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REVIEW

Serum tumor markers and testicular germ cell tumors: a primer for radiologists

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Abstract
Serum tumor markers (STMs) play a critical role in the diagnosis, staging and follow-up of both seminomatous and nonseminomatous testicular germ cell neoplasms. Levels of alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH), especially those measured after orchiectomy, also have implications for patient prognosis. Given that testicular germ cell tumors represent the most common solid tumor in men aged 20–34, radiologists must have familiarity with the clinical utilization and implications of these STMs. This article will review the classical patterns of STM elevation most commonly seen in pure seminomatous and nonseminomatous germ cell tumors while also providing case-based examples highlighting the importance of STM correlation with imaging. The role of STMs in clinical staging and disease surveillance will also be discussed.

Keywords Testicular germ cell tumor · Seminoma/diagnosis · Testicular neoplasms · Radiology · Biomarkers · Tumor · Radiologists

Introduction and background

Testicular cancer is the most common solid malignancy found in males aged 15–35 years of age, accounting for 1% of all cancers in men [1]. In 2017, there were an estimated 8850 new cases of testicular cancer which resulted in 410 deaths in the United States. Although the incidence of testicular cancer has increased over the last several decades, it is also one of the most curable solid neoplasms [2, 3]. Today, the 5-year survival rate is about 97%, due in part to advanced therapies along with better surgical techniques and the availability of highly sensitive serum tumor markers [2]. In particular, the serum concentrations of alpha-fetoprotein (AFP), human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH) play a critical role in the screening, diagnosis, treatment monitoring, and surveillance of testicular germ cell tumors (GCTs) [4].

The most updated WHO classification, released in 2016, divides testicular neoplasms into two principal categories: those arising from Germ Cell Neoplasia in situ (GCNIS) and those arising in prepubertal patients, which are not considered a derivation of GCNS. This article will focus on the former, which arise predominately in the post-pubertal patients [5]. Around 95% of all malignant testicular cancers are GCTs, with the remainder consisting of the much less common testicular lymphomas, sex cord stromal tumors (i.e., Leydig or Sertoli cell tumors), and mesotheliomas. Classically, GCNIS-derived tumors are divided into either seminomas or nonseminomatous germ cell tumors (NSGCT). Mixed GCTs, that is tumors with both seminomatous and nonseminomatous inclusions, are considered to be of the NSGCT subcategory [6]. Furthermore, the term NSGCT includes teratomas, yolk sac tumors, embryonal cell tumors, and choriocarcinomas, which may present solitarily or in mixtures of two or more.

The surgical and chemotherapeutic management of germ cell tumors, both seminomatous and nonseminomatous, relies heavily on the evaluation of serum tumor markers, most pointedly those measured immediately after orchiectomy and in trends thereafter [7]. As metabolic and advanced imaging (i.e., PET/CT and MRI, respectively) have no clearly defined role in the management of these patients, radiologists must understand the clinical utility of

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serum tumor marker levels in order to accurately interpret imaging performed at the time of presentation, after orchiectomy, and in long-term follow-up. What follows is an overview of the biological genesis of serum tumor markers from a histological perspective, discussing seminomatous and nonseminomatous neoplasms each as an individual entity, with the understanding that oftentimes these lesions occur in varying combination. Cases which highlight the clinical importance contemporaneously acquired serum tumor markers will be presented. Finally, the current role of serum tumor markers in the initial staging of testicular germ cell tumors, as well as in follow-up after orchiectomy and adjuvant chemotherapy, will be elucidated.

Pure seminomas

Around 50% of testicular GCTs are seminomas, with about 80–85% being stage 1 at the time of diagnosis [7]. In these cases, 83–85% shows no relapse 5 years after orchiectomy alone. These patients typically receive clinical and laboratory (i.e., STMs) surveillance without additional adjuvant therapy [8–10]. However, patients with risk factors for relapse, including tumor invasion of the rete testis or tumor size greater than 4 cm, may be candidates for adjuvant therapy, most commonly with a combination of bleomycin, etoposide, and cisplatin (BEP), with overall reduction in the risk of relapse by 83% [7].

Patients with pure seminomas classically have no significant elevation in AFP at presentation. However, up to 20% of patients with advanced disease may have elevated beta-HCG [11]. By definition, elevations in AFP should not be observed, although several case reports have described borderline increases in AFP values [12]. In such cases, it should be suspected that there is a nonseminomatous element to the tumor, and subsequently treatment will reflect a NSGCT paradigm [13].

High serum levels of lactate dehydrogenase (LDH) may be seen in patients with pure seminoma. LDH is an enzyme produced in many isoforms within an assortment of organs, including muscle, liver, kidney, and red blood cells [14]. Due to this variability, LDH is a somewhat less sensitive and specific marker for NSGCTs when compared to beta-hCG [11]. Nevertheless, LDH is increased in 40–60% of men with testicular GCTs [11]. Serum LDH is known to correlate with tumor burden, growth rate, cellular proliferation, and is commonly higher in patients with advanced disease [6]. LDH therefore also plays an important role in disease surveillance and follow-up of these patients (Fig. 1).

Testicular choriocarcinoma

Of the NSGCTs, choriocarcinoma is a rare yet aggressive form which may be purely choriocarcinoma in 0.3% of patients though is more commonly a component of a mixed GCT. It occurs in males with either descended or undescended testicles and can also be found in extra-testicular locations. Commonly, choriocarcinomas present in post-pubertal men, up to approximately age 69 [6]. Pure testicular choriocarcinoma has a relatively high mortality and poor response to treatment, with a 5-year survival rate of less than 80% in the United States [15]. Choriocarcinomas are known to secrete markedly elevated levels of HCG (generally $> 50{,}000$ mIU/mL), a protein synthesized by syncytiotrophoblasts. This protein contains an alpha subunit that is also shared by luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH); its beta subunit is unique in its terminal amino acid sequence [14]. While other GCTs also secrete HCG, very rarely will these rise to the levels seen in choriocarcinoma [16]. In total, HCG is elevated in about 10–20% with clinical stage 1 NSGCTs and in up to 40% with advanced disease [11].

Choriocarcinoma syndrome may arise due to rapid metastatic hematologic dissemination. These patients may present with high serum HCG, multiple pulmonary metastases, intracranial manifestations, hyperthyroidism, gynecomastia, and non-pulmonary visceral organ involvement [17]. CT of the chest, abdomen, and pelvis, as well as an MRI of the brain is often indicated (Fig. 2). Many of these complications are a direct result of the increased levels of HCG and the subsequent increased stimulation of the shared endocrine receptors by the HCG alpha subunit [18].

Treatment centered on levels of HCG was first described by Dr. Min Chiu Li in the 1950s. He used serum HCG levels to monitor chemotherapy treatment and would continue treatment if levels remained elevated in lieu of clinical evidence suggesting the disease had resolved. Ultimately, his theory was proven correct as patients with elevated levels of HCG at the time of treatment completion would eventually relapse, while those with undetectable levels often achieved cure [19].

Testicular yolk sac tumors

Yolk sac tumors are the most common testicular tumors in children aged 6 months to 4 years old and account for 70–80% of prepubertal malignant testicular tumors [6, 20]. Pure yolk sac testicular tumors comprise about 1–2% of GCTs in adults and occur as a component of mixed GCTs

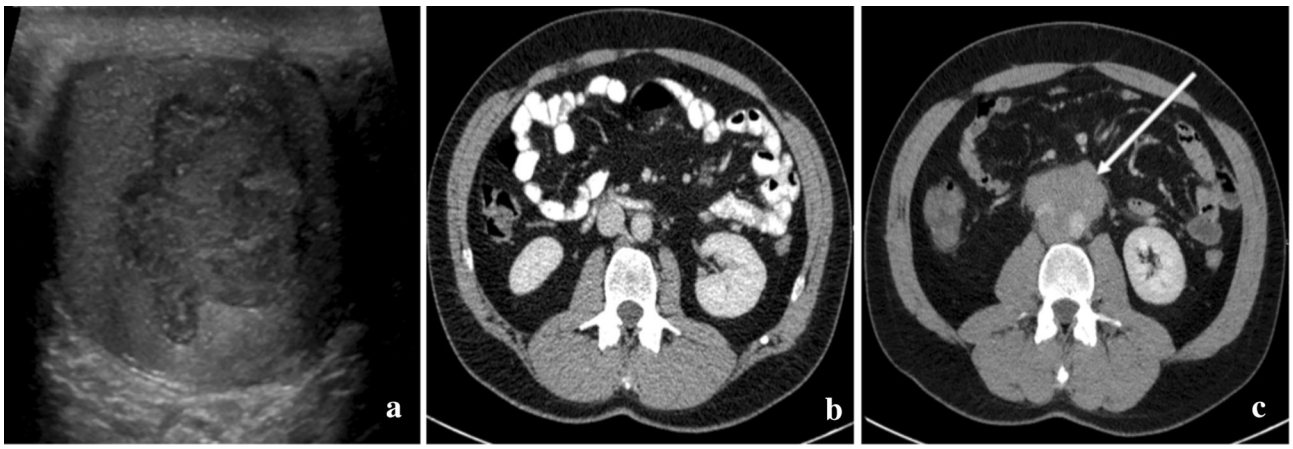

Fig. 1 37-year-old male with left testicular seminoma. At the time of presentation, ultrasound (**a**) and CT of the abdomen (**b**) revealed a heterogenous lesion in the left testicle without metastatic retroperitoneal adenopathy, respectively. Serum tumor markers, including AFP, HCG, and LDH, were within normal limits. Routine evaluation of tumor markers at 6 months after orchiectomy revealed an elevated LDH of 290 U/L (normal 84–246 U/L). Subsequent CT (**c**) demonstrated metastatic retroperitoneal adenopathy. Both imaging and serum tumor markers returned to baseline after adjuvant bleomycin, etoposide, and cisplatin (not shown)

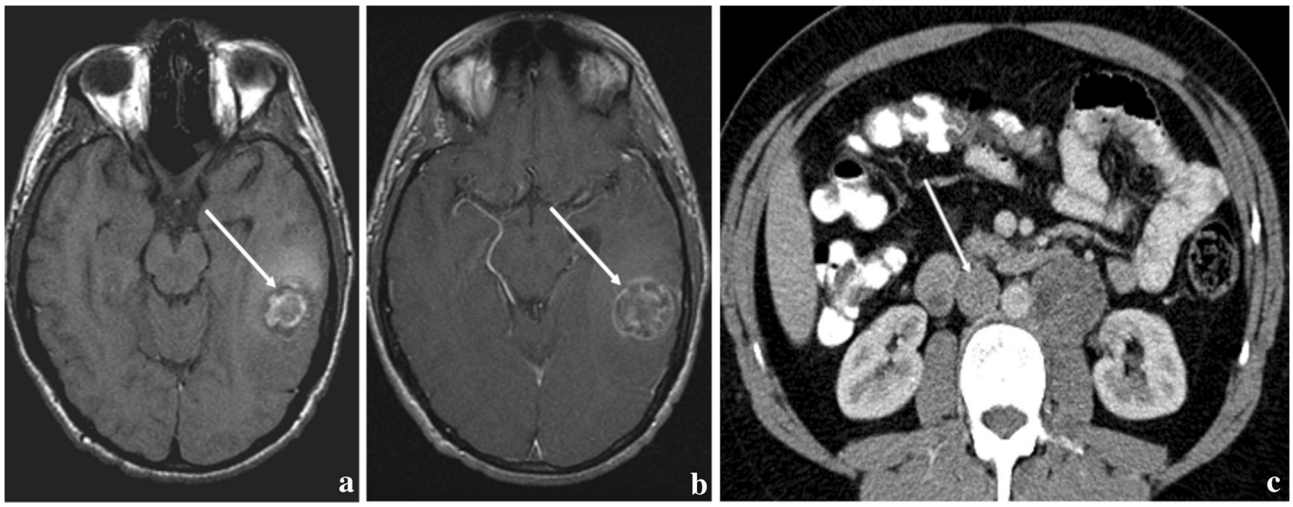

Fig. 2 32-year-old male with metastatic choriocarcinoma. At the time of presentation, markedly elevated HCG (approximately 7000 mIU/mL) raised clinical suspicion for choriocarcinoma. FLAIR (**a**) and T1w post-gad (**b**) MRI images reveal vasogenic edema circumferentially around an enhancing intra-axial mass centered at the gray-white junction of the left temporal lobe, compatible with intracranial metastatic disease. Contemporaneous CT of the abdomen (**c**) demonstrated enlarged retroperitoneal lymphadenopathy

in about 42% of cases. Patients at risk for yolk sac tumors include those with a history of cryptorchidism, microlithiasis, or a family history of cancer [20].

An elevated AFP level is closely associated with these tumors, and seen in more than 90% of cases [21]. AFP is a glycoprotein produced by the liver, intestines, and fetal yolk sac with a half-life around 5–7 days [14]. There is evidence to suggest that infants less than 1 year of age with serum AFP levels > 100 ng/mL should be presumed to have a yolk sac tumor, and that these levels should be monitored post-orchiectomy to evaluate tumor recurrence during follow-up. If AFP levels do not decrease 5 days after operation, residual disease or metastasis should be considered [22]. In one review of 61 patients over the age of 19 years, Wei et al. demonstrated that patients with yolk sac tumors should have initial AFP monitoring for 2–3 weeks after operation with long-term surveillance (> 48 months) recommended [20]. Interestingly, the absence of yolk sac tumor was previously shown to predict relapse in patients who undertook surveillance for clinical stage 1 NSGCT [23]. Additionally, normal AFP levels prior to orchiectomy have been associated with the absence of yolk sac inclusions and an increased risk for occult retroperitoneal metastasis [24, 25].

Nonetheless, similar to beta-HCG, AFP is elevated more frequently as clinical stage advances in mixed NSGCT. In

men with stage 1 disease, AFP is elevated in 10–20% while those with advanced disease have elevated AFP 40–60% of the time [11]. Thus, AFP, just as beta-HCG, serves an important role in monitoring therapy response as well as serving as a tool for surveillance.

Testicular embryonal cell tumors

Pure embryonal cell carcinoma represents only about 3–4% of GCTs, though embryonal histology is a component of mixed GCTs in up to 40% of cases [6]. Both AFP and beta-HCG, while primarily produced by yolk sac tumors and choriocarcinoma respectively, can be found to lesser extents within pure embryonal cell tumors [26]. The levels of either of these markers is directly proportional to tumor burden, and higher serum levels of either marker has been recognized as poor prognostic indictors [27] (Fig. 3). Indeed, a predominantly embryonal histology serves as a prognostic indicator that is frequently associated with the rate of relapse in stage I NSGCT disease [28]. A study conducted between 1978 and 2000 found that the presence of an embryonal histological component to a NSGCT of the 132 patients being followed (median follow-up of 38 months) was the only significant risk factor for disease relapse. Of these patients, the relapse rate was 24% and all occurred before 23 months with 87% diagnosed in the first year [29]. In another group, the 10-year results of a surveillance study of clinical stage I NSGCT patients showed that 25 of 85 men demonstrated relapse after a median disease-free interval of 7 months. All 25 patients had predominant embryonal carcinoma histology in their primary tumor, showing significant association with disease relapse ($p = 0.008$) [29].

Similar to choriocarcinomas, a common site of metastatic disease for these neoplasms is the central nervous system. In a study of 242 patients, brain metastasis occurred in 16% of patients with NSGCTs. Of these, 13% were purely embryonal carcinomas, 83% were pure choriocarcinomas, and 18% were mixed between the two. It was also noted that pulmonary metastases often preceded or coincided with the brain metastases [30]. Other documented complications include mediastinal invasion, subcutaneous manifestations, vascular invasion, and hyperthyroidism [31–34].

Testicular teratomas

Testicular teratomas occur in their pure form in about 2–7% of patients, while 50% of mixed GCTs may have a teratoma component. In general, pure teratomas do not cause elevations in serum AFP or HCG (Fig. 4) [6]. However, AFP elevation has been found in up to 20–25% of teratomas with mucinous or hepatoid differentiation [35]. In fact, the absence of serum tumor marker elevation in teratomas presents a challenge during post-therapy surveillance. Lack of elevation in tumor markers post-therapy or a normalization of serum tumor makers does not ensure the patient is disease-free [26]. Therefore, diligent imaging evaluation still remains a mainstay of follow-up for these patients.

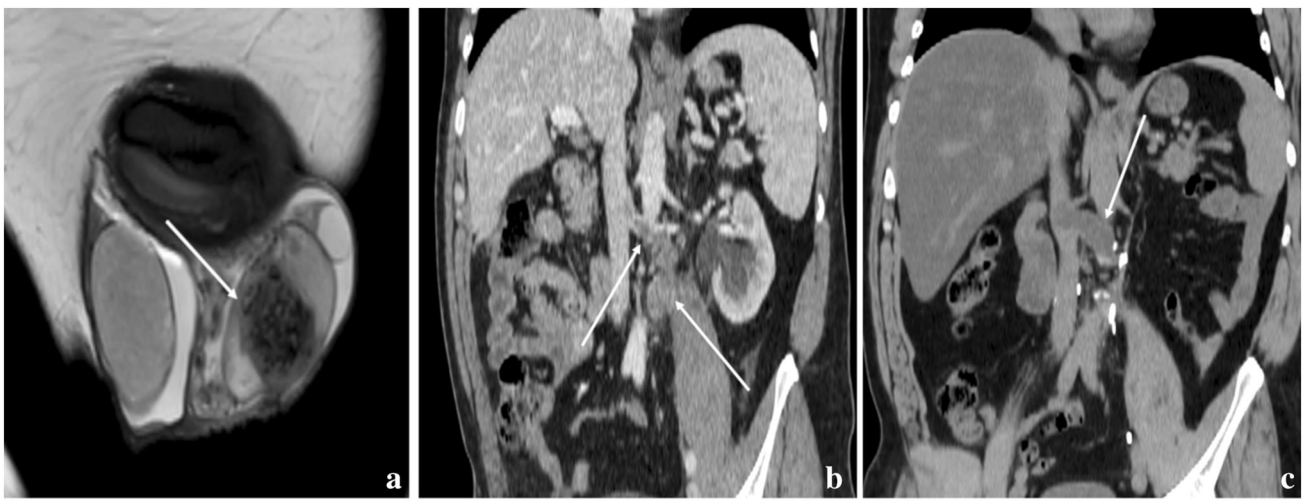

Fig. 3 55-year-old male with left testicular malignant NSGCT of primarily embryonal carcinoma elements. At the time of presentation, T2w MRI (**a**) and coronal, contrast-enhanced CT (**b**) demonstrated an ill-defined, hypointense left testicular mass with left para-aortic adenopathy and secondary left hydronephrosis with renal vein thrombosis (arrows in **b**). Serum tumor markers were elevated, with AFP of 177 (0–9 ng/mL), HCG of 386 IU (< 5 IU), and LDH of 315 (84–246 U/L). Coronal CT after orchiectomy, retroperitoneal lymph node dissection, and left nephrectomy (**c**) shows persistent left renal vein thrombus. As serum tumor markers had normalized, bland thrombus was suspected and the patient treated without additional chemotherapy

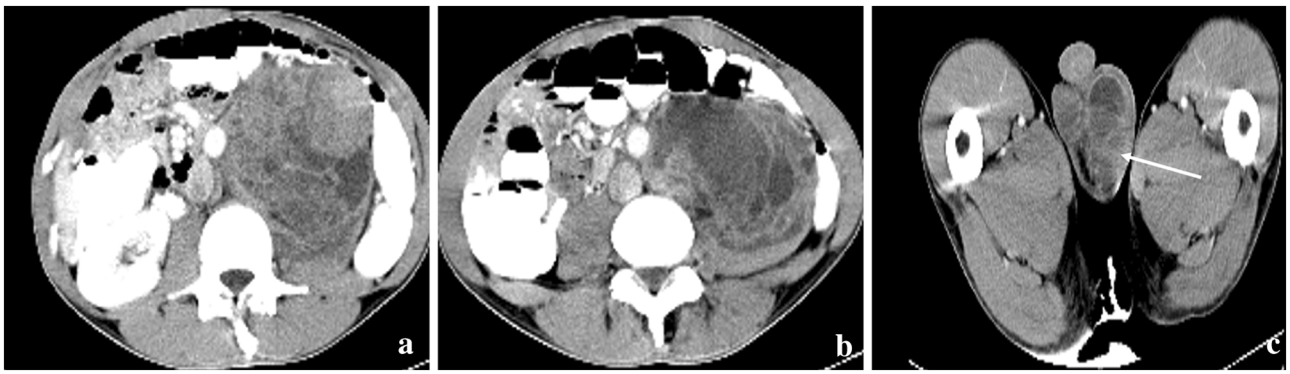

Fig. 4 26-year-old male with metastatic left testicular teratoma. Sequential axial, contrast-enhanced CT images demonstrate a large, mixed solid/cystic mass in the left retroperitoneum, displacing the aorta and small bowel (**a** and **b**). The primary neoplasm is identified within the left testicle (arrow in **c**). All serum tumor markers at the time of presentation and follow-up were normal

Imaging and tumor markers at presentation

The National Comprehensive Cancer Network, American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) publish uniform consensus guidelines on the incorporation of serum tumor markers into GCT staging systems [36, 37], highlighting the importance of laboratory evaluation in the diagnosis and management of testicular GCTs. Furthermore, serum tumor marker levels, along with findings on imaging, comprise the principal components of the most frequently used risk stratification system for GCT as developed by International Germ Cell Cancer Collaborative Group (IGCCCG) [27].

Patients with a suspected testicular mass typically undergo initial assessment with ultrasound to evaluate the size and structural alterations of the involved testicle as well as used to explore the contralateral testicle [38]. Sonographic evaluation is often followed with CT of the chest, abdomen, and pelvis to assess lymph nodes in the thorax, mediastinum and retroperitoneal space, in an investigation for any distant metastasis [39].

Determination of retroperitoneal lymph node status and evaluation for the presence or absence of lung, brain, or bone metastasis are central in the staging of these patients. Critically to radiologists, indeterminate retroperitoneal lymph nodes (that is, those measuring between 1.0 and 1.5 cm) found within the expected drainage zones of right or left testicular neoplasm of patients with otherwise Stage I disease may have an up to 30% chance of being uninvolved with malignancy [40]. As such, serial follow-up with repeat CT in 6–8 weeks is recommended.

Imaging and tumor markers during follow-up

Commonly, serial measurements of tumor markers are obtained prior to each chemotherapy cycle and finally upon completion of chemotherapy [41]. Often, downward serum tumor marker concentration will mirror involution on imaging, indicative of both laboratory and imaging response to treatment (Fig. 5). Reduction in size or changes in appearance may indicate positive response even if malignant cells persist inside of the residuum. [42]. Specifically pertaining to HCG, slower than expected drops in levels have been described when initial levels are $> 50{,}000$ mIU mL [43]. In general, however, lag in time between treatment and marker normalization needs to be considered within the greater context of the patient's clinical and imaging findings [26].

A new rise in serum tumor marker concentration may be the earliest harbinger of disease recurrence [26]. Most frequently, the marker which was initially elevated at the time of presentation will be the same marker elevated at the time of recurrence. Furthermore, even men with negative serum tumor markers at the time of orchiectomy may present with elevated concentrations of serum tumor markers at the time of recurrence, [44]. Similarly, negative serum tumor markers in the setting of lesions in determinate for metastasis may prove to be of useful negative predictive value (Fig. 6). Overall, the entirety of the patient's clinical picture must be assessed, upholding the importance of both imaging and serum tumor markers used in conjunction while following patients with GCTs.

PET/CT is not used in the initial staging of testicular germ cell tumors. However, the National Comprehensive Cancer Network does suggest a role for metabolic imaging in select patients, specifically in men with pure seminomas and residual tumors of > 3 cm and normal levels of AFP and HCG at least 6 weeks after post-chemotherapy [37].

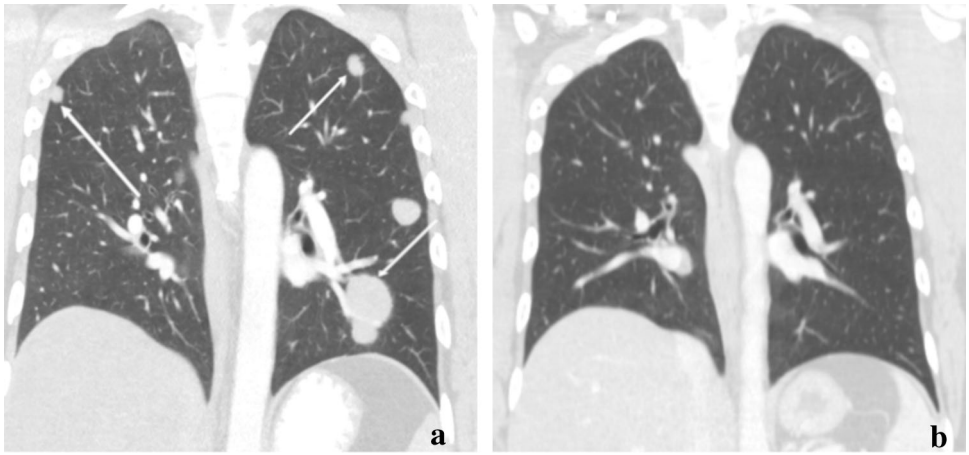

Fig. 5 34-year-old male with mixed NSGCT of embryonal, yolk sac, and teratoma elements. Coronal CT of the chest 2 months after orchiectomy (**a**) was performed after AFP had risen from 33 to 43 ng/mL and HCG had risen from 21 to 30 IU/mL. Multiple metastatic pulmonary nodules are present, new from imaging done at initial staging (not shown). CT of the chest 3 months after adjuvant chemotherapy (**b**) revealed resolution of pulmonary metastases and coincided with normalization of all serum tumor markers

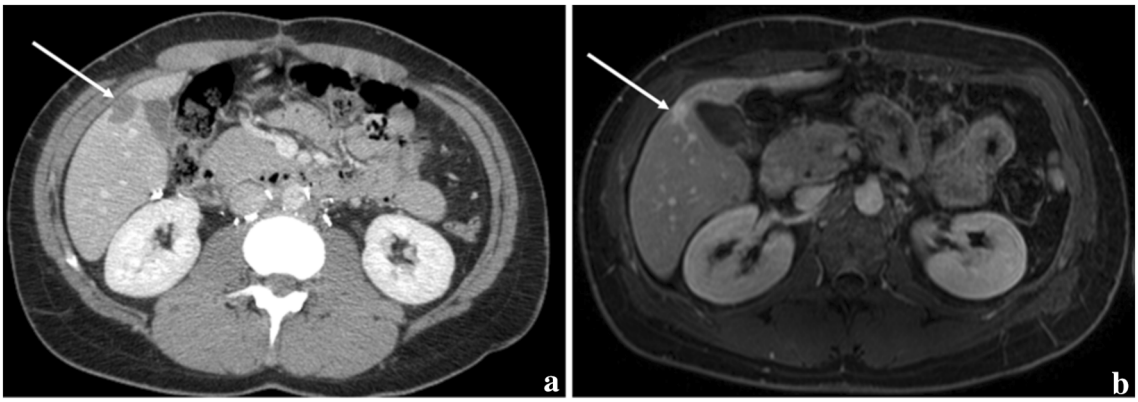

Fig. 6 27-year-old male with NSGCT of primarily embryonal histology. CT of the abdomen after retroperitoneal lymph node dissection (**a**) revealed an indeterminate liver lesion which was considered suspicious for metastasis. A follow-up contrast-enhanced MRI was obtained (post-Gd T1w image in **b**), which again demonstrated the corresponding lesion, the enhancement pattern of which was deemed inconclusive. In spite of normalization of all serum tumor markers, the patient underwent focal liver biopsy to evaluate for metastatic disease. Final pathology of the focal lesion was hemangioma, serving to highlight the negative predictive value of STM evaluation

Though ^{18}F-FDG-PET and CT have poor capacity to detect small-volume lesions, and lower grade neoplasms such as mature cystic teratomas may be non-FDG avid, positive and negative predictive values approaching 90% have been reported in the evaluation of residual disease when using ^{18}F-FDG-PET. In the future, ^{18}F-FDG-PET may have a role in defining sites of relapse in patients whom have elevated serum markers but normal CT scans [45].

Conclusion

Radiologists interpreting imaging performed for the assessment of testicular germ cell tumors must be familiar with the clinical utility of relevant serum tumor marker concentrations. Importantly, as described in National Comprehensive Cancer Network Guidelines, radiologists should be aware that clinical staging of these patients, and the determination of re-imaging intervals thereafter, is dependent on STM levels at the beginning of post-orchiectomy therapy. Classic patterns of serum tumor marker elevation with respect to histologic subtypes of seminomatous and nonseminomatous GCTs have been discussed. Radiologists must recognize the importance of waxing and waning levels of AFP, HCG, and LDH and appreciate the subsequent implications these have in the management of patients in the post-orchiectomy setting and in surveillance for disease progression or recurrence. Given this complexity, a thorough understanding of the natural course of these markers is necessary to accurately

evaluate studies performed for this patient population and positively affect their care.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30. https://doi.org/10.3322/caac.21442.
2. Cancer Facts & Figures 2017 n.d.
3. Einhorn LH. Treatment of testicular cancer: a new and improved model. J Clin Oncol Off J Am Soc Clin Oncol 1990;8:1777–81. https://doi.org/10.1200/JCO.1990.8.11.1777.
4. Klein EA. Tumor markers in testis cancer. Urol Clin North Am 1993;20:67–73.
5. Williamson SR, Delahunt B, Magi-Galluzzi C, Algaba F, Egevad L, Ulbright TM, et al. The World Health Organization 2016 classification of testicular germ cell tumours: a review and update from the International Society of Urological Pathology Testis Consultation Panel. Histopathology 2017;70:335–46. https://doi.org/10.1111/his.13102.
6. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers | Clinical Chemistry n.d.
7. Feldman DR. State-of-the-Art Management of Germ Cell Tumors. Am Soc Clin Oncol Educ Book 2018:319–23. https://doi.org/10.1200/edbk_201139.
8. Aparicio J, Maroto P, García del Muro X, Sánchez-Muñoz A, Gumà J, Margelí M, et al. Prognostic factors for relapse in stage I seminoma: a new nomogram derived from three consecutive, risk-adapted studies from the Spanish Germ Cell Cancer Group (SGCCG). Ann Oncol Off J Eur Soc Med Oncol 2014;25:2173–8. https://doi.org/10.1093/annonc/mdu437.
9. Motzer RJ, Jonasch E, Agarwal N, Beard C, Bhayani S, Bolger GB, et al. Testicular Cancer, Version 2.2016. J Natl Compr Cancer Netw JNCCN 2015;13:772–99.
10. Groll RJ, Warde P, Jewett M a. S. A comprehensive systematic review of testicular germ cell tumor surveillance. Crit Rev Oncol Hematol 2007;64:182–97. https://doi.org/10.1016/j.critrevonc.2007.04.014.
11. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Borgonovo K, Lonati V, et al. Surveillance or Adjuvant Treatment With Chemotherapy or Radiotherapy in Stage I Seminoma: A Systematic Review and Meta-Analysis of 13 Studies. Clin Genitourin Cancer 2015;13:428–34. https://doi.org/10.1016/j.clgc.2015.04.005.
12. Gilligan TD, Seidenfeld J, Basch EM, Einhorn LH, Fancher T, Smith DC, et al. American Society of Clinical Oncology Clinical Practice Guideline on uses of serum tumor markers in adult males with germ cell tumors. J Clin Oncol Off J Am Soc Clin Oncol 2010;28:3388–404. https://doi.org/10.1200/JCO.2009.26.4481.
13. Yuasa T, Yoshiki T, Ogawa O, Tanaka T, Isono T, Mishina M, et al. Detection of alpha-fetoprotein mRNA in seminoma. J Androl 1999;20:336–40.
14. Javadpour N. Significance of elevated serum alphafetoprotein (AFP) in seminoma. Cancer 1980;45:2166–8.
15. Morris MJ, Bosl GJ. Recognizing abnormal marker results that do not reflect disease in patients with germ cell tumors. J Urol 2000;163:796–801.
16. Stang A, Jansen L, Trabert B, Rusner C, Eberle A, Katalinic A, et al. Survival after a diagnosis of testicular germ cell cancers in Germany and the United States, 2002–2006: A high resolution study by histology and age. Cancer Epidemiol 2013;37:492–7. https://doi.org/10.1016/j.canep.2013.03.017.
17. Kaba M, Pirinççi N, Yüksel MB, Geçit İ, Güneş M, Demir M, et al. Serum Levels of Trace Elements in Patients with Testicular Cancers. Int Braz J Urol Off J Braz Soc Urol 2015;41:1101–7. https://doi.org/10.1590/S1677-5538.IBJU.2014.0460.
18. Logothetis CJ. The choriocarcinoma syndrome. Cancer Bull.1984;36:118 – 20. Original article that first describes the choriocar- cinoma syndrome. n.d.
19. Cole LA. Biological functions of hCG and hCG-related molecules. Reprod Biol Endocrinol RBE 2010;8:102. https://doi.org/10.1186/1477-7827-8-102.
20. Reilley MJ, Pagliaro LC. Testicular choriocarcinoma: a rare variant that requires a unique treatment approach. Curr Oncol Rep 2015;17:2–2. https://doi.org/10.1007/s11912-014-0430-0.
21. Wei Y, Wu S, Lin T, He D, Li X, Liu J, et al. Testicular yolk sac tumors in children: a review of 61 patients over 19 years. World J Surg Oncol 2014;12. https://doi.org/10.1186/1477-7819-12-400.
22. Ross JH, Rybicki L, Kay R. Clinical behavior and a contemporary management algorithm for prepubertal testis tumors: a summary of the Prepubertal Testis Tumor Registry. J Urol 2002;168:1675–8; discussion 1678-1679. https://doi.org/10.1097/01.ju.0000030749.27823.f5.
23. Patel P, Balise R, Srinivas S. Variations in normal serum alpha-fetoprotein (AFP) levels in patients with testicular cancer on surveillance. Onkologie 2012;35:588–91. https://doi.org/10.1159/000342695.
24. Read G, Stenning SP, Cullen MH, Parkinson MC, Horwich A, Kaye SB, et al. Medical Research Council prospective study of surveillance for stage I testicular teratoma. Medical Research Council Testicular Tumors Working Party. J Clin Oncol Off J Am Soc Clin Oncol 1992;10:1762–8. https://doi.org/10.1200/JCO.1992.10.11.1762.
25. Germà-Lluch JR, Garcia del Muro X, Maroto P, Paz-Ares L, Arranz JA, Gumà J, et al. Clinical pattern and therapeutic results achieved in 1490 patients with germ-cell tumours of the testis: the experience of the Spanish Germ-Cell Cancer Group (GG). Eur Urol 2002;42:553–62; discussion 562-563.
26. Beck SDW, Foster RS, Bihrle R, Donohue JP. Significance of primary tumor size and preorchiectomy serum tumor marker level in predicting pathologic stage at retroperitoneal lymph node dissection in clinical Stage A nonseminomatous germ cell tumors. Urology 2007;69:557–9. https://doi.org/10.1016/j.urology.2006.12.011.
27. Milose JC, Filson CP, Weizer AZ, Hafez KS, Montgomery JS. Role of biochemical markers in testicular cancer: diagnosis, staging, and surveillance. Open Access J Urol 2011;4:1–8. https://doi.org/10.2147/OAJU.S15063.
28. IInternational Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. International Germ Cell Cancer Collaborative Group. J Clin Oncol Off J Am Soc Clin Oncol 1997;15:594–603. https://doi.org/10.1200/JCO.1997.15.2.594.
29. Atsü N, Eskiçorapçi S, Uner A, Ekici S, Güngen Y, Erkan I, et al. A novel surveillance protocol for stage I nonseminomatous germ cell testicular tumours. BJU Int 2003;92:32–5.
30. Nicolai N, Pizzocaro G. A surveillance study of clinical stage I nonseminomatous germ cell tumors of the testis: 10-year followup. J Urol 1995;154:1045–9.
31. Vugrin D, Cvitkovic E, Posner J, Hajdu S, Golbey RB. Neurological complications of malignant germ cell tumors of testis: biology of brain metastases (I). Cancer 1979;44:2349–53.
32. Kawanami K, Wakao N, Kamiya M, Takeuchi M, Hirasawa A, Takahashi E, et al. A case of mediastinal embryonal carcinoma successfully treated by integrative therapy. Nagoya J Med Sci 2014;76:225–33.

33. Pokharna P, Sharma N, Tiwari A, Devgaraha S, Mathur RM. Testicular embryonal cell carcinoma presenting as haemoptysis and skin nodules. Indian J Chest Dis Allied Sci 2014;56:125–7.
34. Moul JW, McCarthy WF, Fernandez EB, Sesterhenn IA. Percentage of embryonal carcinoma and of vascular invasion predicts pathological stage in clinical stage I nonseminomatous testicular cancer. Cancer Res 1994;54:362–4.
35. Gama R, Smith MG, White WF, Kwong P. Hyperthyroidism from an embryonal carcinoma. J R Soc Med 1997;90:446–7.
36. Richie J, Steele G. Neoplasms of the testis. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, editors. Campbell-Walsh Urology. Philadelphia, PA: Saunders; 2007. pp. 907–908 n.d.
37. Greene FL, Sobin LH. A worldwide approach to the TNM staging system: collaborative efforts of the AJCC and UICC. J Surg Oncol 2009;99:269–72. https://doi.org/10.1002/jso.21237.
38. NCCN Guidelines. NCCN Clin Pract Guidel Oncol Testic Cancer 22018 n.d. https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf.
39. Oldenburg J, Fosså SD, Nuver J, Heidenreich A, Schmoll H-J, Bokemeyer C, et al. Testicular seminoma and non-seminoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24:vi125–32. https://doi.org/10.1093/annonc/mdt304.
40. Tandstad T, Cohn-Cedermark G, Dahl O, Stierner U, Cavallin-Stahl E, Bremnes RM, et al. Long-term follow-up after risk-adapted treatment in clinical stage 1 (CS1) nonseminomatous germ-cell testicular cancer (NSGCT) implementing adjuvant CVB chemotherapy. A SWENOTECA study. Ann Oncol Off J Eur Soc Med Oncol 2010;21:1858–63. https://doi.org/10.1093/annonc/mdq026.
41. Gilligan TD, Hayes DF, Seidenfeld J, Temin S. ASCO Clinical Practice Guideline on Uses of Serum Tumor Markers in Adult Males With Germ Cell Tumors. J Oncol Pract 2010;6:199–202. https://doi.org/10.1200/JOP.777010.
42. Husband J, Barrett A, Peckham M. The role of computer tomography in the assessment of tumour volume in patients with malignant testicular teratoma. Br J Radiol 1981; 15:50-53.
43. Zon RT, Nichols C, Einhorn LH. Management strategies and outcomes of germ cell tumor patients with very high human chorionic gonadotropin levels. J Clin Oncol Off J Am Soc Clin Oncol 1998;16:1294–7. https://doi.org/10.1200/JCO.1998.16.4.1294.
44. Trigo JM, Tabernero JM, Paz-Ares L, García-Llano JL, Mora J, Lianes P, et al. Tumor markers at the time of recurrence in patients with germ cell tumors. Cancer 2000;88:162–8.
45. Husband JE, Koh D-M. Multimodality imaging of testicular tumours. Cancer Imaging 2005;4:S101–7. https://doi.org/10.1102/1470-7330.2004.0052.