ORIGINAL ARTICLE

ACR Appropriateness Criteria Staging of Testicular Malignancy

Joseph H. Yacoub, MD[a], Aytekin Oto, MD[b], Brian C. Allen, MD[c], Fergus V. Coakley, MD[d],
Barak Friedman, MD[e], Matthew S. Hartman, MD[f], Keyanoosh Hosseinzadeh, MD[g],
Christopher Porter, MD[h], V. Anik Sahni, MD[i], Gary S. Sudakoff, MD[j], Sadhna Verma, MD[k],
Carolyn L. Wang, MD[l], Erick M. Remer, MD[m], Steven C. Eberhardt, MD[n]

Abstract

Testicular cancer represents only 1% of all malignancies occurring in men. However, it is the most frequent malignancy in men between the ages of 20 and 34 years, accounting for 10% to 14% of cancer incidence in that age group. In most instances, the diagnosis of testicular tumors is established with a carefully performed physical examination and scrotal ultrasonography. Tumor markers are useful for determining the presence of residual disease. Cross-sectional imaging studies (CT, MRI) are useful in determining the location of metastases. Chest radiography and CT are used to assess pulmonary disease. Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) PET scans have slightly higher sensitivity than CT, but their role in staging testicular cancer has not been determined in a large study. FDG PET may play a role in the follow-up of higher stage seminoma after chemotherapy. Bone scans are useful in the absence of FDG PET scans and should be used when bone metastases are suspected.

The ACR Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed annually by a multidisciplinary expert panel. The guideline development and revision include an extensive analysis of current medical literature from peer reviewed journals and the application of well-established methodologies (the RAND/UCLA Appropriateness Method and the Grading of Recommendations Assessment, Development, and Evaluation) to rate the appropriateness of imaging and treatment procedures for specific clinical scenarios. In those instances in which evidence is lacking or equivocal, expert opinion may supplement the available evidence to recommend imaging or treatment.

Key Words: Appropriateness Criteria, testis, cancer, staging, imaging

J Am Coll Radiol 2016;■:■-■. Copyright © 2016 American College of Radiology

SUMMARY OF LITERATURE REVIEW

Introduction/Background

Although carcinoma of the testicle is relatively uncommon, representing only 1% of all malignancies occurring in men, it is the most frequent malignancy in men between the ages of 20 and 34 years, accounting for 10% to 14% of cancer incidence in that age group [1]. The National Cancer Institute estimated that there would be about 8,430 new

[a]Loyola University of Chicago, Chicago, Illinois.

[b]University of Chicago, Chicago, Illinois.

[c]Duke University Medical Center, Durham, North Carolina.

[d]Oregon Health and Science University, Portland, Oregon.

[e]Long Island Jewish Medical Center, New Hyde Park, New York.

[f]Allegheny General Hospital, Pittsburgh, Pennsylvania.

[g]Wake Forest University School of Medicine, Winston Salem, North Carolina.

[h]Virginia Mason Medical Center, Seattle, Washington, American Urological Association, Linthicum, Maryland.

[i]Brigham & Women's Hospital, Boston, Massachusetts.

[j]Medical College of Wisconsin, Milwaukee, Wisconsin.

[k]University of Cincinnati Medical Center, Cincinnati, Ohio.

[l]University of Washington, Seattle Cancer Care Alliance, Seattle, Washington.

[m]Cleveland Clinic, Cleveland, Ohio.

[n]University of New Mexico, Albuquerque, New Mexico.

Corresponding author: Joseph H. Yacoub, MD, Loyola University of Chicago, 1032 W. Sheridan Rd., Chicago, IL 60660; e-mail: joeyacoub@gmail.com.

Reprint requests to: publications@acr.org.

cases of testicular cancer in the United States and about 380 deaths from the disease in 2015 [1].

More than 90% of testicular tumors are of germ cell origin and are malignant. Of these, 40% are seminomas. The nonseminomatous tumors are clinically more aggressive and include embryonal cell carcinoma (15%-20%), teratoma (5%-10%), and choriocarcinoma (<1%) [2,3]. Testicular cancer has an excellent prognosis, with 10-year survival rates exceeding 96% [4]. Non-germ-cell tumors are typically benign and have their origins from the Leydig and Sertoli cells or from connective tissue stroma.

Various systems have been used for staging patients with testicular cancer, but most commonly the American Joint Commission on Cancer's system for staging and end results reporting is used [5].

Testicular tumors metastasize by either the hematogenous or lymphatic route. Most follow the testicular lymphatic drainage alongside the testicular veins to regional lymph node groups. Tumors from the left testis will typically metastasize to the left para-aortic nodal group just below the left renal vein, and right testicular tumors will typically metastasize to the paracaval, precaval, and aortocaval nodes. Crossover of lymphatic involvement may occur in either right-sided or left-sided tumors; however, it is unusual to have contralateral metastasis without involvement of the ipsilateral nodes [6]. Regional lymph node disease can further spread to nonregional lymph node groups, including common iliac, internal iliac, and external iliac nodes, or via the thoracic duct to the left supraclavicular nodes and subsequently to the lungs, constituting distant metastasis [5]. Prior scrotal/inguinal surgery can alter the lymphatic drainage, and therefore external iliac and inguinal lymph nodes are considered regional in that context [7].

Tumor Markers

Tumor markers such as lactate dehydrogenase, α-fetoprotein (AFP), and β–human chorionic gonadotropin are helpful not only in diagnosing patients with testicular tumors but in staging them as well. Approximately 90% of patients with advanced nonseminomatous tumors will have elevated levels of one or more of these markers [5].

AFP is elevated in approximately 50% to 70% of those with embryonal cell carcinoma, yolk sac carcinoma, or tumors of mixed composition [3,8]. Beta–human chorionic gonadotropin is elevated in 40% to 60% of patients with testicular cancer, including all those with choriocarcinoma, 80% of those with embryonal cell

carcinoma, and 10% to 25% of those with histologically pure seminoma [9,10]. Elevated AFP is never found in pure seminomas or choriocarcinomas.

Obtaining tumor markers before and after orchiectomy is also very helpful in determining whether any residual disease is present and in planning further therapy. Additionally, tumor markers are essential in the follow-up evaluation to assess both the need for and response to therapy (eg, chemotherapy). Some patients may exhibit an elevation in serum markers at any time despite normal clinical findings and imaging studies. If causes for false-positive marker elevation are ruled out, these patients need to be treated for active disease [11]. Significant marker elevation at presentation often portends a worse prognosis for the patient.

A minority of patients with nonseminomatous tumors after treatment may develop retroperitoneal masses of relatively low attenuation, which represent mature teratoma (differentiated teratoma in the British literature) rather than new or residual lymphadenopathy [12]. This process is referred to as growing teratoma syndrome. It is a benign process; however, the tumors continue to grow over time and may result in significant morbidity because of their bulk. Mature teratoma is treated by surgical resection. Differentiation between mature teratoma and residual or recurrent lymphadenopathy may be possible by measuring serum marker levels. Treatment options may differ depending on the histology of the mass(es). Neither CT nor MRI can reliably separate the two entities, which may sometimes coexist.

Overview of Imaging Modalities

Many imaging studies have been used in assessing patients with testicular tumors. In years past, intravenous urography and lymphangiography [2,13-15] were commonly used for staging purposes; however, with the development of newer techniques, the use of these imaging studies is of historical interest for this purpose. Studies used today to assess the retroperitoneum include abdominal ultrasonography, CT, MRI, and PET imaging with fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG). Studies used to assess pulmonary disease include chest radiography and chest CT. Ultrasonography continues to be used preferentially for assessing the primary tumors (see Variant 1).

Scrotal Ultrasonography. Scrotal ultrasonography is frequently used and should always be the initial imaging modality in assessing patients with scrotal masses. This study can differentiate fluid-filled spermatoceles and

100% [2,14,15,23-26]. Experience also indicates that accuracy declines in patients with limited disease (stage N1 and stage N2) and also if the upper limit of normal lymph node size is lowered to 4 mm [20,23,25]. Of note, most of these studies are relatively old and were done with single-slice CT. Limited new data suggest similar accuracy with multislice CT compared with single-slice CT [27]. It is important to recognize that a significant percentage of metastatic lymph nodes will be <1 cm, up to 60% in one series [28]. For this reason, some authors suggest using a cutoff value of 0.7 to 0.8 cm in testicular cancer, at the expense of reduced specificity [28,29]. These cutoff values are for the short-axis measurement when assessing the likelihood of nodal disease (N0 vs N1 disease); however, when assessing the nodal burden, the lymph nodes should be measured in long axis (N1 vs N2 and N3 disease) [7,29]. For reporting purposes as regards staging, providing bidimensional measures for lymph nodes is a useful solution.

Surveillance is becoming the strategy of choice for an increasing number of patients with stage I germ cell tumor, with repeated CT imaging playing a critical role in this strategy [30]. Because of the young age of this patient population, increasing use of CT has led to concerns regarding the increasing risk of radiation exposure. However, available data are still controversial. Studies have estimated an increased lifetime risk for cancer in patients on surveillance, on the basis of the observed cumulative effective dose [31,32]; nevertheless, in a population-based study of patients with stage I testicular cancer, secondary malignancies of the abdomen-pelvis were found to be uncommon, and the risk for secondary cancer did not vary with the amount of diagnostic radiation exposure [33]. The concern about radiation exposure has led to radiation reduction strategies in surveillance protocols, which no longer include chest CT [34], but eliminate pelvic CT except in cases in which the pelvis is deemed high risk [35,36], and include the use of a low-dose multidetector CT protocol [37]. The 2014 National Comprehensive Cancer Network guidelines reduced the maximum number of CT scans to 13 over six years [38].

MRI. MRI has also been used in the staging of testicular tumors [13,39-42]; evidence indicates that it is comparable to CT [13,40]. It can be useful in patients in whom iodinated contrast cannot be given [43,44]. Diffusion-weighted imaging is a promising technique that can improve the identification of lymph nodes on the basis of degree of restricted diffusion; however, it is still limited by significant overlap between benign and malignant lymph nodes [7]. As more attention is turned to radiation exposure in patients with testicular cancer undergoing repeated cross-sectional imaging at a young age [31], MRI may represent an advantageous alternative to CT [27,42]. The disadvantages of MRI are longer examination time, high cost, and low availability.

MRI could also be useful as a second-line investigation for preoperative evaluation of the testes when ultrasonography is inconclusive, with some evidence that it can distinguish germ cell tumors from benign mimics and lymphoma and therefore may have the potential to spare a small subset of patients from getting unnecessary orchiectomies [45-48]. MRI of the brain is indicated in few cases in which there is clinical suspicion of brain metastases.

Chest Radiography and Chest CT. Many studies have addressed the value of chest radiography in assessing pulmonary metastases [49,50]. These studies indicate that chest radiography alone is satisfactory in the initial staging of patients with testicular malignancies. Chest CT offers little in these patients; however, it is indicated in patients with positive results on abdominal CT or abnormal findings on chest radiography. Although CT is more sensitive for detecting recurrent disease in the chest [34,51], recent studies indicate that chest radiography is sufficient for follow-up for stage I seminomas [34,36,50,52] and stage I nonseminomas [34,50]. In stage II and higher nonseminomas, chest CT is the study of choice, with no additional value for routine chest radiography [36,49,53]. There were no studies specifically addressing seminomas with retroperitoneal lymphadenopathy. Therefore, chest CT remains the study of choice for follow-up in those patients.

PET

FDG PET has been used in assessing patients with testicular cancers, but its true value in staging patients has yet to be defined. In initial staging, PET may be only slightly more sensitive than CT [54-59]. FDG PET is superior to CT in the prediction of viable tumor in postchemotherapy seminoma residuals [60-65], and therefore it can be helpful for follow-up of patients with stage IIB, IIC, and III seminoma who have residual masses >3 cm and normal markers. In nonseminoma, on the other hand, the value of FDG PET is limited. It has limited predictive value for the evaluation of tumor viability in residual masses [66] and cannot differentiate mature teratoma from necrosis or fibrosis [34,43,67].

Table 1. Relative radiation level designations

RRL	Adult Effective Dose Estimate Range (mSv)	Pediatric Effective Dose Estimate Range (mSv)
○	0	0
☢	<0.1	<0.03
☢☢	0.1-1	0.03-0.3
☢☢☢	1-10	0.3-3
☢☢☢☢	10-30	3-10
☢☢☢☢☢	30-100	10-30

Note: Relative radiation level (RRL) assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "varies."

Furthermore, a recent trial by the National Cancer Research Institute's Testis Cancer Clinical Studies Group using FDG PET in an effort to predict relapse in patients with high-risk stage I nonseminomatous germ cell tumors was terminated early because of unacceptable relapse rates among PET-negative patients [68].

Bone Scan. Bone scans can be useful in assessing early bone lesions before they are detectable by CT [69], although one study suggests that FDG PET scans are more sensitive and can substitute for conventional bone scans [70].

Summary of Evidence

Of the 70 references cited in "ACR Appropriateness Criteria Staging of Testicular Malignancy," 63 are categorized as diagnostic references, including 12 good-quality studies and 18 quality studies that may have design limitations. Additionally, six references are categorized as therapeutic references, including one good-quality study and one quality study that may have design limitations. There are 37 references that may not be useful as primary evidence. There is one reference that is a meta-analysis study.

The 70 references cited in "ACR Appropriateness Criteria Staging of Testicular Malignancy" were published from 1981 to 2015.

Although there are references that report on studies with design limitations, 13 good-quality studies provide good evidence.

RELATIVE RADIATION LEVEL INFORMATION

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that seems to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower compared with those specified for adults (see Table 1). Additional information regarding radiation dose assessment for imaging examinations can be found in *ACR Appropriateness Criteria: Radiation Dose Assessment Introduction* [71].

SUPPORTING DOCUMENTS

For additional information on the ACR Appropriateness Criteria methodology and other supporting documents, go to www.acr.org/ac.

TAKE-HOME POINTS

- In most instances, the diagnosis of testicular tumors is established with a carefully performed physical examination and scrotal ultrasonography.
- Tumor markers are useful for determining the presence of residual disease.
- Cross-sectional imaging studies (CT, MRI) are useful in determining the location of metastases.
- FDG PET scans have slightly higher sensitivity than CT, but their role in staging testicular cancer has not been determined in a large study. FDG PET may play a role in follow-up of higher stage seminoma after chemotherapy.
- Bone scans are useful in the absence of FDG PET scans and should be used when bone metastases are suspected.

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