INCIDENTAL FINDINGS AND HOW TO MANAGE THEM: TESTIS— A WFUMB POSITION PAPER

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Abstract—Testicular incidentalomas are non-palpable, asymptomatic lesions, most frequently detected on ultrasound examinations. Each incidentaloma should undergo a standardized diagnostic workup to exclude malignancy and recognize other potentially significant non-malignant conditions that may first present with an incidental finding on scrotal ultrasound. This position statement of the World Federation of Ultrasound in Medicine and Biology (WFUMB) summarizes the available evidence on management of testicular incidentalomas and describes efficient management strategies with particular reference to the role of ultrasound techniques. (E-mail: c.f.dietrich@googlemail.com)

Key Words: **Testis, Incidental findings, Ultrasound, Follow-up.**

INTRODUCTION

Definition

Incidentalomas are incidental findings on imaging studies, serendipitously diagnosed in an asymptomatic patient or symptomatic patient undergoing imaging for an unrelated reason (O'Sullivan et al. 2018; Dietrich et al. 2013, 2016, 2020). Testicular incidentalomas are non-palpable and asymptomatic lesions, most frequently detected on ultrasound (US) examinations. Other terms for them are small testicular masses or non-palpable testicular tumour. The ability to identify a testicular mass on clinical examination depends on its size, position within the testis and testicular volume (Rocher et al. 2016b, 2018).

Advances in US technology, particularly transducer design and imaging processing, now permit identification of very small intratesticular lesions, sometimes as small as 1−2 mm in diameter. Managing these testicular incidentalomas is a frequent and growing dilemma in scrotal US practice. Most incidentalomas are benign, and optimal management will frequently avoid the need for radical orchidectomy (Figs. 1 and 2).

Epidemiology

Palpable testicular tumours are, in 90%−95% of cases, germ cell tumours (GCTs). These represent about 5% of genitourinary tumours and about 1% of all neoplasms in men. They are broadly divided into seminomas and non-seminoma germ cell tumours (NSGCTs). The age of peak incidence is the third and fourth decades of life (Laguna et al. 2020). Radical orchidectomy via an inguinal approach is the standard treatment.

Increased detection of testicular incidentalomas results from the improved resolution of US and an expansion of the indications for scrotal US beyond evaluation of palpable scrotal abnormalities to a wide range of conditions in which there is no clinical suspicion of a scrotal mass. No detailed epidemiological data are available regarding the incidence of incidentalomas. Studies on surgically treated patients indicate that they are detected in 0.8%−7.4% of US examinations of the scrotum; however, this estimate may suffer from selection

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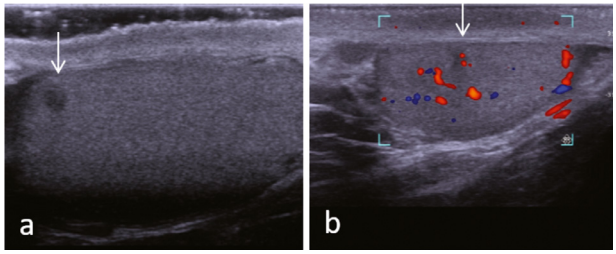

Fig. 1. Ultrasound images of an incidentally detected testicular Leydig cell tumour (*arrows*) in a patient diagnosed with infertility. (a) B-Mode longitudinal projection reveals a hypo-echoic, well-defined lesion 3 mm in diameter. (b) Color Doppler imaging transversal projection reveals that the vascularity of the lesion is sparse and located peripherally.

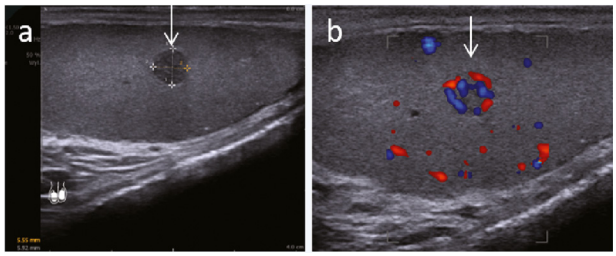

Fig. 2. Ultrasound images of incidentally detected seminoma of the testis (*arrows*). (a) B-Mode longitudinal projection reveals a hypo-echoic well-defined lesion. (b) Color Doppler imaging transverse projection reveals increased vascularity of the tumour.

bias as small lesions (<5 mm) were often omitted from surgical series (Connolly et al. 2006; Avci et al. 2008; Toren et al. 2010; Isidori et al. 2014; Rocher et al. 2016b, 2018).

Unlike palpable masses, the majority of testicular incidentalomas (50%−80%) are benign (Carmignani et al. 2003; Shilo et al. 2012; Galosi et al. 2016; Rocher et al. 2016b, 2018). There is a direct correlation with small size: In one series of 131 consecutive patients undergoing surgery for suspected testicular tumours, benign lesions represented only 8% of cases overall but small lesion size had a strong correlation with a benign histology; 50% of lesions ≤10 mm were benign; using a cutoff size of 18.5 mm, 38% of lesions were benign (Shilo et al. 2012). Leydig cell tumours constitute the majority of solid incidentalomas; in a literature review of six series of patients treated by testis-sparing surgery (TSS), 45% of lesions were Leydig cell tumours, with GCTs found in only 10% of cases (Brunocilla et al. 2013). Radical orchidectomy for testicular incidentalomas will therefore represent significant overtreatment for the majority of men, particularly where there are no clearly suspicious features for malignancy on US or on clinical evaluation (Rocher et al. 2016b).

Although the presence of a normal contralateral testis has traditionally been considered sufficient to maintain normal hormonal and reproductive function, there is evidence that unilateral orchidectomy may lead to adverse effects on gonadal function, fertility and mental health (Huddart et al. 2006; Tuinman et al. 2006; Brunocilla et al. 2013). The aim of managing testicular incidentalomas is therefore to reduce the number of unnecessary radical orchidectomies whilst preserving oncological safety.

Testicular incidentalomas are regularly identified in men being investigated for infertility; in one study, a focal testicular sonographic abnormality was found in 34% of infertile male patients, including 14% with a focal hypo-echoic solid mass (Eifler et al. 2008). In infertile men, differentiating between benign and malignant lesions is of particular importance to avoid unnecessary orchidectomy and preserve sperm-producing testicular parenchyma. Several studies have reported that the proportion of incidentalomas that are malignant is particularly low in infertile men (Eifler et al. 2008; Toren et al. 2010; Bieniek et al. 2018). It is, however, also important to note that male factor infertility may be an independent risk factor for developing testicular cancer (Walsh et al. 2009), particularly when associated with testicular microlithiasis (TM) (Barbonetti et al. 2019). Karyotype abnormalities should be specifically considered in these patients, particularly Kleinfelter syndrome, which is associated with benign tumours and Leydig cell hyperplasia (Rocher et al. 2016a).

US surveillance is appropriate for the majority of testicular incidentalomas in infertile men, where tumour markers are negative, there are no clearly suspicious US characteristics and conservative management is acceptable to the patient; this applies particularly to lesions <5 mm in diameter.

Summary

- The majority of incidentally discovered non-palpable focal testicular masses are benign, and management should avoid radical orchidectomy wherever possible.
- US surveillance is a procedure of increasing importance for cases in which tumour markers are negative and there are no clearly suspicious US features.

EVALUATING TESTICULAR INCIDENTALOMAS

Several tools are available for evaluating incidentalomas that help to differentiate benign from malignant lesions and guide further management. These include clinical history and examination, laboratory tests, multiparametric ultrasound (mpUS), other imaging techniques (particularly magnetic resonance imaging [MRI]), US surveillance, percutaneous biopsy and TSS (Ramanathan and Dogra 2018; Laguna et al. 2020).

Clinical history and examination

History taking should be focused on testicular cancer risk factors, particularly the patient's age and a personal or family history of GCT, cryptorchidism, gonadal dysgenesis and infertility. Clinical features that might indicate a non-neoplastic etiology should be excluded such as suspicion of infection, trauma, history of granulomatous disease (sarcoidosis and tuberculosis) and endocrine disease (congenital adrenal hyperplasia). A history of non-testicular malignancy (particularly lymphoma) may indicate metastatic disease. Clinical examination should assess for testicular atrophy, features of tumour hormone production (such as gynecomastia or premature virilization in boys) and karyotype abnormality.

Laboratory tests

Tumour markers are critical in managing patients with testicular incidentalomas. Between 50% and 60% of testicular cancers produce markers that facilitate diagnosis, staging and response to treatment. The most commonly measured markers are α-fetoprotein, human chorionic gonadotropin β subunit (β-hCG) and lactate dehydrogenase. At least one of the markers is elevated in 90% of NSGCT patients. α-fetoprotein levels are elevated in about 50%−70% of patients with NSGCT; β-hCG is elevated in about 40%−60% of patients with NSGCT and in 30% of seminoma patients. Lactate dehydrogenase is less specific; it is elevated in 40%−60% of men with GCT, particularly in those with large-volume disease (Laguna et al. 2020). These tumour markers are highly valuable in clinical practice but they are imperfect and lack sensitivity and specificity. Given these limitations, a number of newer markers are being developed that may have superior diagnostic performance but none are yet in routine clinical use (Milose et al. 2012).

Ultrasound

US is the imaging modality of choice for evaluating the scrotum. Scrotal US is recommended even when there is a clinically evident tumour (Laguna et al. 2020). Standard B-mode and color Doppler (CD) techniques have high sensitivity and negative predictive values in differentiating neoplastic from non-neoplastic testicular lesions but have limited specificity (Schröder et al. 2016).

B-Mode US is highly accurate in determining whether a lesion is intra- or extra-testicular in origin. It can further categorize focal lesions into those that are entirely cystic, solid and cystic and solid; this is of prime importance as purely cystic lesions are invariably benign (Fig. 3).

Solid lesions can be further categorized into those that are hyperechoic relative to normal testicular parenchyma and those that are iso-echoic, hypo-echoic or of mixed echogenicity. Most malignant lesions are hypo-

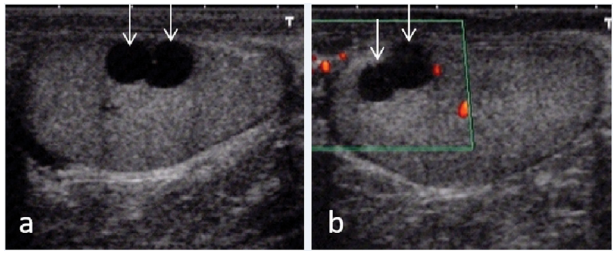

Fig. 3. Ultrasound images of two superimposed simple testicular cysts (*arrow*). (a) Transverse projection. (b) Transverse projection with power Doppler imaging; the cysts are avascular.

echoic or of mixed echogenicity containing regions with decreased echogenicity. US can also be used to assess testicular volume, identify testicular micro- and macrocalcifications and evaluate the contralateral testis.

All focal testicular lesions should be evaluated with CD techniques. The lack of identifiable vascularity within a testicular lesion increases the likelihood of a benign etiology; however, blood flow may be difficult to visualize in small non-palpable tumours with conventional CD techniques (Horstman et al. 1992), and a substantial proportion of hypo-echoic testicular masses that are avascular with CD are malignant (Ma et al. 2017). In one study, the addition of CD to grey-scale US increased diagnostic specificity twofold but did not improve overall diagnostic accuracy in differentiating neoplastic from non-neoplastic lesions (Schröder et al. 2016). Newer Doppler techniques that are able to separate very low Doppler shift frequencies from motion artifacts, based on microvascular detection, have shown promise in visualizing testicular perfusion and may help to visualize vascularity in small hypovascular lesions, but there is no published evidence indicating an advantage over conventional Doppler techniques (Fu et al. 2021).

New US technologies, such as contrast-enhanced ultrasound (CEUS) and US elastography, have been developed that can be added to standard B-mode and CD examinations. These multifaceted studies have been described as "multiparametric ultrasound" (mpUS) and can be successfully applied to improve characterization of testicular incidentalomas (Huang and Sidhu 2012; Sidhu 2015; Bertolotto et al. 2018).

Because of the high frequency of transducers used for scrotal US, a higher dose of contrast microbubbles is required for testicular CEUS than is used for most abdominal applications (Sidhu et al. 2018). CEUS greatly increases the visualization of testicular perfusion, revealing flow in vessels that are many times smaller than those in which flow can be visualized with Doppler techniques (Greis 2009; Clevert et al. 2013) (Fig. 4).

Several studies have found that CEUS significantly improves differentiation of benign from malignant testicular lesions, revealing intralesional flow in some cases where no flow is visible on conventional CD (Isidori et

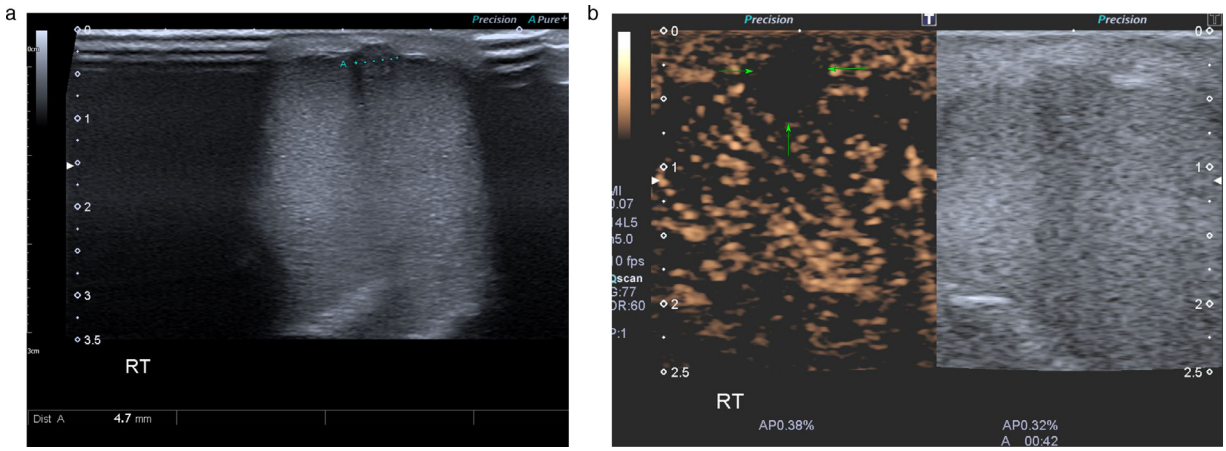

Fig. 4. (a) Incidentally discovered 5-mm subtunical testicular mid-echogenicity mass smoothly deforming the testicular capsule. (b) On contrast-enhanced ultrasound the lesion is completely avascular, making it almost certainly benign. The patient elected for surgical excision, and the final histology was a benign spindle cell proliferation.

al. 2014; Schröder et al. 2016; Auer et al. 2017). There is also limited evidence that quantitative CEUS may detect differences between GCTs and Leydig cell tumours (Drudi et al. 2016), with rapid wash-in and washout reported in malignant tumours and rapid filling but prolonged wash-out in Leydig tumours (Isidori et al. 2014; Lock et al. 2014); however, this remains an area of research and is not recommended for routine clinical use (Sidhu et al. 2018) (Fig. 5).

Some non-neoplastic conditions may also reveal contrast enhancement, particularly if inflammatory, and rim enhancement is frequently seen around testicular abscesses and areas of segmental infarction (in the subacute stage) (Huang and Sidhu 2012). Contrast enhancement will also be expected in secondary testicular tumours (lymphoma and metastases) (Kachramanoglou et al. 2017). In mixed solid and cystic lesions, enhancement of the solid component increases concern for a malignancy.

Evaluation of focal testicular lesions is now a well-established and evidence-based indication for CEUS. Demonstration of avascularity on CEUS is an important finding as virtually all testicular tumours are thought to show vascularity with this technique (Sidhu et al. 2018).

Ultrasound elastography is the equivalent of clinical palpation, assuming that malignant lesions are more likely to be hard in consistency; it now has a wide range of clinical applications (Cosgrove et al. 2013) (Fig. 6).

There are two types of US elastography. Strain elastography (SE, also known as tissue elastography) is a qualitative or semiquantitative technique that provides information on the relative stiffness between different tissues, displayed as a color map superimposed on the

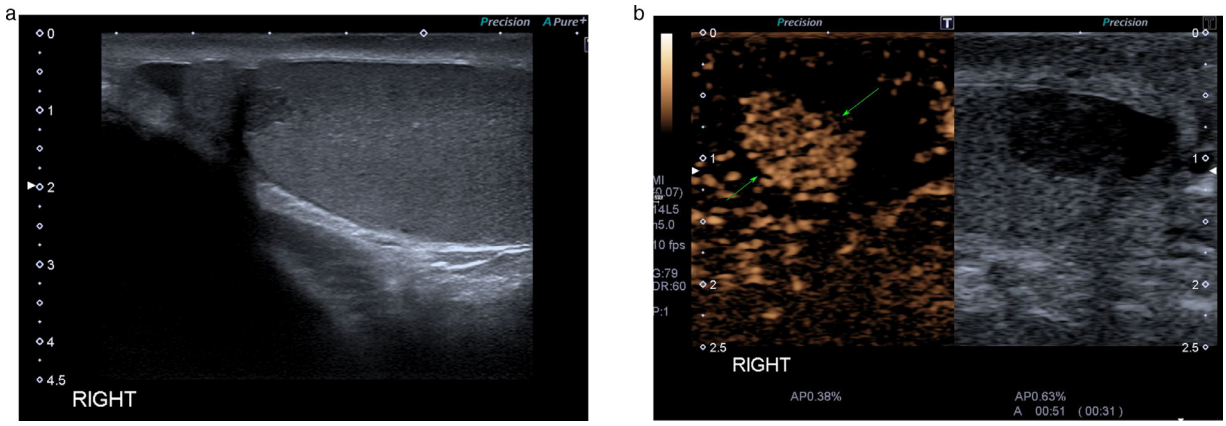

Fig. 5. Incidentally discovered small hypo-echoic mass in the upper pole of the testis (a) that exhibits intense vascularity on contrast-enhanced ultrasound (b, *arrows*). Surgical excision was performed, and the final histology result was Leydig cell tumour.

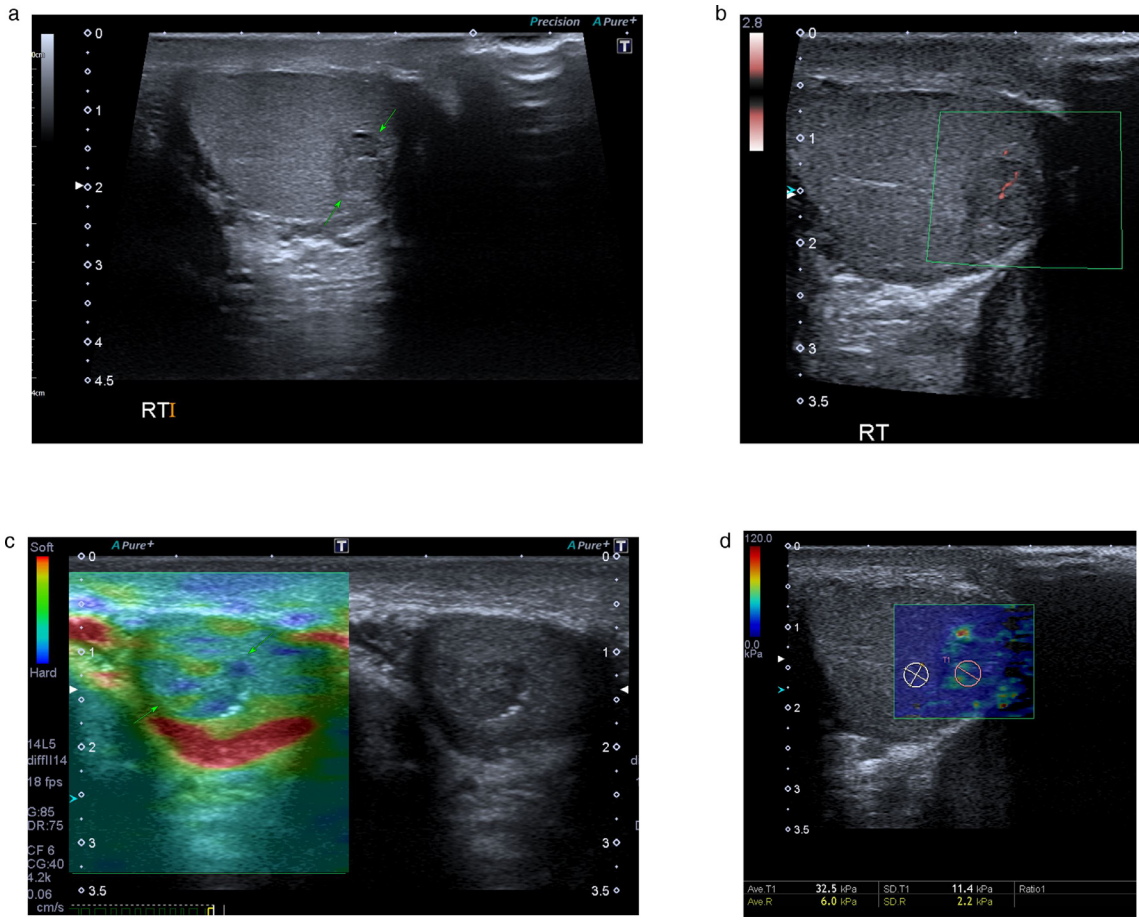

Fig. 6. Incidentally detected small testicular mass (a, *arrows*) revealing low-level internal vascularity on sensitive Doppler examination (microflow detection mode) (b). The lesion in hard on strain elastography, appearing mainly *blue* with small areas of *green* (*arrows*, Visual Elastography Score [VES] = 5/6) (c). On shear wave elastography, the lesion is much harder than surrounding testicular parenchyma (32.5 kPa vs. 6.0 kPa) (d). Surgical excision was recommended; the final histology result was mixed non-seminoma germ cell tumour.

B-mode image (elastogram). Tissue deformation is measured after application of mild pressure, usually with the transducer (Dietrich et al. 2017). Shear-wave elastography (SWE) is a quantitative technique that evaluates tissue stiffness by measuring the speed of propagation of an US shear wave through the tissue under investigation (DeWall 2013).

Strain elastography has been more widely studied in the testis; the normal testis has a soft parenchyma with a thin rim of harder subtunical tissue. Visual patterns of strain elastography color representation have been developed to differentiate between soft and hard lesions and adapted for use in the testis including 6-point (Konstantatou et al. 2019) and 3-point (Pozza et al. 2016) scales (Fig. 7). Several studies have also used semiquantitative measurements of strain ratios to assess lesion hardness by assessing differences in stiffness between the testicular lesion and normal testicular parenchyma.

Many investigators have reported the potential value of strain elastography as part of an mpUS assessment of focal testicular lesions and as a guide to malignancy; unfortunately, there is a lack of consistency between visual assessment scales, strain ratio values and differences between different US systems in these studies, making direct comparison problematic. One report revealed very high accuracy for strain elastography in identifying malignant lesions (Goddi et al. 2012); however, the majority of studies report that it has a high sensitivity but low specificity for differentiation between benign and malignant lesions (Schröder et al. 2016; Fang et al. 2019). It is also unclear whether visual assessment scores are more or less accurate than strain ratios in determining the likelihood of malignancy (Pozza et al. 2016; Konstantatou et al. 2019). Many studies conclude that strain elastography cannot be used in isolation but can be a valuable component of a mpUS evaluation of a testicular mass when considered with the other US

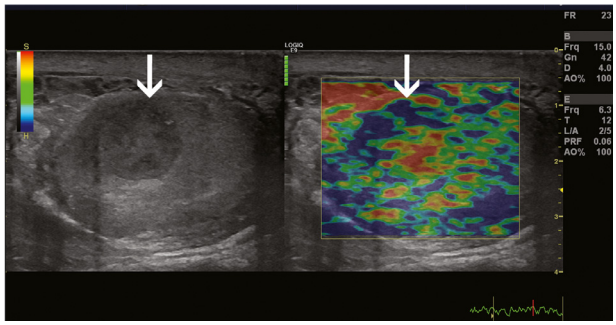

Fig. 7. A soft lesion (*arrow*) on strain elastography that was verified as an abscess.

parameters (Pastore et al. 2014; Pozza et al. 2016; Auer et al. 2017; Reginelli et al. 2019); the addition of CEUS in cases of hard lesions appears to be of particular value in improving the specificity of this method (Auer et al. 2017). Several of these studies address small or non-palpable lesions (Goddi et al. 2012; Pastore et al. 2014; Pozza et al. 2016), and therefore, strain elastography appears to be applicable to assessment of testicular incidentalomas.

SWE is less extensively studied in the testis. In normal men, standard values for testicular stiffness have been reported, indicating that values differ between the center of the testis and the periphery (Trottmann et al. 2016). SWE has been reported to have potential applications in men with suspected spermatic cord torsion (Xue et al. 2020), varicocele (Turna and Aybar 2020) and infertility (Rocher et al. 2017a; Yavuz et al. 2018; Erdoğan et al. 2020). There is limited evidence for the role of SWE in evaluating focal testicular lesions. One study found that SWE-measured stiffness was significantly higher in pathological lesions than in normal testicular parenchyma; when different pathologies were separately analyzed, GCT stiffness was higher than seen in orchitis and lower than in fibrosis (Roy et al. 2020). This study also found an increased stiffness of testicular parenchyma in men with TM, a finding also reported by other researchers (Aslan et al. 2018)

Summary

- Determining the pre-test probability for testicular malignancy with clinical history and examination and evaluation of tumour markers is essential when an indeterminate testicular incidentaloma is identified on US.
- The addition of CEUS and elastography to standard B-mode and CD US (mpUS) is valuable in indeterminate US cases to improve accuracy in differentiating benign from malignant lesions. This permits triage of most patients into standard surgical, TSS/biopsy and surveillance categories (Fig. 8).
- Testicular incidentalomas that are avascular on CEUS are almost certainly benign and should be considered for surveillance rather than surgical treatment.
- Elastography is a valuable component of mpUS but cannot be used in isolation.

Other imaging techniques

Although US remains the prime imaging modality for scrotal pathology, MRI is the most valuable additional imaging investigation when a testicular lesion is indeterminate on US (Tsili et al. 2018). It is estimated that MRI can add valuable additional information in approximately 80% of lesions that are indeterminate on US (Muglia et al. 2002). The use of MRI as a second-line imaging modality is recommended by the European Society of Urogenital Radiology (ESUR) (Rocher et al. 2016b; Tsili et al. 2018). American Urology Association (AUA) guidelines for diagnosis and treatment of early testicular cancer indicate that MRI does not have a clear diagnostic benefit over US but can be considered when lesions are thought most likely benign on US (Stephenson et al. 2019). Recommendations have been produced for the indications and examination protocol for scrotal MRI by the ESUR (Tsili et al. 2018). The widespread use of scrotal MRI is limited because of cost, time constraints and lack of diagnostic standards and expertise in interpretation. Studies have found that MRI has a high sensitivity and specificity (up to 100% and 88%, respectively) for differentiating between benign and malignant testicular lesions (Tsili et al. 2010, 2018) although these studies have not been specifically focused on testicular incidentalomas.

Summary

- MRI is a valuable second-line investigation in selected patients with indeterminate testicular lesions on mpUS.

Ultrasound surveillance

Because of the high probability that most testicular incidentalomas represent benign lesions, particularly in low-risk tumour marker-negative patients, US surveillance is an attractive management strategy (Fig. 9).

In comparison with many other malignancies, the 5-year survival rate for patients with GCTs is very high (95% for all stages: 99% for localized disease, 96% for regional disease and 73% for distant disease) (American Cancer Society 2021). A good prognosis applies to all stages of seminoma and patients with stage I and II NSGCTs (Gori et al. 2005). Even in most patients presenting with disseminated disease, the 5-y survival rate has significantly improved after treatment with modern cisplatin-based chemotherapeutic regimes (Daugaard et al. 1990). The risk to the patient with a small testicular

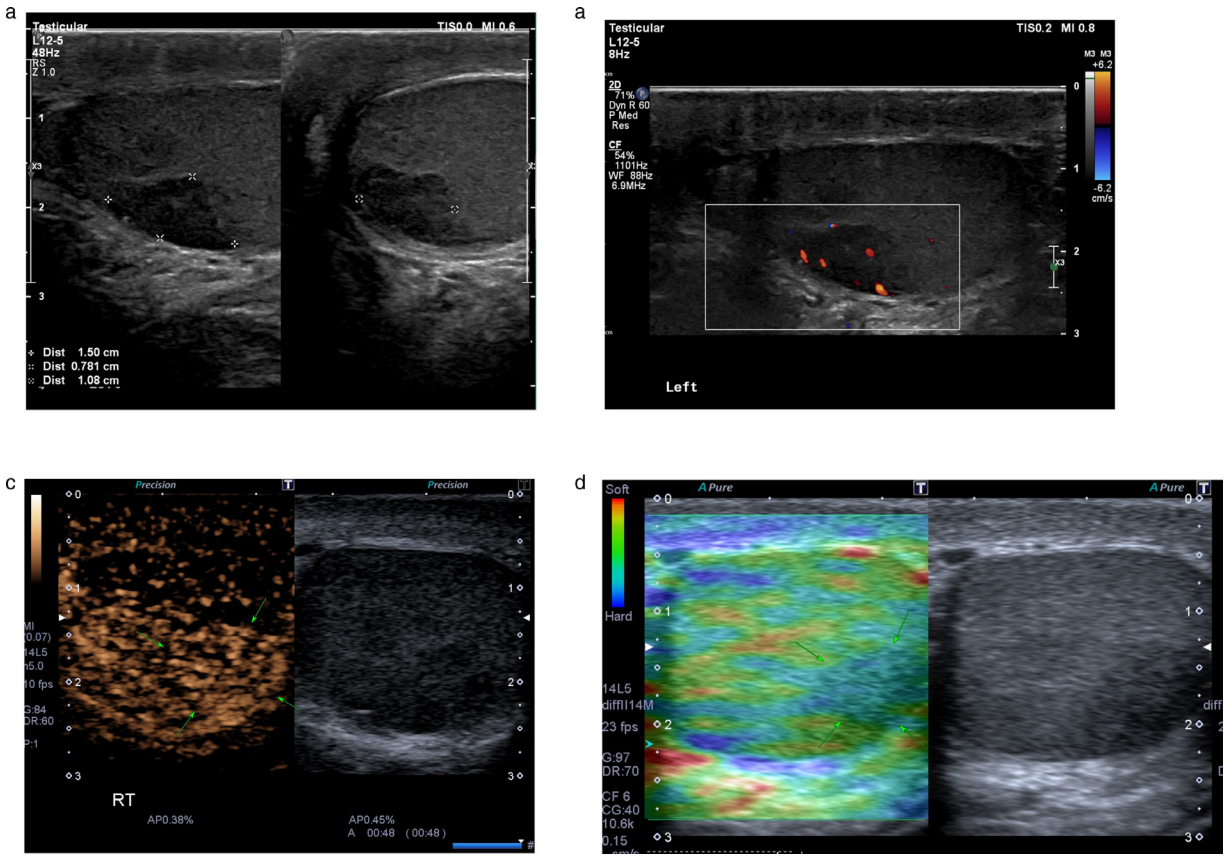

Fig. 8. Multiparametric ultrasound with malignant features. Fifteen-millimeter subtunical echo-poor mass (a) exhibiting vascularity on color Doppler (b), enhancement on contrast-enhanced ultrasound (c, *arrows*) and hard color on strain elastography (d). The final histology result was seminoma germ cell tumour.

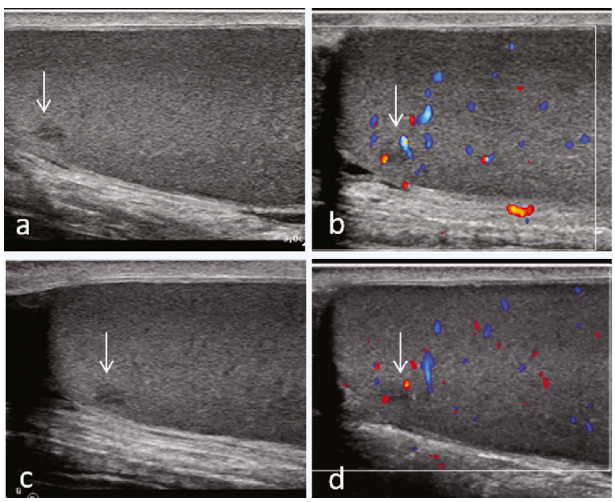

Fig. 9. Testicular incidentaloma ultrasound images (*arrows*) reveal a lesion 3.5 mm in diameter. (a) longitudinal projection. (b) Transverse projection on color Doppler imaging. (c,d) Analogous images on a control examination after 8 wk; the monitored area has not changed.

mass opting for US surveillance rather than surgical excision is therefore very low, even if it subsequently proves to be a GCT. There is further reassurance as poor-prognosis tumours are often predictable by tumour marker positivity, primary tumour size and advanced stage at presentation (Leman and Gonzalgo 2010). Malignant testicular incidentalomas are therefore highly unlikely to represent poor-prognosis tumours and are likely to have a very high cure rate even if the diagnosis is delayed.

In infertile men with incidentalomas, a management algorithm has been proposed based on the size and vascularity of the lesion as well as marker levels (Eifler et al. 2008). Avascular lesions smaller than 5 mm with normal marker levels are recommended for surveillance, which consists of US examinations every 3 mo for the first year. An increase in size, appearance of vascularity or patient's preference is the indication for surgical treatment. Lesions remaining stable after the first year are then monitored with monthly self-examination and annual US with additional US in cases where there is a change in self-examination. AUA guidelines recommend

a shorter first-interval scan of 6−8 wk for indeterminate clinical or US findings (Stephenson et al. 2019). Other authors also consider surveillance to be oncologically safe for lesions <10 mm, especially in patients being investigated for infertility (Toren et al. 2010; Bieniek et al. 2018). Guidelines of the ESUR recommend that US follow-up can be an alternative to orchidectomy if the lesion is <5 mm and tumour markers are negative; the 5-mm size threshold is not considered absolute where no other malignant US findings are present (Rocher et al. 2016b). There is no generally accepted recommendation for the duration of US follow-up.

It should, however, be noted that surveillance US for testicular incidentalomas does not currently form part of the recommended management for testicular cancer by the European Association of Urology (Laguna et al. 2020).

Summary

- US surveillance is a procedure of increasing importance for cases in which tumour markers are negative and there are no clearly suspicious US features.
- Men with testicular incidentaloma being managed by surveillance should be encouraged to self-examine regularly, and an urgent US evaluation is indicated if a change is reported.
- Where a testicular incidentaloma exhibits growth or increasing vascularity on interval imaging, surgical excision should be recommended. If a GCT is confirmed, the delay in diagnosis is unlikely to adversely affect the patient's overall prognosis.
- Even though US surveillance for testicular incidentaloma is oncologically safe in appropriately selected cases, this management option carries a degree of uncertainty and must be acceptable to the patient.

PERCUTANEOUS TESTICULAR BIOPSY

Percutaneous biopsy is a standard diagnostic technique in most organs. Although standard practice in investigating men with infertility (Dohle et al. 2012), it has not been widely used for the diagnosis of testicular masses because of theoretical concerns that scrotal violation will result in needle-tract seeding, altering the pattern of metastatic lymphatic spread as a result of different lymphatic drainage for the testis (abdominal retroperitoneal nodes) and scrotum (inguinal nodes), and that this might lead to a worse prognosis. The evidence for needle-tract seeding is, however, minimal, and the risk is considered to be extremely low, particularly in early-stage tumours (Ramanathan and Dogra 2018). Even in surgical procedures that employ a scrotal incision (open biopsy, scrotal orchidectomy), rather than inguinal orchidectomy, there is only a slightly increased risk of local recurrence and this is usually in advanced tumours, with no statistical differences in distant disease recurrence or overall survival (Giguere et al. 1988; Capelouto et al. 1995; Aki et al. 2000). Percutaneous biopsy is therefore highly unlikely to adversely affect the prognosis of a patient with a small testicular mass, even if it proves to be a GCT.

Percutaneous biopsy is much less invasive than open testicular biopsy and can be a useful technique for testicular incidentalomas that are indeterminate at imaging. Possible indications include imaging and clinical features suspicious for a malignancy that may not require orchidectomy (haematological malignancy and non-haematological metastases), inhomogeneous testicular parenchyma caused by atrophy, multifocal or bilateral lesions or a focal lesion in a solitary testis (Shaida and Berman 2012; Ramanathan and Dogra 2018).

The procedure is performed under local anesthesia with US guidance; both core biopsy and fine-needle aspiration techniques are described; for testicular incidentalomas <10 mm in diameter, fine-needle aspiration may be technically easier to perform than core biopsy. The procedure is usually well tolerated; complications are uncommon and usually minor (Shaida and Berman 2012; Ramanathan and Dogra 2018).

Summary

- Percutaneous biopsy can be a possible diagnostic technique for selected cases of testicular incidentaloma in which clinical, laboratory and imaging tests are indeterminate and that may not require orchidectomy.
- Fears that trans-scrotal biopsy will adversely affect the patient's outcome for early-stage GCT are not evidence based.

TESTIS-SPARING SURGERY (SURGICAL ENUCLEATION OR PARTIAL ORCHIDECTOMY)

Testis-sparing surgery applies the same principles of oncological safety as radical orchidectomy. After an inguinal incision and clamping of the spermatic cord, the testis is delivered, the tunica is incised and the mass is excised with a margin of 3−5 mm. Cold ischemia of the testis may also be employed during cord clamping. Immediate frozen-section histology of the mass is undertaken; if malignant, a completion radical orchidectomy

is usually performed if the patient has a normal contralateral testis. In benign histology, the testis is repaired and returned to the scrotum. Biopsies of the adjacent testicular parenchyma should also be taken to identify foci of germ cell neoplasia *in situ*. If the testicular incidentaloma is non-palpable, intra-operative US may be used to guide the surgeon (Hopps and Goldstein 2002; Browne et al. 2003). In selected cases of small malignant lesions on frozen-section histology, particularly where there is a functionally single testis or bilateral lesions, TSS may still be performed. Combined TSS and local adjuvant radiotherapy results in excellent long-term cancer-specific survival and low recurrence rates and may preserve endocrine function (Giannarini et al. 2010). AUA guidelines recommend TSS for patients who wish to preserve gonadal function with lesions <2 cm when there are bilateral synchronous lesions, the patient has a single functioning testis or the clinical and imaging features are equivocal and tumour markers are negative (Stephenson et al. 2019). European Association of Urology guidelines also recommend an organ-sparing procedure for small US-detected, non-palpable intraparenchymal lesions to obtain a histological diagnosis (Laguna et al. 2020).

The risk of local recurrence after TSS for GCT can be significantly reduced by post-operative adjuvant radiotherapy (Heidenreich et al. 2001). Residual testicular parenchyma frequently harbors germ cell neoplasia *in situ*, which will progress to invasive cancer in 50% of cases within 5 y if untreated (Paffenholz et al. 2020). Radiotherapy will, however, result in infertility and may lead to Leydig cell insufficiency requiring androgen replacement treatment. Patient management will therefore depend on priorities for maintenance of endocrine function and fertility; where these are important priorities, radiotherapy may be deferred and close surveillance implemented (Stephenson et al. 2019; Paffenholz et al. 2020).

Summary

- TSS is a procedure of increasing importance for small US-detected, non-palpable intraparenchymal lesions to obtain a histological diagnosis and prevent unnecessary radical orchiectomy. This technique is also suitable for patients unwilling to undergo the uncertainty of US surveillance.
- Intra-operative US is a valuable tool for locating lesions during TSS
- For selected testicular incidentalomas <2 cm in diameter, TSS is oncologically safe provided that a standard surgical technique is applied and that lesions proving to be GCTs (that do not proceed to completion orchidectomy) have biopsy of the tumour bed, adjuvant radiotherapy and close follow-up.

TESTICULAR INCIDENTALOMAS: SPECIFIC CONSIDERATIONS

Testicular calcifications

Testicular Microlithiasis (TM). TM is defined as multiple punctate hyperechogenic foci 1−3 mm in diameter with no posterior acoustic shadowing. Diagnostic criteria differ between greater than five microliths in a single US image and greater than five microliths in the whole testis (Richenberg et al. 2015). TM is present in about 5% of healthy asymptomatic young men (Peterson et al. 2001) and is seen in 0.6%−9% of scrotal US examinations (Miller et al. 2007). TM has been considered to be a feature of the testicular dysgenesis syndrome, increasing risk for germ cell neoplasia *in situ*, previously known as intratubular germ cell neoplasia of unclassified type, which is a precursor of GCT (Tan and Eng 2011); however, this theory has been challenged by epidemiological studies that question the existence of this condition (Akre and Richiardi 2009). It remains unclear whether there is a causal association between TM and GCT, despite the frequent presence of TM in patients presenting with testicular GCT (Fig. 10). Understandably this has led to confusion regarding the significance of TM as an incidental finding in scrotal US (Shetty et al. 2014).

Current AUA (Stephenson et al. 2019) and ESUR (Richenberg et al. 2015) guidelines do not recommend US surveillance for men with TM who do not have a

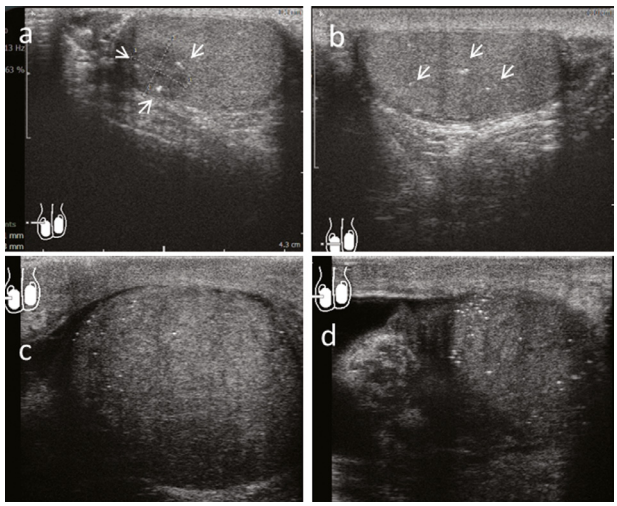

Fig. 10. Ultrasound images of germ cell tumours in two patients coinciding with testicular microlithiasis. (a) Seminoma of the right testicle after orchidopexy; the tumour (between the markers) with microliths (*arrowheads*). (b) microcalcifications are also visible within testicular parenchyma (*arrowheads*), longitudinal projection. (c) Transverse projection, the testicular parenchyma is completely overgrown by an embryonal carcinoma. (d) Numerous microcalcifications are visible within the tumour.

second risk factor for testicular GCT (previous GCT, history of cryptorchidism or orchidopexy, testicular atrophy or history of GCT in a first-degree relative). All men with TM should be encouraged to perform regular self-examination. In men with an additional risk factor for GCT, annual US surveillance is recommended to the age of 55 (Richenberg et al. 2015)

The finding of TM in association with a focal mass is, however, a feature that increases the concern for a malignant etiology, particularly if the mass is hypo-echoic; such lesions are frequently seminomas (Rocher et al. 2016b).

Summary

- All men with TM should be instructed on regular testicular self-examination. Any reported changes should prompt an urgent US examination
- Routine US surveillance is not required for men with TM who do not have a second risk factor for testicular GCT
- When TM is present in association with a hypo-echoic focal mass, the risk of malignancy is increased. Such cases should be managed in a specialist urological center and will usually require surgical treatment

Testicular macrocalcifications. Testicular macrocalcifications measure >3 mm in diameter and may show posterior acoustic shadowing; these are usually an incidental finding on scrotal US. Macrocalcifications have traditionally been regarded as benign findings, related to chronic microtrauma, infection or inflammation, sometimes associated with hydrocoele formation (Frauscher et al. 2001; Pedersen et al. 2018). Testicular macrocalcifications are, however, sometimes found in association with benign and malignant testicular masses (Sidhu et al. 2012), raising concern that macrocalcifications might increase the risk of malignancy (Fig. 11).

In a large retrospective study, non-TM calcification was found in 1.7% of patients, with a significant association of both TM and non-TM calcification with testicular tumour (Miller et al. 2007). There is one small case series of six patients with testicular macrocalcifications subsequently developing testicular tumours (five seminomas, one Leydig cell); five patients had no other risk factor for testicular GCT (Pedersen et al. 2018). This limited evidence suggests that patients with any type of testicular calcification may be at increased risk of co-existing malignancy and also future development of a testicular tumour.

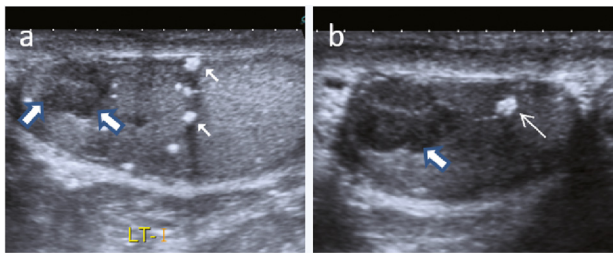

Fig. 11. Ultrasound images of testicular seminoma (*bold arrow*) in a patient with atrophic left testis after orchidopexy. Macrocalcifications (*arrows*) and microliths are visible within normal parenchyma of the testis. (a) Longitudinal projection. (b) Transverse projection.

Summary

- Testicular macrocalcifications are associated with co-existing GCT, and there is a possible association with future development of GCT. There is no generally agreed recommendation for follow-up but management protocols similar to those for patients with TM should be considered.

Burned out tumour (spontaneous regression of GCT, Azzopardi tumour). Testicular burned out tumour (BOT) represents 2.5%−4% of testicular tumours and occurs when rapid growth of a GCT (most commonly seminoma) exceeds its vascular supply, leading to ischemia and spontaneous tumour regression; this may also have an immunological component. Residual intratubular malignancy or viable tumour foci may still be present within the lesion. Patients usually present with constitutional symptoms related to metastatic disease (most commonly palpable abdominal mass and pain caused by abdominal metastatic lymphadenopathy) and without scrotal symptoms. On US, the residual tumour scar may have variable appearances with small hyperechoic linear foci, focal or diffuse hypo-echoic lesions and testicular calcifications; however, the US findings are non-specific (Tasu et al. 2003; Angulo et al. 2009; Rocher et al. 2017b) (Fig. 12).

On mpUS, BOT may be non-vascular or only weakly enhancing with CEUS (unlike most conventional GCTs) and exhibit increased stiffness on elastography (Rocher et al. 2017b).

Extragonadal primary GCT is a rare condition and, in many patients with extra-testicular GCT, there is uncertainty as to whether this is a true primary tumour or metastatic spread from an unrecognized non-palpable tumour or BOT (Scholz et al. 2002). This distinction is of significance because if residual viable tumour cells remain within the BOT they may be resistant to treatment with systemic chemotherapy because of the blood−testis barrier and form a site for possible tumour recurrence. Scrotal US is therefore indicated in male patients presenting with extragonadal GCT; an abnormal

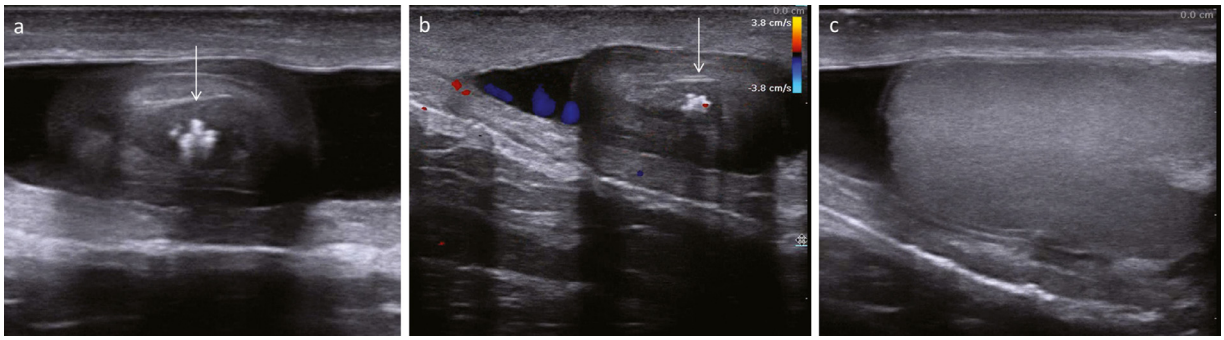

Fig. 12. Ultrasound images of a hypotrophic testis with "burned out tumour" lesion (*arrows*) reveal an area of heterogeneous echotexture (scar tissue) and centrally located calcifications. (a) B-Mode, longitudinal projection. (b) Color Doppler image, longitudinal projection. (c) Ultrasound image of normal contralateral testis, transverse projection.

finding suggestive of a viable non-palpable tumour or BOT should lead to surgical exploration.

As an incidental finding when a possible BOT is encountered on scrotal US management is less certain because of the non-specific appearances of these lesions, which overlap with many benign testicular pathologies, there are no generally agreed guidelines. In the subgroup of infertile men, the presence of a focal hypo-echoic nodule where there is associated TM raises concern for a BOT, even in the absence of metastatic disease or constitutional symptoms, and a management algorithm has been proposed that involves tumour marker measurement, mpUS and, in selected cases, MRI and abdominal and thoracic CT (Rocher et al. 2017b).

Summary

- Male patients diagnosed with extra-gonadal GCT should undergo scrotal US to identify a non-palpable GCT or evidence of a BOT.
- BOT should be considered in the differential diagnosis of an incidental hypo-echoic nodule in association with TM found in an infertile man, and further assessment is indicated.

Testicular cysts. Testicular cysts are identified in 4% of US examinations and are usually an incidental finding (Hamm et al. 1988). Cysts exhibiting no sonographic complexity can be assumed to be benign and do not require follow-up (Rocher et al. 2016b). They may arise within the testicular parenchyma, most commonly adjacent to the mediastinum testis, or may arise from the tunica albuginea.

Complex cysts with solid components, septa or thickened walls are of more concern. They may have a number of different etiologies including benign causes (inflammation, trauma, hemorrhage into a cyst) and malignant cystic tumours. Demonstration of avascularity with CEUS is an indicator that a complex cyst is likely to be benign (Sidhu et al. 2018). Where vascularity is present these lesions are frequently excised in view of the risk of malignancy (particularly teratoma in children). TSS is preferable when technically possible (Valla and Group D'Etude En Urologie Pediatrique 2001; Shukla et al. 2004).

Other benign cystic lesions of the testis such as cystic ectasia of the rete testis and intra-testicular varicocele do not usually cause diagnostic difficulty on US.

Epidermoid cysts (ECs) represent approximately 1% of testicular tumours and are most frequently diagnosed between 20 and 40 y of age (Dogra et al. 2001; Manning and Woodward 2010). They are frequently palpable but may present as a testicular incidentaloma. They do not elevate tumour markers. Four US patterns of EC have been described comprising the onion-ring configuration of concentric hyper- and hypo-echogenic layers, a densely calcified mass, peripheral rim or central calcification and a mixed pattern (Atchley and Dewbury 2000). No internal vascularity is present on conventional Doppler or CEUS examination although rim enhancement may be seen with CEUS (Patel et al. 2012) (Fig. 13).

The onion-ring configuration is the most common and characteristic type and, where no vascularity is present with normal tumour markers, allows for a confident sonographic diagnosis (Manning and Woodward 2010); TSS can by recommended for smaller lesions (Heidenreich et al. 1996; Mahdavi-Zafarghandi et al. 2014; Anheuser et al. 2019). Similar morphological features of ECs may be seen with MRI (Langer et al. 1999).

Summary

- Incidentally detected intratesticular or tunical cysts that are sonographically simple can be considered benign and do not require follow-up.
- Complex cysts may have benign or malignant causes. Lack of vascularity on CEUS indicates a benign lesion.

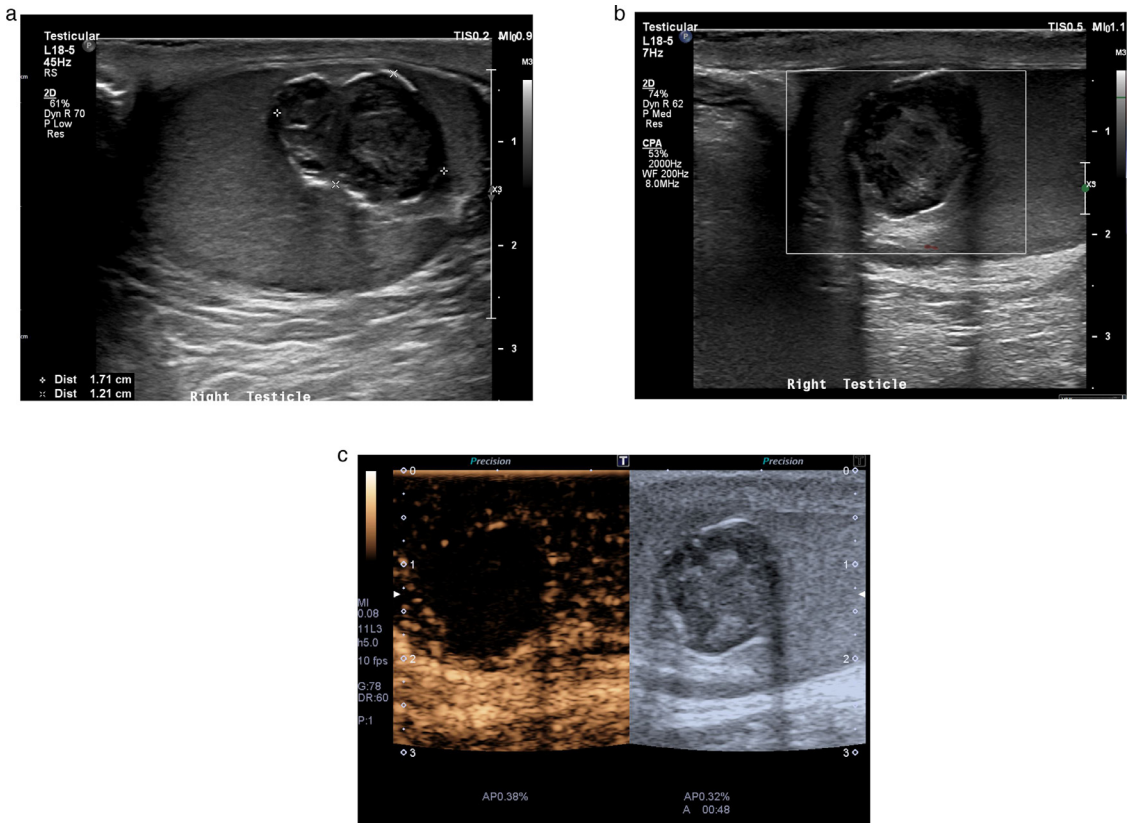

Fig. 13. Epidermoid cyst. The mass exhibits an onion ring pattern on B-mode ultrasound (a) with no detectable internal vascularity on standard color Doppler (b) or contrast-enhanced ultrasound (c).

- Epidermoid cysts may have a characteristic US appearance leading to a recommendation for TSS rather than radical orchidectomy.

Small solid masses

Although the majority of non-palpable testicular incidentalomas will have a benign etiology, GCTs will sometimes present as an incidental finding on scrotal US. Most seminomas are homogeneously hypo-echoic and well defined but sometimes lobulated on US, often with increased vascularity on Doppler examination (Schwerk et al. 1987; Dogra et al. 2003; Sidhu et al. 2012). NSGCTs will frequently have more than one histological type, resulting in a more inhomogeneous US appearance with mixed echogenicity, irregular or ill-defined margins, cystic components and calcifications (McDonald et al. 2012; Sidhu et al. 2012; Shtricker et al. 2015; Kawamoto et al. 2018). Sex-cord stromal tumours represent less than 5% of testicular tumours in adults but form a large proportion of small testicular incidentalomas. They are usually benign although 10% will be malignant. Leydig cell tumours are the most common type and are frequently detected incidentally; they are usually homogeneously hypo-echoic on US and cannot be reliably differentiated from GCTs (especially seminoma) (Sidhu et al. 2012; Moch et al. 2016). Secondary tumours of testis are less likely to present as incidental lesions. Lymphoma is the most common in older men and may exhibit a variety of sonographic patterns (Sidhu et al. 2012; Bertolotto et al. 2015). Metastases from other sites are uncommon (García-González et al. 2000), most frequently arising from prostate, gastrointestinal tract, lung, kidney and

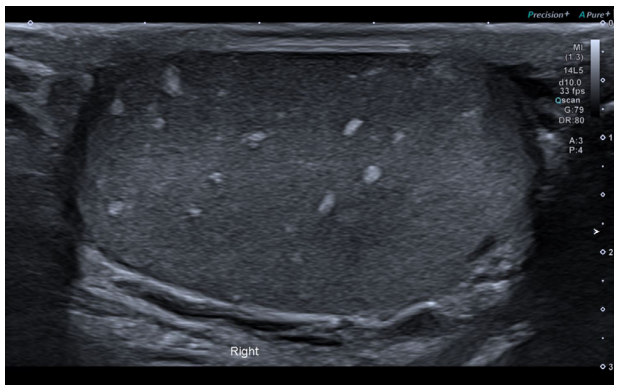

Fig. 14. Cowden disease. The testis contains multiple small echogenic nodules representing testicular lipomatosis.

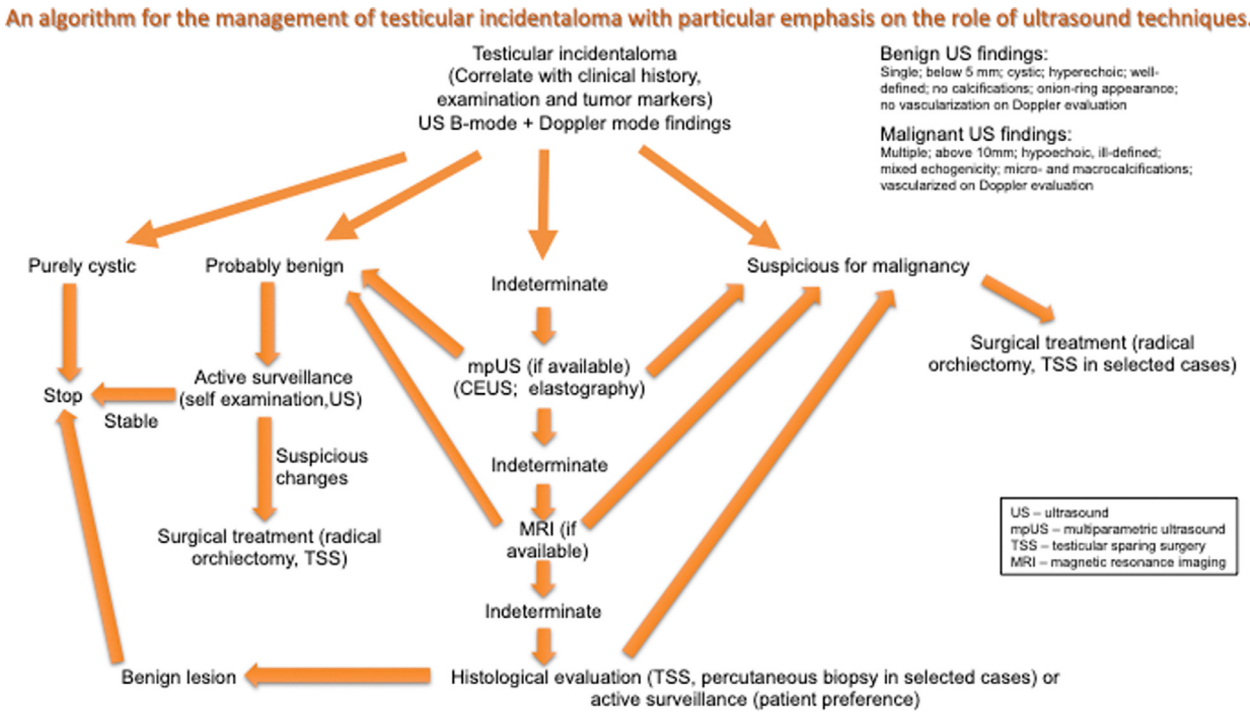

Fig. 15. Chart 1. Comment: Ultrasound findings should always be evaluated in their clinical context. CEUS = contrast-enhanced ultrasound; mpUS = multiparametric ultrasound; MRI = magnetic resonance imaging; TSS = testicular sparing surgery; US = ultrasound

melanoma (Sidhu et al. 2012; Moch et al. 2016). Patients usually have disseminated disease. Sonographic patterns suggestive of a benign or malignant nature of testicular lesions have been proposed by the ESUR and include lesion size, solid or cystic composition, echogenicity, margin and the presence of an abnormal background testicular parenchyma (including micro- and macrocalcifications) (Rocher et al. 2016b). Benign pathologies may also present with testicular incidentalomas that have US appearances similar to those of testicular tumours. Certain conditions such as epidermoid cysts (Atchley and Dewbury 2000), testicular lipomatosis in Cowden disease (Woodhouse et al. 2005) and segmental testicular infarction (Bilagi et al. 2007; Bertolotto et al. 2011) may have characteristic US features (Fig. 14).

In other cases, the history, clinical examination and laboratory tests may point to a likely etiology including adrenal rest tumours in men with congenital adrenal hyperplasia (Wang et al. 2015), Leydig cell hyperplasia (Cooper et al. 1989; Carucci et al. 2003) and sarcoidosis (Sidhu et al. 2012; Joel et al. 2014). Focal orchitis/abscess or intra-testicular hematoma are unlikely to present as incidental findings.

Whilst testicular GCT may occasionally be multifocal, the presence of multiple or bilateral lesions should alert the US practitioner to the possibility of secondary tumour, benign tumour or non-neoplastic causes.

CONCLUSIONS

Testicular incidentalomas will be regularly encountered by most US practitioners undertaking scrotal US examinations. Unlike palpable masses, the majority of those incidental findings are benign, and radical orchidectomy should be avoided whenever possible, particularly in infertile men; this does not risk oncological safety. Clinical evaluation and tumour markers are essential for accurate patient management. US is a powerful imaging tool in predicting the probability of malignancy, particularly mpUS, and can be used to help triage patients into those requiring biopsy or surgery and those that can be safely managed by surveillance (see Fig. 15). Solid hypo-echoic vascular lesions are the most worrying for malignancy, particularly when associated with TM. Even if a testicular incidentaloma initially managed by surveillance subsequently proves to be a GCT, the increased risk to the patient from a delayed diagnosis is very low. Although surveillance is safe, it carries a degree of uncertainty, and this must be discussed with, and be acceptable to, the patient.

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Conflict of interest disclosure—The authors declare they have no conflicts of interest.

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