotal US, further US screening or biopsy. US may be recommended in the follow-up of patients at risk, when risk factors other than microlithiasis are present.

Testicular microlithiasis (TML)

TML is a condition in which calcium deposits form in the lumina of seminiferous tubules or arise from the tubular basement membrane components [1–4]. The histology shows micro calcium deposits with surrounding fibrosis. The microliths do not cause pain or symptoms and are impalpable. TML is an imaging diagnosis, almost invariably made with testicular US, where an echogenic non-shadowing focus less than 3 mm will be seen.

Two possible definitions for TML have been proposed: five or more microliths in the whole testis [5, 6], or five or more microliths per field of view. The former is more straightforward— if there are five foci in imaging the testis, there is TML. The latter definition captures the idea of clustering better, but not rigorously. Clustering may be important, and in fact, five microliths per field in a cluster may be more worrying than 10 scattered throughout the testis. The clustering may herald a dysgenic 'unstable' area in the testis, wherein carcinoma in situ (CIS) can develop. In any case, a cluster of five microliths would fulfil the first definition; the committee declared an overwhelming preference for the second definition. The microcalcifications are not visible on MRI.

Table 1 Literature search parameters

Search parameter	MEDLINE	EMBASE
Keyword	TM or lithiasis or microlithiasis or microcalcification	TM or lithiasis or microlithiasis or microcalcification
And keyword	Testicular or testicle or testis	Testicle or testis
And keyword	Adult or adult (age group)	Adult or adult (age group)
Mesh	Lithiasis Testicular diseases Testis	Testis disease

Table 2 MEDLINE literature search summary re genetic conditions relevant to TML

Search parameter no.	Term	Results
5	TESTIS/ OR TESTICULAR DISEASES/	59,804
6	(testicular OR testis OR testes OR testic* OR scrotum OR scrotal).ti,ab	99,356
7	5 OR 6	116,917
8	(KLINEFELTER OR “MCCUNE-ALBRIGHT”).ti	1,097
9	exp KLINEFELTER SYNDROME/	3,398
10	exp FIBROUS DYSPLASIA, POLYOSTOTIC/	1,046
11	8 OR 9 OR 10	4,533
12	7 AND 11	730
13	12 [Limit to: Publication Year 2003–Current]	212

Testicular ultrasound

The testes are ideally suited to US evaluation due to their superficial position within the scrotum, which permits imaging with high frequency linear array transducers, producing images of high resolution. A number of advances in US technology in recent years have further increased US image quality; it is likely that this has resulted in increased detection of testicular microliths. The major advance in image quality has been through improved transducer technology. Transducer frequency has been increased such that modern small-part linear array transducers will typically have a centre frequency of at least 12 MHz producing images of high spatial resolution. Development of high bandwidth transducers has also permitted adoption of harmonic imaging technology where the fundamental (transmitted) frequency is removed from the received signal and the image formed from harmonic frequencies; this contributes to higher image quality by reduction of artefacts due to clutter from beam side lobes and reverberation artefacts. A number of innovations in post processing have been developed to increase contrast resolution and reduce speckle. These include spatial compounding and frequency compounding. The increase in computing power has underpinned these developments, enabling large volumes of data to be quickly processed. This has allowed the development of a wide variety of post processing algorithms to further improve image quality.

When evaluating the testes, US should be performed with a high frequency transducer of at least 15 MHz. A lower frequency transducer may be considered for large scrotums where US beam penetration may be an issue. We concur with the European Association of Urology (EAU) statement ‘The incidence (of testicular microlithiasis) reported seems to be higher with high-frequency ultrasound machines’ [<http://www.ncbi.nlm.nih.gov/pubmed/10524881>].

TML may be detected in different clinical scenarios which may require a tailored approach for follow-up. When TML is discovered, it may be useful to complete a checklist for risk factors at the end of the US examination to decide which

recommendation to follow. A sample checklist is provided as Appendix 2.

Some common clinical scenarios where TML may be discovered include:

1. As an isolated finding at scrotal US, in the absence of any risk factors (Table 3).

The current recommendations, including those of the EAU [7–10] are that the presence of microlithiasis alone is not an indication for a regular scrotal US [9], and that in the absence of other risk factors, TML is not an indication for biopsy or further US screening [8, 10].

The patient may be discharged with advice about performing monthly scrotal self-examination and a patient information leaflet (Appendix 1). The rationale for this approach is discussed further below.

2. When TML is discovered in the setting of another risk factor, regardless of whether it is unilateral or bilateral (Table 3), and provided that there is no focal lesion within either testis, the following may be advised:

- a. Annual follow-up with US.
- b. Monthly self-examination: the patient may need to be taught the procedure in the urology clinic.
- c. If self-examination reveals a new mass within the scrotum, there should be direct access to fast track US, without the need for repeat clinical referral.

An important advantage of the annual surveillance is to maintain the patient’s engagement with the

Table 3 Risk factors that warrant follow-up of men with TML

Previous germ cell tumour
History of maldescent
History of orchidopexy
Atrophy <12 ml volume
History of germ cell tumour in 1st degree relative

process, as indefinite self-examination without intermittent contact with medical care is likely to fail.

3. If TML is discovered together with a focal testicular mass/ marked hypoechoic area, immediate referral should be made to a specialist urology centre.
4. If there are too many microliths to adequately assess the testicular parenchyma, or if TML appears clearly asymmetric with alterations of echotexture, guidelines suggest that referral is made to a specialist centre.

Follow-up is recommended up to the age of 55 years, based on European data on the incidence of testicular cancer by age in male populations from UK, France, Greece and Poland. However, doubt exists whether the incidental detection of a subclinical mass on annual screening US confers any survival advantage over early clinical detection achieved by regular self-examination [11].

On referral to a specialist centre, depending on local practice, further tests may include:

- a. Measurement of tumour markers
- b. Further imaging, such as gadolinium-enhanced MRI or contrast enhanced US
- c. Surveillance US
- d. Surgical biopsy or orchidectomy

Testicular macrocalcification, that is any intratesticular focus of coarse calcification (larger than TML), separate from any intratesticular mass, may also be found during a testicular US. It has been suggested that patients with any intratesticular calcification should be considered to be at higher risk of a co-existing testicular malignant lesion, and possibly also of developing a neoplasm in the future [12]. Recommendations for surveillance of testicular macrocalcification lie outside the remit of this paper.

MRI

MRI has no direct role in the monitoring of TML and microliths are not visible on MRI. If an intratesticular mass is suspected and US findings are indeterminate, MRI may be used as a problem-solving modality.

Evidence: risk factors

A helpful summary of the risk factors has been presented by Manecksha and Fitzpatrick [13].

Testicular dysgenesis syndrome (TDS)

At the turn of the millennium, around the same time that TML was being proposed as a premalignant condition, papers were

published advocating the concept of testicular dysgenesis syndrome.

‘There is evidence that poor semen quality, testicular cancer, undescended testes and hypospadias are symptoms of one underlying entity, testicular dysgenesis syndrome (TDS), which may be increasingly common due to adverse environmental influences.’ The same authors asserted that there was increasing evidence of the importance of TDS in initiating testicular germ cell tumour (GCT) and that it was also associated with microlithiasis [14–16]. Further evidence for the TDS hypothesis came from a UK-based meta-analysis [17] as well as a 2009 review [18] that concluded that ‘Dysgenetic testes often have an irregular ultrasound pattern, where microliths may also be visible. However, the cause of TDS in humans remains to be determined.’

More recently, and mirroring the move away from insisting that TML is premalignant, reports challenge the TDS model. Epidemiological studies provide little support for existence of a widespread TDS because there are no consistent non-causal associations between its different manifestations. There is furthermore little evidence of shared causes between the alleged components of the syndrome [19–21]. A Norwegian study gauging relative fertility between men with GCT and matched control concluded that fatherhood was slightly more frequent among men developing testicular cancer (TC) than in controls. Prediagnosis fertility rates of men who developed TC were similar to those of age-matched men from the general population. Interestingly, men developing TC in both testicles did not have inferior fatherhood rates before diagnosis. These results challenge the appropriateness of the TDS which would predict that infertility would be higher in those predisposed by virtue of TDS to GCT [1].

History of germ cell tumour

Patients with a history of prior malignancy may fall into the following categories:

Family history, 1st degree male relative

Approximately 1.4 % of newly diagnosed GCT patients report a positive family history. The relative risk to a brother of a GCT case is 8–10 and the relative risk to a father/son of a GCT case is 4–6. Moreover, a 37/67.5-fold elevated risk of GCT in dizygotic/monozygotic twin brothers of men with GCT has been reported [22]. In the nationwide Swedish Family-Cancer Database study to analyse the risk for testicular cancer by Hemmink that included 4,856 patients with testicular cancer, aged 0–70 years, standardised incidence ratios for familial risk were 3.8-fold when a father and 7.6-fold when a brother had testicular cancer [23].

Age at diagnosis is 2–3 years younger for familial versus sporadic cases. Mai et al. reported that familial cases on

average were diagnosed 2–3 years younger than population cases, with seminoma demonstrating a larger difference [24].

TML is significantly more common among family members of men with GCT than in the general population [22, 25, 26].

Maldescent and/or orchidopexy

These are established as independent risk factors for developing GCTs even in the absence of TML.

Reduced volume of testis

Testicular atrophy should not just be based on testicular volume measurement as testicular morphology is also important in recognition of this condition in ‘acquired’ atrophy rather than in ‘primary hypoplasia’. For patients up to 18 years of age, normative values have been provided by Goede et al. [27]. Beside evaluation of the volume, a difference greater than 20 % between the volume of the two testes should also be considered, to assess atrophy. It is worth noting that the left testis is usually smaller than the right testis.

The size of testes in many publications is evaluated by comparison with some models (Prader orchidometer)—the method overestimates the testicular volume by about 20–25 %, even if it correlates very strongly with the US volumetry. Measurements in US are used to measure the volume, but there are also several formulae. For this

document, the normal mean testicular volume is estimated at 18 ml (12–30 ml) with the interpretation that a testis less than 12 ml in volume should be considered as small. Accepting that it may not be routine practice to measure the testicular volume in each case, volumetry should be performed if the maximum testicular dimension is 35 mm or less.

Referred for scrotal ultrasound with relevant genetic disorder

Klinefelter’s syndrome

Sporadic case reports of TML in Klinefelter’s syndrome have been published, although there is no evidence that the incidence is higher than background. The majority of patients with this syndrome have infertility and/or testicular atrophy [28], and TML in association with atrophy should trigger surveillance. In the setting of infertility and TML but otherwise normal scrotal US findings, management should be as for the general population. Incidental testicular nodules (small nodules) are seen more frequently in patients with Klinefelter’s syndrome than in the general population, and most nodules represent benign Leydig cell nodules/hyperplasia.

Testicular pathology in McCune-Albright syndrome

The incidence of gonadal pathology in McCune-Albright syndrome is equal in men and women. Testicular abnormality

Table 4 Summary of ESUR guidelines on imaging and follow-up in testicular microlithiasis

US finding	<5 ML per FoV	>5 ML per FoV	Diffuse ^a	<5 ML per FoV but ≥5 total ^b
Normal testis, no risk factor	Discharge	Discharge	Annual US	Discharge with open access
Normal testes but prior GCT ^c , maldescent, orchidopexy or atrophic testis	GCT under oncology surveillance	F/U annual US	F/U annual US	GCT under oncology surveillance Maldescent, orchidopexy, atrophy: D/C with advice
Genetic disease (Klinefelter)	Maldescent, orchidopexy, atrophy: D/C with advice	F/U ultrasound at 6 & 12 months looking for nodule >3 mm, D/C if none detected	Refer to specialist	D/C
Focal lesion	F/U US at 6 & 12 months looking for a nodule >3 mm, discharge if none detected	F/U at 6 & 12 months looking for nodule >3 mm, D/C home if none detected		
Macrocalcification	Refer to specialist centre (for urology ± oncology input) Consider close follow-up (4–6 weekly), MRI with contrast, biopsy or orchidectomy NOTE: Association of microliths and hypoechoic region suggestive of seminoma or burned out GCT irrespective of number NOTE: Clustering of microliths adjacent to a focal non-cystic lesion is highly suggestive of GCT	As for focal lesion above		

RF risk factors which include previous malignancy, maldescent, small testis, orchidopexy, TML testicular microlithiasis, 5 or more microcalcifications per field of view, FoV field of view, D/C discharge from follow-up with advice about self-examination, F/U follow-up, MRI scrotal MRI with gadolinium sequences, CEUS contrast enhanced (microbubble) ultrasound, US scrotal ultrasound, GCT germ cell tumour, ML microliths

^a Often associated with atrophy and infertility

^b Very unlikely in reality to have >10 ml in total, as would then be ≥5 in a FoV

^c Men with prior history of GCT will be under surgical/oncological review

is seen on US in about 80 % including 30 % with microlithiasis and 11 % focal calcifications [29, 30]. The predominant histopathological finding is Leydig cell hyperplasia, which carries a low risk of malignant transformation and can be managed conservatively. Recommendations for this condition, and for disparate other syndromes including congenital adrenal hyperplasia, are the same as for the general population.

Referred for scrotal ultrasound with infertility

The additional risk, if any, of GCT in men with subfertility, who on scrotal US have TML, is hard to determine, not least because of lack of subclassification within the literature [31]. The group that may warrant follow-up are those with primary infertility, non-obstructive and non-endocrine i.e. testicular aetiology. In this group, the relationship between TML and infertility is unclear, but may relate to dysgenesis of the testes, with degenerate cells being sloughed inside an obstructed seminiferous tubule and failure of the Sertoli cells to phagocytose the debris. Subsequently, calcification occurs [18, 32].

The majority of focal lesions discovered during US for infertility are benign [33].

Paediatric population [33–37]

Scrotal US may be performed in children/adolescents for atrophy, maldescent, in those with a syndrome or in patients with clinical symptoms [34–38]. Recognition of TML in these groups should be managed as follows:

1. Atrophy [27]: annual US follow-up, inform parents/guardians and teach scrotal examination
2. Maldescent/post orchidopexy: annual US follow-up, inform parents/guardians and teach scrotal examination
3. Syndrome: see section above
4. Symptoms: as for general recommendations

Testicular biopsy in TML: recommendations

Patients with small or atrophic testes with microcalcifications/microliths or an irregular echo pattern on US are at increased risk of harbouring CIS [39]. At orchidectomy in men with GCT, if there is TML in the contralateral testis, or if the contralateral testis is atrophic, biopsy of contralateral testis may be indicated to look for CIS. A policy of ‘open access’ wherein the man may refer himself directly for follow-up scrotal US if an intratesticular mass is felt on self-examination can be very worthwhile; in our experience it has sped up treatment in men with interval GCTs and has *not* led to a flood of self-referrals.

Conclusion

The presence of TML alone in the absence of other risk factors is not an indication for regular scrotal US, further US screening or biopsy.

Ultrasound is recommended in the follow-up of patients at risk, where risk factors other than microlithiasis are present. A summary of the guidelines is presented in Table 4.

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Appendix 1

Patient leaflet for testicular microlithiasis

What is testicular microlithiasis?

Small lumps of calcium lie in the small tubes within the testicle. There must be at least 5 such calcifications in one (or both) testicles before the label testicular microlithiasis (TML) is applied. TML is seen in about 2 or 3 men in every hundred.

How is TML detected?

The calcium lumps cannot be felt and they do NOT cause discomfort. They can only be seen on ultrasound. In other words, TML was discovered incidentally during your ultrasound scan of the testes.

Why is TML important?

At the end of the 1990s, there was some concern that TML *might* lead to cancer of the testicle. Since then, many studies across the world have looked at TML. They have NOT confirmed the initial worries.

There is no evidence that TML on its own leads to cancer.

What should I do?

Like every man, including men who do not have TML, you should practice monthly self-examination of the testicles. If you are uncertain about how to do this, please ask your doctor. Nothing else is required. You do not need regular ultrasound scans. The calcium in the testicles is not related to your diet or to any sexual or other activity.

What should I do if I feel a new lump during self-examination?

Please contact your family doctor or specialist. Your family doctor or specialist will examine you and if thought appropriate will refer you on for a specialist opinion. It is likely that you will be referred also for an urgent ultrasound scan. This will be usually at the hospital where the initial scan was performed.

Appendix 2

Checklist to be completed in men discovered to have TML

If you discover a patient has TML during ultrasound scanning, risk factors for developing GCT should be ascertained.

Risk factor	Comments	Yes \geq 5 ML per FoV	Yes Diffuse	No TML i.e. no FoV contains 5 or more microliths
Maldescent	Ask patient for relevant history	Annual US	Annual US	Discharge
Orchidopexy	Ask patient for relevant history	Annual US	Annual US	Discharge
Previous GCT	Likely to have orchidectomy so this should be easy to ascertain. If there is any doubt, ask the patient	Annual US	Annual US	Discharge
Genetic disease	Ask patient for relevant history	Repeat US at 6 and 12 months, D/C if no nodule $>$ 3mm	Refer	Discharge
Family history of GCT	Ask patient for relevant history	Encourage self-examination and offer open access	Encourage self-examination and offer open access	Discharge
Atrophic testis	Should be noted during the ultrasound examination	Annual US	Annual US	Discharge

References

1. De Jong BW, De Gouveia Brazao CA, Stoop H, Wolffenbuttel KP, Oosterhuis JW, Puppels GJ et al (2004) Raman spectroscopic

analysis identifies testicular microlithiasis as intratubular hydroxyapatite. *J Urol* 171(1):92–96

2. Kim B, Winter TC, Ryu JA (2003) Testicular microlithiasis: clinical significance and review of the literature. *Eur Radiol* 13(12):2567–2576

3. Renshaw AA (1998) Testicular calcifications: incidence, histology and proposed pathological criteria for testicular microlithiasis. *J Urol* 160(5):1625–1628

4. Drut R, Monica R (2002) Testicular microlithiasis: histologic and immunohistochemical findings in 11 pediatric cases. *Pediatr Dev Pathol* 5(6):544–550

5. Bennett HF, Middleton WD, Bullock AO, Teefey SA (2001) Testicular microlithiasis: US follow-up. *Radiology* 218(2):359–363

6. Backus ML, Mack LA, Middleton WD, King BF, Winter TC 3rd, True LD (1994) Testicular microlithiasis: imaging appearances and pathologic correlation. *Radiology* 192(3):781–785

7. Jungwirth A, Diemer T, Dohle GR, Giwercman A, Kopa Z, Toumaye H, Krausz C (2013) Guidelines on male infertility: European Association of Urology. Available from: http://www.uroweb.org/gls/pdf/16_Male_Infertility_LR.pdf

8. Elzinga-Tinke JE, Sirre ME, Looijenga LH, van Casteren N, Wildhagen MF, Dohle GR (2010) The predictive value of testicular ultrasound abnormalities for carcinoma in situ of the testis in men at risk for testicular cancer. *Int J Androl* 33(4):597–603

9. DeCastro BJ, Peterson AC, Costabile RA (2008) A 5-year followup study of asymptomatic men with testicular microlithiasis. *J Urol* 179(4):1420–1403

10. Montgomery JS, Bloom DA (2011) The diagnosis and management of scrotal masses. *Med Clin North Am* 95(1):235–244

11. Tan IB, Ang KK, Ching BC, Mohan C, Toh CK, Tan MH (2010) 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* 116(19):4520–4532

12. Miller FN, Rosairo S, Clarke JL, Sriprasad S, Muir GH, Sidhu PS (2007) Testicular calcification and microlithiasis: association with primary intra-testicular malignancy in 3,477 patients. *Eur Radiol* 17(2):363–369

13. Manecksha RP, Fitzpatrick JM (2009) Epidemiology of testicular cancer. *BJU Int* 104(9 Pt B):1329–1333

14. Skakkebaek NE (2003) Testicular dysgenesis syndrome. *Horm Res* 60(Suppl 3):49

15. Skakkebaek NE, Holm M, Hoei-Hansen C, Jorgensen N, Rajpert-De E, Mayer F et al (2003) Association between testicular dysgenesis syndrome (TDS) and testicular neoplasia: evidence from 20 adult patients with signs of maldevelopment of the testis. *APMIS* 111(1):1–11

16. Joensen UN, Jorgensen N, Rajpert-De E, Skakkebaek NE (2008) Testicular dysgenesis syndrome and Leydig cell function. *Basic Clin Pharmacol Toxicol* 102(2):155–161

17. Martin OV, Shialis T, Lester JN, Scrimshaw MD, Boobis AR, Voulvoulis N (2008) Testicular dysgenesis syndrome and the estrogen hypothesis: a quantitative meta-analysis. *Environ Health Perspect* 116(2):149–157

18. Wohlfahrt-Veje C, Main KM, Skakkebaek NE (2009) Testicular dysgenesis syndrome: foetal origin of adult reproductive problems. *Clin Endocrinol* 71(4):459–465

19. James WH (2010) Further grounds for abandoning the concept of testicular dysgenesis syndrome: a response to the paper of Akre and Richiardi (2009). *Hum Reprod* 25(4):1084–1086

20. Akre O, Richiardi L (2009) Does a testicular dysgenesis syndrome exist? *Hum Reprod* 24(9):2053–2060

21. Cvancarova M, Oldenburg J, Sprauten M, Stensheim H, Fossa SD (2011) Reproduction rates prior to diagnosis of testicular cancer:

- does the testicular dysgenesis syndrome exist? *J Clin Oncol* 29(15 Suppl 1)
22. Greene MH, Kratz CP, Mai PL, Mueller C, Peters JA, Bratslavsky G et al (2010) Familial testicular germ cell tumors in adults: 2010 summary of genetic risk factors and clinical phenotype. *Endocr Relat Cancer* 17(2):R109–R121
 23. Hemminki K, Chen B (2006) Familial risks in testicular cancer as aetiological clues. *Int J Androl* 29(1):205–210
 24. Mai PL, Chen BE, Tucker K, Friedlander M, Phillips KA, Hogg D et al (2009) Younger age-at-diagnosis for familial malignant testicular germ cell tumor. *Fam Cancer* 8(4):451–456
 25. Coffey J, Huddart RA, Elliott F, Sohaib SA, Parker E, Dudakia D et al (2007) Testicular microlithiasis as a familial risk factor for testicular germ cell tumour. *Br J Cancer* 97(12):1701–1706
 26. Korde LA, Premkumar A, Mueller C, Rosenberg P, Soho C, Bratslavsky G et al (2008) Increased prevalence of testicular microlithiasis in men with familial testicular cancer and their relatives. *Br J Cancer* 99(10):1748–1753
 27. Goede J, Hack WW, Sijstermans K, van der Voort-Doedens LM, Van der Ploeg T, Meij-de Vries A et al (2011) Normative values for testicular volume measured by ultrasonography in a normal population from infancy to adolescence. *Horm Res Paediatr* 76(1):56–64
 28. Okada H, Fujioka H, Tatsumi N, Kanzaki M, Okuda Y, Fujisawa M et al (1999) Klinefelter's syndrome in the male infertility clinic. *Hum Reprod* 14(4):946–952
 29. Boyce AM, Chong WH, Shawker TH, Pinto PA, Linehan WM, Bhattacharyya N et al (2012) Characterization and management of testicular pathology in McCune-Albright syndrome. *J Clin Endocrinol Metab* 97(9):E1782–E1790
 30. Daneman A, Daneman D (2007) McCune-Albright syndrome. *J Pediatr Endocrinol Metab* 20(12):1265
 31. Thomas K, Wood SJ, Thompson AJ, Pilling D, Lewis-Jones DI (2000) The incidence and significance of testicular microlithiasis in a subfertile population. *Br J Radiol* 73(869):494–497
 32. Albers P, Albrecht W, Algaba F, Bokemeyer C, Cohn-Cedermark G, Fizazi K et al (2011) EAU guidelines on testicular cancer: 2011 update. *Eur Urol* 60(2):304–319
 33. Butruille C, Marcelli F, Ghoneim T, Lemaitre L, Puech P, Leroy X et al (2012) Management of testicular lesions in a population of infertile patients. [French] *Prise en charge des nodules testiculaires dans une population de patients infertiles. Prog Urol* 22(1):45–52
 34. Furness PD 3rd, Husmann DA, Brock JW 3rd, Steinhardt GF, Bukowski TP, Freedman AL et al (1998) Multi-institutional study of testicular microlithiasis in childhood: a benign or premalignant condition? *J Urol* 160(3 Pt 2):1151–1154, discussion 78
 35. Goede J, Hack WW, van der Voort-Doedens LM, Sijstermans K, Pierik FH (2009) Prevalence of testicular microlithiasis in asymptomatic males 0 to 19 years old. *J Urol* 182(Suppl 4):1516–1520
 36. Chiang LW, Yap TL, Asiri MM, Phaik Ong CC, Low Y, Jacobsen AS (2012) Implications of incidental finding of testicular microlithiasis in paediatric patients. *J Pediatr Urol* 8(2):162–165
 37. Goede J, Hack WW (2012) Clinical aspects of testicular microlithiasis in boys: a review. *J Pediatr Urol* 8(5):459–469
 38. Deganello A, Svasti-Salee D, Allen P, Clarke JL, Sellars ME, Sidhu PS (2012) Scrotal calcification in a symptomatic paediatric population: prevalence, location, and appearance in a cohort of 516 patients. *Clin Radiol* 67(9):862–867
 39. Hoei-Hansen CE, Olesen IA, Jorgensen N, Carlsen E, Holm M, Almstrup K et al (2007) Current approaches for detection of carcinoma in situ testis. *Int J Androl* 30(4):398–404, discussion 404–405