Diagnostic Applications of Nuclear Medicine: Testicular Cancer

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Abstract

Testicular cancer is the most common solid-non hematological cancer diagnosed in young adult men. Personal history of testicular cancer is a major risk factor for developing testicular cancer. Testicular germ cell tumors are the most common tumors, these are further divided into seminomas and non seminomatous germ cell tumors. Tumors generally present as painless testicular mass, the first investigation is testicular ultrasound followed by serum biomarkers. MRI can be used as a problem solver only in equivocal cases. Radical orchiectomy provides therapy as well as pathological T staging. CT scan is the primary investigation for assessing lymph node status and for evaluation of distant metastasis. [^{18}F]FDG PET/CT is not recommended for diagnosis of primary testicular cancer with reported unsatisfactory negative predictive value. Nevertheless PET/CT offers several advantages over CT particularly for patients with equivocal CT findings and in patients who exhibit elevated tumor markers and negative CT scan. In addition, [^{18}F]FDG PET/CT is especially useful for evaluation of post chemotherapy residual masses in metastatic seminoma. [^{18}F]FDG PET/CT is, however, not routinely indicated for post chemotherapy evaluation of non seminomatous germ cell tumors because of high false negative rate in teratomas.

Keywords

PET/CT • Testicular cancer • Seminoma • Germ cell tumor • Non germ cell tumor • Teratoma

Glossary

[^{18}F]FDG	2-Deoxy-2-[^{18}F]fluoro-D-glucose
AFP	α-Fetoprotein
AJCC	American Joint Committee on Cancer
Beta-hCG	Beta-human chorionic gonadotropin
BRAF	Gene encoding for the B-Raf protein, a serine/threonine-protein kinase (also known as the proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B)

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C-KIT	Proto-oncogene encoding for tyrosine-protein kinase Kit (or CD117), also known as mast/stem cell growth factor receptor (SCFR)
CT	X-ray computed tomography
CXCR4	Gene encoding for C-X-C chemokine receptor type 4 (CXCR-4), also known as fusin or CD184 (cluster of differentiation 184)
EGFR	Epidermal growth factor receptor; the mutated form EGFRvIII plays a prominent role in tumorigenesis and proangiogenic signaling
GCT	Germ cell tumor
IGD	In greatest dimension
IGF	Insulin-like factor
LDH	Lactate dehydrogenase
M	Metastasis status according to the AJCC/UICC TNM staging system
MRI	Magnetic resonance imaging
N	Lymph node status according to the AJCC/UICC TNM staging system
NCCN	National Comprehensive Cancer Network
NSGCT	Nonseminomatous germ cell tumor
p53	Tumor protein p53, also known as cellular tumor antigen p53, phosphoprotein p53, tumor suppressor p53, antigen NY-CO-13, or transformation-related protein 53 (TRP53)
PET	Positron emission tomography
PET/CT	Positron emission tomography/Computed tomography
RAS	Oncogene regulating signaling cascades
SDF-1	Gene encoding for the stromal cell-derived factor 1, also known as C-X-C motif chemokine 12 (CXCL12)
SNP	Single nucleotide polymorphism
SPECT	Single-photon emission tomography
SPECT/CT	Single-photon emission tomography/Computed tomography
T	Tumor status according to the AJCC/UICC TNM staging system
TGCT	Testicular germ cell tumor
TNM	AJCC/UICC staging system based on parameters "T" (tumor status), "N" (lymph node status), and "M" (distant metastasis status)
UICC	Union Internationale Contre le Cancer (International Union Against Cancer)
ULN	Upper limit of normal range
US	Ultrasonography
WHO	World Health Organization

Contents

Epidemiology of Testicular Cancer

The incidence of testicular cancer was estimated at 5.6 cases per 100,000 men in the United States in 2011, with a rising trend over the past decades in the United States and in the Western world in general [1]. Testicular cancer can affect men at all ages; its incidence peaks at ages between 25 and 29 years, with 14.3 cases diagnosed per 100,000 men per year in this age group. With this incidence, testicular cancer is the most common solid non-hematological cancer diagnosed in young adult men. There is a wide variability of incidence of testicular cancer among different races, the highest rates being reported among Caucasians and the lowest rates among Blacks and Asians. In the United States, the incidence of testicular cancer in White Americans is fivefold more common than in Black Americans and fourfold more common than in Asians [1].

Risk Factors

Personal history of prior testicular cancer is a major risk factor for developing testicular cancer, as there is actually a 12-fold increase in the risk of developing another testicular cancer in patients with prior cancer in the contralateral testicle [2]. In addition, 2% of germ cell testicular cancers is bilateral at presentation. History of surgically uncorrected undescended testicle increases the risk for developing testicular cancer by up to eightfold; this risk remains high in cases where surgical correction was performed after puberty [2]. There is a growing body of evidence suggesting that exposure to toxic substances increases the risk of testicular cancer. The main substances with a potential association with testicular cancer include organic chlorides, polychlorinated biphenyls, polyvinyl chlorides, phthalates, marijuana, and tobacco [1]. Prenatal exposure to estrogens has been suggested as a risk factor as well, although this notion remains controversial [1]. Male infertility increases the risk of developing testicular cancer by nearly threefold, an observation that suggests a common etiology between testicular cancer and the testicular dysgenesis syndrome, Hiwi protein and chromosome 12 aneuploidy, DNA mismatch repair, and Y chromosome instability [1]. Microcalcifications are often seen on testicular ultrasonography; although this finding is not known to be a risk factor per se, testicular tumors are more likely to be found in young men with microcalcifications than in those without [1, 3].

Histologically, the presence of intratubular germ cell tumor (carcinoma in situ) is considered to be a well-established risk factor for testicular cancer. Intratubular germ cell tumors are frequently seen in surgical specimens of orchiectomy and in the contralateral testis of patients with history of testicular cancer [1].

Genetic Predisposition

There is evidence that family history of testicular cancer is a significant risk factor for developing the disease, and it has been estimated that sons or brothers of patients with testicular cancer are at a six- to tenfold higher risk of developing the cancer themselves. It is not clear, however, whether this familial risk factor is genetic or environmental. Furthermore, linkage analysis studies have failed to identify any significant genetic linkage in these cases of familial testicular germ cell tumors (TGCTs) [1, 4].

In sporadic cases, the most common genetic alteration in patients with infertility is a deletion of 1.6 Mb (deletion gr/gr) in the AZF region of the Y chromosome, which doubles the risk for developing TGCTs [5]. In addition, at least 25 single nucleotide polymorphism (SNPs) associated with genetic predisposition in several chromosomal regions have been identified in patients with TGCTs; these SNPs most likely increase genetic susceptibility to develop TGCT [5]. Although these SNPs may be biologically

significant, they account for less than 20% of the familial risk of TGCTs [5].

Underlying Molecular Biology Changes

A number of molecular alterations have been described in testicular germ cell tumors. C-KIT mutations are the most common single-nucleotide variations, with 10% of all TGCTs and 20% of seminomas harboring a C-KIT mutation microsatellite instability (MSI); BRAF mutations are associated with chemo-refractory TGCT. One study has shown evidence for epidermal growth factor receptor (EGFR) amplification as a possible genetic aberration associated with chemoresistance [6]. A small subset of TGCTs (predominantly seminomas) have mutations in this RAS oncogene family, but these mutations are of unclear clinical and pathobiologic significance. TP53 mutations are not common in TGCTs; however, overexpression of wild-type p53 may be seen at immunohistochemistry [5, 7].

Genomic DNA methylation studies have shown a contrast in methylation patterns between TGCT tissue and normal tissue, as well as between seminoma and normal tissue (generally decreased/hypomethylated) versus nonseminomatous TGCT (generally methylated) [5, 7].

Skakkebæk proposed a model that suggests that fetal gonocytes beyond normal development in spermatogonia could present abnormal cell division mediated by a receptor/SCF kit, a paracrine circuit leading to uncontrolled proliferation of gonocytes. The subsequent invasive growth is mediated by stimulation of postnatal and pubertal gonadotropins [5, 8]. A second model proposed by Chaganti and Houldsworth suggests that aberrant chromatid exchange during meiotic division could lead to block p53-dependent apoptotic response and to cell cycle reset, therefore to genomic instability [5, 9].

Several molecular mediators in the testicular microenvironment have recently been associated with the transition from germ cell tumor in situ to an aggressive phenotype of TGCT cells. Several data indicate that the IGF-1/IGF1R and SDF-1/CXCR4 signaling pathways are important mediators in the pathogenesis of TGCTs and also in the acquisition of phenotypic features associated with metastatic ability, such as proliferation, differentiation, migration, cellular survival, and angiogenesis [5].

Histopathology of Testicular Cancer

Testicular germ cell tumors (TGCTs) are the most common testicular cancers, as this group constitutes approximately 95% of all testicular cancers. TGCTs arise from the germinal epithelium in seminiferous tubules. Other rare sites of GCTs are the pineal gland, neurohypophysis, mediastinum, and retroperitoneum [1, 7, 10].

TGCTs are currently subdivided according to the 2004 World Health Organization (WHO) classification into seminomas and nonseminomatous germ cell tumors (NSGCTs). Pure seminomas are the most common TGCTs, accounting for approximately 50% of all TGCTs. Typically, seminomas occur in older men when compared with NSGCT; the mean age of patients at presentation is 40 years, and more than 80% occur after the age of 30. The clinical and pathological diagnosis of a seminoma is restricted to pure seminoma histology and a normal serum concentration of α-fetoprotein (AFP). Seminomas are chemo- and radiosensitive, and these tumors are characterized by a high 5-year survival – reaching approximately 95% [1, 7].

NSGCTs are clinically more aggressive than pure seminomas and often include multiple cell types including embryonal cell carcinomas, choriocarcinomas, yolk sac tumors, and teratomas. Approximately one-third of TGCTs contain mixed features of seminomas and NGCTs; when both features of seminomas and NSGCT are present, clinical management is adopted according to guidelines for nonseminoma tumors. These mixed neoplasms are actually the second most common testicular cancer after seminomas [1, 7, 10].

Pure embryonal carcinomas are only occasionally encountered, whereas choriocarcinomas and yolk sac tumors are rarely seen after puberty. Yolk sac tumor is the most common testicular cancer in boys younger than 2 years. Pure choriocarcinomas

are exceedingly rare; in contrast to other TGCTs, choriocarcinomas usually present with symptoms of metastasis rather than as a testicular mass. Teratomas are further classified into mature or immature type, depending on cell differentiation. Rarely, a teratoma histologically resembles a somatic cancer, such as sarcoma or adenocarcinoma, and is then referred to as a teratoma with malignant transformation. Pure teratoma is uncommon in the postpubertal setting, accounting for fewer than 5% of all TGCTs. In children, prepubertal pure teratoma comprises nearly one-third of the testicular tumors; mature prepubertal teratomas are benign and do not metastasize. Postpubertal teratomas may be associated with metastasis in approximately one-third of the cases and typically contain other TGCT components [1, 7, 10].

Non-germ cell tumors are rare and comprise approximately 5% of testicular cancers; they include Leydig cell, Sertoli cell, and granulosa cell tumors. In men older than 60 years, lymphoma is the most common testicular malignancy. Other rare testicular tumors include leukemia, sarcoma, leiomyoma, vascular tumors, fibromas, and neurofibromas [7, 10, 11].

Serum Biomarkers

The serum tumor markers α-fetoprotein (AFP), lactate dehydrogenase (LDH), and beta-human chorionic gonadotropin (beta-hCG) are critical in the diagnosis and management of TGCTs. These serum tumor-associated markers should be evaluated before and after treatment, as well as throughout follow-up. Serum tumor markers are very useful for monitoring all stages of nonseminomas and in monitoring metastatic seminomas. AFP is a serum tumor marker produced by nonseminomatous cells (i.e., embryonal carcinoma, yolk sac tumor) and may be seen at any stage. The half-life of AFP (a glycoprotein that can be considered as the fetal precursor of serum albumin) in serum is 5–7 days. In the absence of testicular malignancy, AFP elevation can occur in infants under 1-year-old, during liver dysfunction (hepatitis, cirrhosis, hepatocellular carcinoma), and in other non-testicular malignancies (liver, pancreatic, gastric, lung). In testicular cancer, AFP is never associated with pure seminoma [12–14].

In patients with choriocarcinomas, beta-hCG is always elevated; it is also elevated in up to 10% of patients with pure seminomas and in some patients with seminomatous or other nonseminomatous tumors. Elevations of beta-hCG must be interpreted with caution, as its serum levels can be abnormally increased in patients with hypogonadism or in marijuana users; its half-life in serum is 1–3 days. LDH (an enzyme with a half-life in serum of 5–7 days) is a less specific marker than either AFP or beta-hCG; it can be elevated in both seminomas and NSGCTs, and high serum levels typically indicate bulky or extensive disease [13, 14].

Clinical Presentation, Staging, and Prognostic Stratification

A testicular tumor typically presents as a painless testicular mass. After history taking and physical examination, the first-line diagnostic test is testicular ultrasound (US), which remains the cornerstone of primary imaging in patients with testicular cancer and should be performed on both testicles. Once a suspected tumor is confirmed, the measurement of serum tumor markers including AFP, beta-hCG, and LDH is the next step for diagnosis and staging. Patients with confirmed testicular tumor must undergo computed tomography (CT) examination of the chest, abdomen, and pelvis as an integral part of the staging evaluation. Bone scan or spine MRI is indicated only in patients with bone pain. Brain MRI is indicated in patients with symptoms, in patients with lung metastasis, and in patients with high beta-hCG levels [14, 15].

Radical inguinal orchiectomy provides therapy-oriented as well as diagnostic and staging information. In particular, orchiectomy provides definitive histopathology information regarding tumor subtype and is considered curative for nearly 80% of low-stage seminomas and for approximately 60–70% of low-stage NSGCTs [14, 15].

The correct interpretation of serum biomarkers, in conjunction with correct histopathology reading and interpretation of CT images, is the mainstays of

Table 1 TNM classification of testicular cancer

pT: primary tumor[a]	
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g., histologic scar in the testis)
pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)
pT1	Tumor limited to the testis and epididymis without vascular/lymphatic invasion; tumor may invade tunica albuginea, but not tunica vaginalis
pT2	Tumor limited to the testis and epididymis with vascular/lymphatic invasion or tumor extending through into the tunica albuginea with involvement of tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion
N: regional lymph nodes (clinical)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass ≤2 cm IGD or multiple lymph nodes, none >2 cm IGD
N2	Metastasis with a lymph node mass >2 cm but not >5 cm IGD or multiple lymph nodes with any one mass >2 cm but not >5 cm IGD
N3	Metastasis with a lymph node mass >5 cm IGD
pN: pathologic lymph nodes	
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass ≤2 cm IGD and ≤5 positive nodes, none >2 cm IGD
pN2	Metastasis with a lymph node mass >2 cm but not >5 cm IGD; or >5 nodes positive, none >5 cm IGD; or evidence of extranodal tumor extension
pN3	Metastasis with a lymph node mass >5 cm IGD
M: distant metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s) or lung
M1b	Other sites
S: serum tumor markers	
SX	Serum marker studies not available or not performed
S0	Serum marker levels within normal limits
S1	LDH <1.5 × ULN and hCG <5,000 mIU/mL and AFP <1,000 ng/mL
S2	LDH 1.5–10 × ULN or hCG 5,000–50,000 mIU/mL or AFP 1,000–10,000 ng/mL
S3	LDH >10 × ULN or hCG >50,000 mIU/mL or AFP >10,000 ng/mL

IGD in greatest dimension, *LDH* lactate dehydrogenase, *hCG* human chorionic gonadotropin, *AFP* α-fetoprotein, *ULN* upper limit of normal range

[a]Except for pTis and pT4, for which radical orchiectomy is not always necessary for classification purposes, the extent of the primary tumor is classified after radical orchiectomy. In other circumstances, TX is used if no radical orchiectomy has been performed

patient staging and prognostic stratification. Tables 1 and 2 summarize TNM staging of testicular cancer [14–16]. The pathologic T stage of the tumor is assigned according to the presence or absence of lymphovascular invasion and depth of invasion (tunica vaginalis, spermatic cord, scrotal involvement). During human development, the gonads are formed in the abdomen at the lumbar level, approximately at 21 weeks after conception; the testicles begin migration to the inguinal canal and then descend into the scrotum by 30 weeks after conception. As a result, blood supply and lymphatic channels drain to the abdominal retroperitoneal nodes, and typically not to the pelvis, unless scrotal violation has occurred. Metastasis from testicular cancer occurs via predictable lymphatic channels to retroperitoneal lymph nodes for right- or left-sided primary tumors (pT) [17–19]. Right-sided tumors typically spread to the aortocaval lymph nodes inferior to the renal hilar vessels, while left-sided tumors commonly spread to the left para-aortic lymph nodes. Para-aortic and aortocaval lymph nodes at the level of the kidneys are usually the first lymph node stations affected by metastasis from testicular cancer. While the spread from the right to the left retroperitoneal lymph nodes is seen frequently, the spread from left to right has never been reported [17–19].

Similarly as in other solid cancers, sentinel lymph node biopsy has been suggested as an approach to reduce the morbidity associated with de novo lymph node dissection, which currently

Table 2 Stage grouping for testicular cancer

Stage	T	N	M	Serum tumor marker
Stage 0	pTis	N0	M0	S0, SX
Stage I	pT1–T4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2–T4	N0	M0	S0
Stage IS	Any patient/TX	N0	M0	S1–3
Stage II	Any patient/TX	N1–N3	M0	SX
Stage IIA	Any patient/TX	N1	M0	S0, S1
Stage IIB	Any patient/TX	N2	M0	S0, S1
Stage IIC	Any patient/TX	N3	M0	S0, S1
Stage III	Any patient/TX	Any N	M1a	SX
Stage IIIA	Any patient/TX	Any N	M1a	S0, S1
Stage IIIB	Any patient/TX	N1–N3	M0	S2
	Any patient/TX	Any N	M1a	S2
Stage IIIC	Any patient/TX	N1–N3	M0	S3
	Any patient/TX	Any N	M1a	S3
	Any patient/TX	Any N	M1b	Any S

constitutes the recognized standard of care for proper N staging of patients with stage I testicular cancer. Funicular block using 2% lidocaine is followed by intratesticular injection of 60–100 MBq ^{99m}Tc-nanocolloidal albumin in 0.2 mL. Early dynamic anterior and lateral images for 10 min are then acquired; subsequently, delayed images at 2 h, preferably with SPECT/CT technique, are obtained (see Fig. 1). Intraoperatively, sentinel lymph nodes are localized and resected under the guidance of a handheld gamma probe; the additional use of a dedicated portable gamma camera can also be useful. As in other types of solid cancers, the identification of early metastasis in sentinel lymph nodes offers proper early treatment (elective lymph node dissection of the affected lymphatic basin) while avoiding overtreatment in patients without metastatic disease. Using this technique, no recurrences developed after a median follow-up of 21 months in patients with stage I testicular cancer and negative sentinel lymph nodes [20].

Distant hematogenous metastasis is rare in testicular cancer, ranging from an uncommon event seen in patients with choriocarcinomas to even less frequent occurrence in yolk sac tumors. Distant hematogenous spread may be seen in the lung, liver, brain, bones, kidney, adrenal gland, gastrointestinal tract, or spleen [1, 14, 15].

A prognostic staging system is used to assist treatment recommendations for patients with metastatic testicular cancer. This system was developed by the International Germ Cancer Collaborative Group in 1997 and classifies patients into either good, intermediate, or poor prognostic groups on the basis of histology, site of primary tumor, metastatic disease, and serum tumor markers (see Tables 2 and 3) [14–16, 21].

Overall Performance of Diagnostic Imaging Other than Nuclear Medicine

Scrotal ultrasound (US) examination is the initial primary imaging procedure for any patient with suspected testicular tumor. US can distinguish between intratesticular lesions (which are commonly malignant) and extra-testicular lesions (which are usually benign). Tumors typically present as a hypoechoic lesion, which can be heterogeneous with calcific or cystic changes particularly in NSGCT; in addition, blood flow is increased within the tumor or at its fibrous septa on Doppler

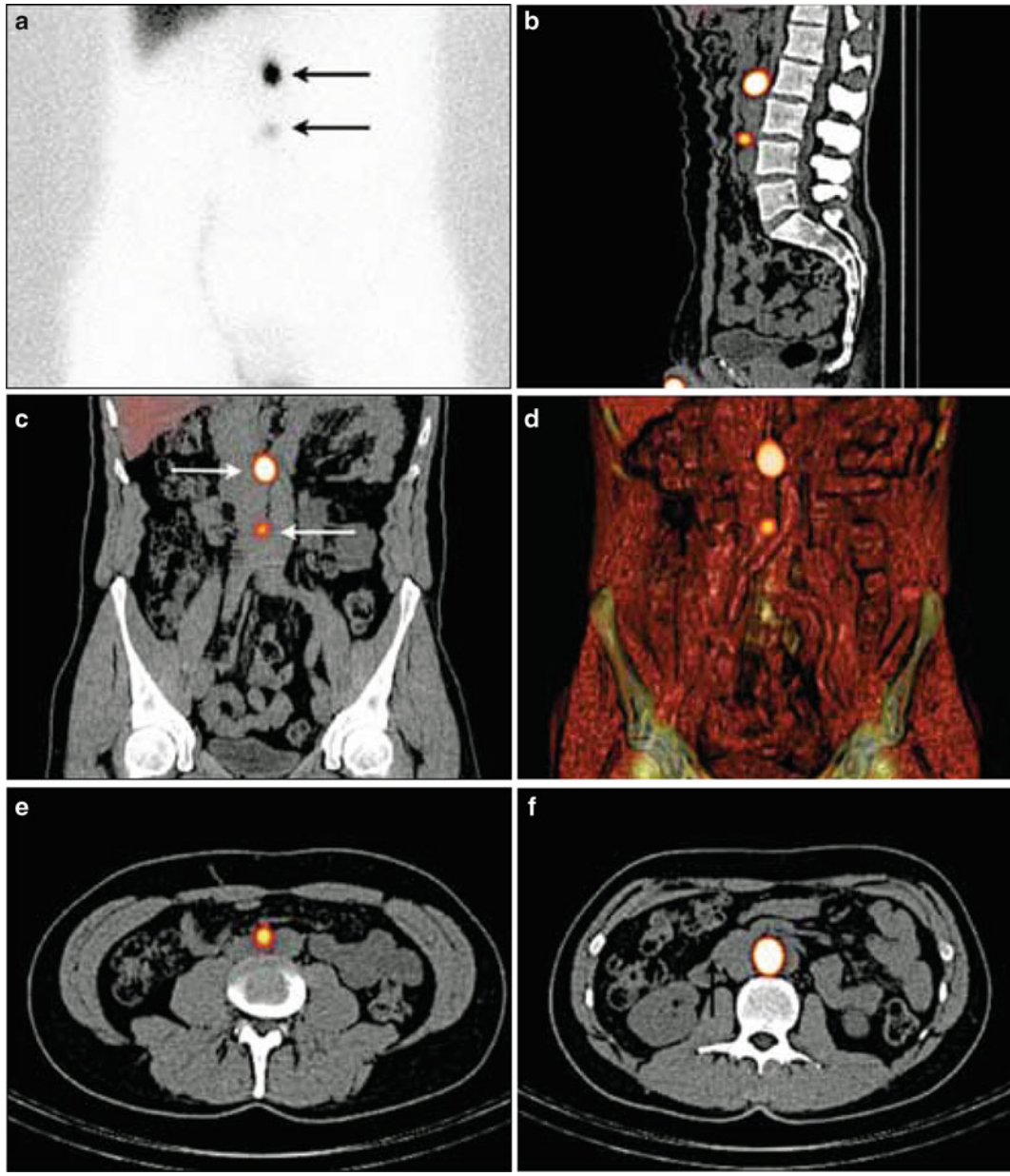

Fig. 1 Preoperative lymphoscintigraphy in a 42-year-old patient with cancer in the right testicle; abdominal CT showed no enlarged lymph nodes. ^{99m}Tc-nanocolloidal albumin (87 MBq) was injected intratumorally under ultrasound guidance. Static planar imaging was acquired about 30 min postinjection, a ^{57}Co flood source being placed beneath the patient's body in order to delineate the body outline; SPECT/CT was acquired about 2 h postinjection. (**a**) Early planar anterior image showing lymphatic drainage to two abdominal sentinel lymph nodes (*arrows*). (**b**) Sagittal SPECT/CT image fusion showing the injection site (at the very *bottom* of the image) and both sentinel nodes along the great abdominal vessels. (**c**, **d**) The coronal SPECT/CT image fusion and 3D volume-rendered image reveal that both sentinel lymph nodes are located interaortocavally (*arrows*). (**e**, **f**) Axial SPECT/CT fused images provide additional information about anatomic location of the two sentinel lymph nodes. Both nodes were harvested laparoscopically and were tumor-free at histopathology (Reproduced with permission from Brouwer et al. [53])

imaging. Overall, US has a high reported sensitivity (92–98%) in detecting testicular cancer, with a specificity of 95–99.8%. False-positive US findings have been reported in patients with testicular infarction, hematoma, or infection as these conditions may also present as mass-like structures with variable blood flow on Doppler images [22–25].

Testicular microlithiasis is a common finding on US examination, with an incidence of 5% in young healthy adults; this is 1,000 times greater than the incidence of testicular malignancy. Testicular microlithiasis in an otherwise normal testicular US scan does not predispose to testicular malignancy. However, clustering of more than ten microlithiasis lesions in certain areas of the testis is associated with an increased risk of developing testicular cancer, and these areas may contain foci of carcinoma in situ [24–28].

Sonoelastography is a new US technique that quantifies the stiffness of tissues; real-time sonoelastography has high sensitivity and specificity for discriminating malignant from benign lesions of the testis, as most malignant testicular lesions demonstrate heterogeneous color pattern with increased stiffness values [28–30].

MRI is usually the second imaging modality of choice for testicular lesions, as it can be considered as a problem-solver procedure when the primary diagnosis is still equivocal after US examination. Low T2 signal intensity with intra-tumoral septal enhancement after contrast administration is more compatible with seminomas, whereas heterogeneous signal intensity on both T1- and T2-weighted images with cystic and necrotic components and a heterogeneous enhancement pattern indicates NSGCT [31]. The sensitivity and specificity of MRI in differentiating benign from malignant intratesticular lesions were reported at 100% and 87.5%, respectively [24, 25, 28]. This diagnostic performance can be further improved by the addition of diffusion-weighted images to routine MRI examinations, with reported sensitivity of 93.3%, specificity of 90%, positive predictive value of 87.5%, and negative predictive value of 94.7% in the characterization of intratesticular masses [32]. Furthermore, MRI can provide useful preoperative information regarding T staging, with reported accuracy of 92.8% [29, 31].

Whereas surgical pathology determines the T stage of the tumor, imaging provides both N and M components of the staging system. CT is the primary imaging technique used in staging testicular cancer, as the scan can efficiently detect lymph node metastasis in addition to distant metastasis involving the liver and lungs. Metastatic lymph nodes are identified based on size criteria, with malignant nodes usually considered to be 8–10 mm or greater in diameter. Using size criteria, abdominopelvic CT offers sensitivity of approximately 70–80%; this criterion is, however, suboptimal because testicular cancer has a high propensity for nodal micrometastases [30]. In 1997, Hilton et al. assessed preoperative CT images in 70 patients who underwent retroperitoneal lymphadenectomy and found that using 10 mm or larger as a cutoff for positive lymph nodes, the sensitivity was only 37% (with 100% specificity); of course, sensitivity improves using 4 mm as cutoff (reaching approximately 93%), associated however with reduced specificity (57%) [33]. In another study, Hudolin et al. adopted a cutoff criterion of 7–8 mm and reported 70% sensitivity and 80% specificity in patients with testicular cancer who underwent retroperitoneal lymphadenectomy [34].

It is currently recommended that lymph nodes 8 mm or larger should be considered suspicious, especially in higher-risk patients who have lymphovascular invasion, which constitute a high proportion of embryonal subtype or T category $\geq$ II [25]. In addition to size criteria, lymph nodes from NSGCT may appear heterogeneous with cystic changes [28]. Because of the growing concern regarding the frequent use of CT in young male patients, more recently MRI has been shown to be equivalent to CT scan in detecting metastatic retroperitoneal lymph nodes, when assessed by experienced specialists [35].

Nuclear Imaging for Diagnosis and Staging

There is at present no sufficient evidence justifying a recommendation to use [^{18}F]FDG PET/CT for diagnosis or staging of testicular cancer. A meta-analysis on the accuracy of the diagnostic

Table 3 Prognostic-based staging system for metastatic germ cell cancer (International Germ Cell Cancer Collaborative Group)

Group	Type	Criteria
Good prognosis	Nonseminoma (56% of cases)	All of the following criteria:
	5-year PFS 89%	Testis/retroperitoneal primary
	5-year survival 92%	No nonpulmonary visceral metastases
		AFP <1,000 ng/mL
		hCG <5,000 mIU/mL (1,000 ng/mL)
		LDH <1.5 × ULN
	Seminoma (90% of cases)	All of the following criteria:
	5-year PFS 82%	Any primary site
	5-year survival 86%	No nonpulmonary visceral metastases
		Normal AFP
		Any hCG
		Any LDH
Intermediate prognosis	Nonseminoma (28% of cases)	All of the following criteria:
	5-year PFS 75%	Testis/retroperitoneal primary
	5-year survival 80%	No nonpulmonary visceral metastases
		AFP 1,000–10,000 ng/mL or
		hCG 5,000–50,000 mIU/mL or
		LDH 1.5–10 × ULN
	Seminoma (10% of cases)	All of the following criteria:
	5-year PFS 67%	Any primary site
	5-year survival 72%	Nonpulmonary visceral metastases
		Normal AFP
		Any hCG
		Any LDH
Poor prognosis	Nonseminoma (16% of cases)	Any of the following criteria:
	5-year PFS 41%	Mediastinal primary
	5-year survival 48%	Nonpulmonary visceral metastases
		AFP >10,000 ng/mL or
		hCG >50,000 mIU/mL (10,000 ng/mL) or
		LDH >10 × ULN
	Seminoma	No patients classified as poor prognosis

Prechemotherapy serum tumor markers should be assessed immediately before administration of chemotherapy (same day)

PFS progression-free survival, *AFP* α-fetoprotein, *hCG* human chorionic gonadotropin, *LDH* lactate dehydrogenase, *ULN* upper limit of normal range

[^{18}F]FDG PET in testicular cancer has recently been published; the analysis included a total of 16 published studies, with an overall 957 [^{18}F]FDG PET scans in 807 patients. Pooled sensitivity and specificity were 75% and 87%, respectively [36]. This reported sensitivity, with a negative likelihood ratio of 0.31, is unsatisfactory to confidently exclude testicular malignancy. False-negative studies are mostly explained by small tumor volume and micrometastases; in addition, teratomas do not demonstrate significant metabolic activity on [^{18}F]FDG PET [36]. Furthermore positive findings have occasionally been reported, due to infective/inflammatory processes [36, 37].

Nevertheless, as a functional/metabolic imaging procedure (see Fig. 2), [^{18}F]FDG PET offers in principle several advantages over CT, which uses mere size criteria to define metastatic lymph node

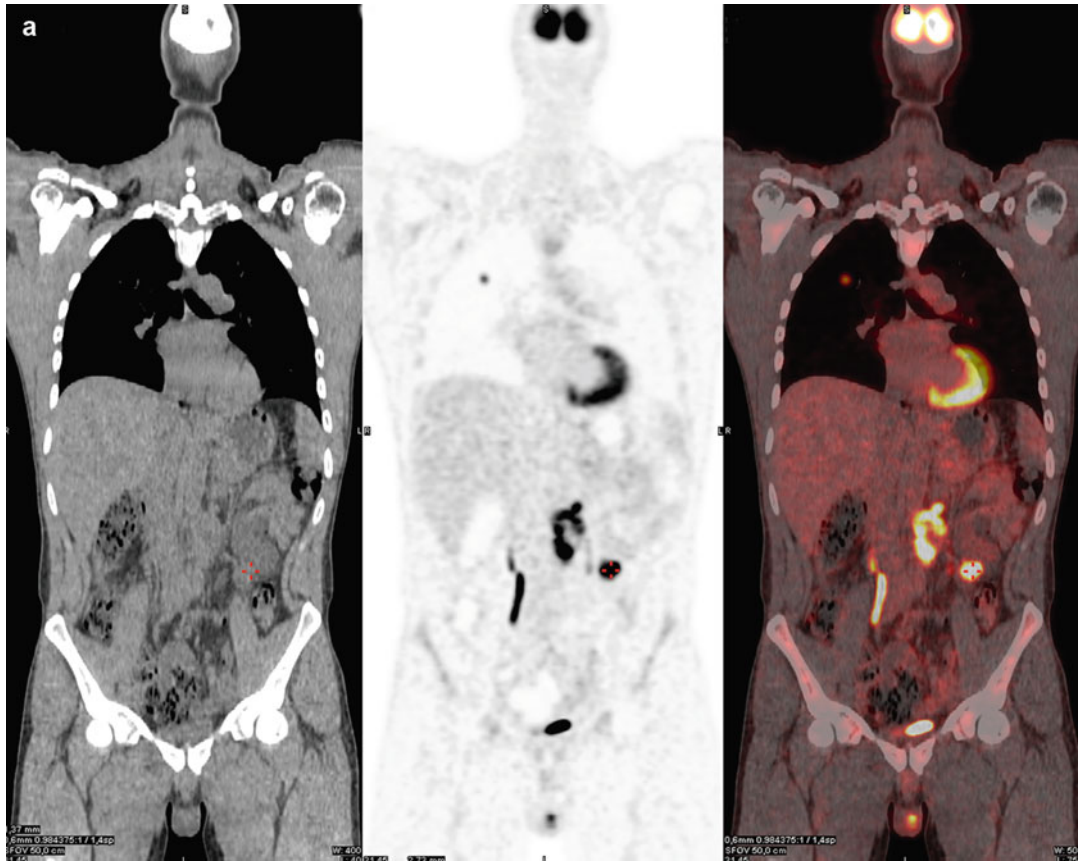

Fig. 2 (continued)

involvement. [^{18}F]FDG PET/CT can be especially useful in patients with a negative CT scan who exhibit elevated tumor markers or in patients with equivocal findings on the CT scan [38–40].

In a recent study by Gary Cook, [^{18}F]FDG PET was used at initial staging of 16 patients (ten with seminoma, five with NSGCTs, and one with mixed GCT). In 11 patients, the PET/CT scans were performed to clarify equivocal staging diagnostic CT results, usually with para-aortic lymph nodes that were in the expected drainage of the primary tumor but were less than the 1 cm cutoff size value required to be classified as positive on CT. In addition, five patients with normal primary staging CT scans but high-risk disease underwent [^{18}F]FDG PET/CT scans to aid decisions for surveillance versus adjuvant chemotherapy [41]. Eight of the 11 patients with equivocal CT scans had true-negative [^{18}F]FDG PET/CT scans, while three patients had a true-positive [^{18}F]FDG PET scan. These findings are in line with previous reports that have concluded that [^{18}F]FDG PET is most useful in patients with equivocal CT scans [38–40]. The five high-risk patients with normal staging CT scans had negative [^{18}F]FDG PET/CT scans, but two subsequently relapsed. This finding is also in line with a previous report that prospectively investigated whether [^{18}F]FDG PET could correctly detect high-risk patients without occult metastatic disease [42]. It is concluded that [^{18}F]FDG PET/CT is helpful when primary staging CT scans are equivocal, but it is insufficiently sensitive to predict relapse in high-risk patients with normal CT scans [41, 42].

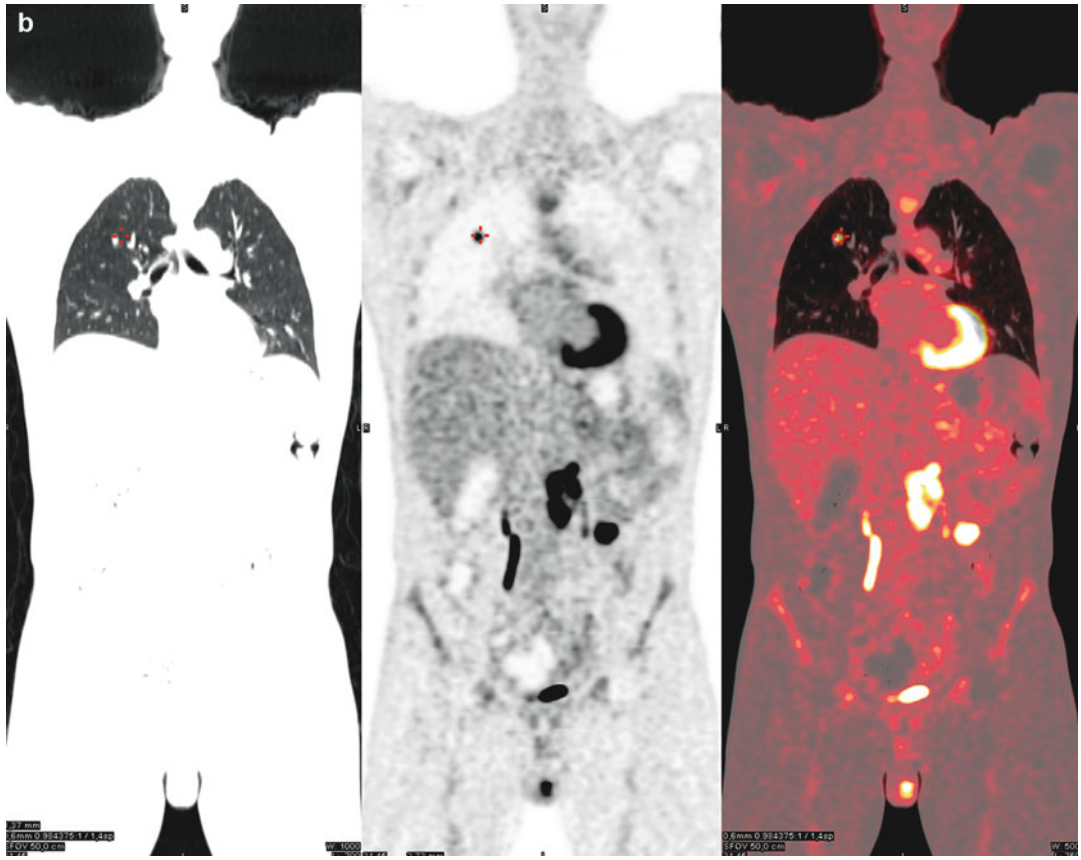

Fig. 2 (continued)

Common Therapies

Management of testicular cancer involves a multidisciplinary team including urologists, medical oncologists, radiation oncologists, and pathologists. As mentioned previously, the survival rate of testicular cancer approaches 97%; however, this high cure rate is achievable in excellent clinical settings, where diagnosis, treatment facilities, and specialized experience are available [14, 15].

One of the important points to emphasize when counseling patients with a new diagnosis of testicular cancer is that it is generally a treatable and highly curable disease. Sperm banking should be offered to the patients prior to commencement of therapy. Over 80% of men with stage I seminoma are cured by radical orchiectomy. Staging procedures reveal that 15–20% of stage I seminomas have subclinical metastatic disease, usually in the retroperitoneum, and will relapse after orchiectomy alone. The decision regarding adjuvant therapy (one cycle of adjuvant carboplatin or adjuvant radiotherapy course) should be based on discussion with the patient, after explaining advantages and disadvantages based on the individual patient's situation. Most clinicians set reduced treatment long-term toxicity as a management goal in patients with stage I seminoma. The overall cancer-specific survival rate under surveillance performed by experienced centers is 97–100% for stage I seminoma [14, 15, 43].

Patients with stage I NSGCT have subclinical metastases in 30% of the cases; they will usually

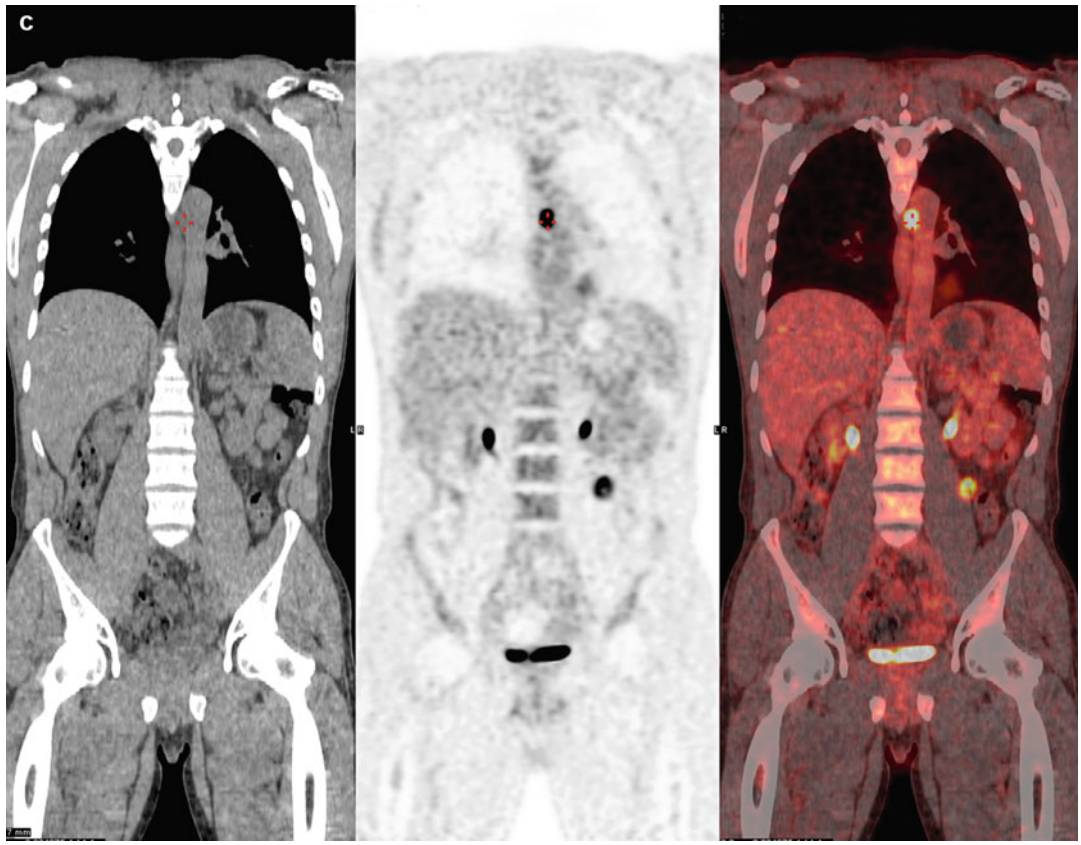

Fig. 2 [^{18}F]FDG PET/CT performed for staging in a 35-year-old male patient after incidental discovery of a mass in the right lung with associated enlarged mediastinal lymph nodes; this had originally been interpreted on CT as possible primary lung cancer with metastatic spread to mediastinal lymph nodes, although with a somewhat atypical pattern. In addition to the expected foci of increased [^{18}F]FDG uptake in the chest lesions, the PET/CT scan detected a distinct focus of increased tracer uptake in the left testicle, subsequently confirmed to be a primary seminomatous testicular cancer. (**a**) Coronal sections of the CT component (*left*), the PET component (*center*), and corresponding fused hybrid PET/CT image (*right*), showing increased [^{18}F]FDG uptake in the left testicle, in left common iliac lymph nodes, and in the mass of the right lung. (**b**) Same sections as in (**a**), but with the CT component being displayed with the imaging window for the lung. (**c**) Coronal sections of the CT component (*left*), the PET component (*center*), and corresponding fused hybrid PET/CT image (*right*) in a more posterior plane than in (**a**) and (**b**); in addition to the still visible increased [^{18}F]FDG uptake in the left common iliac lymph nodes, there is distinct tracer uptake in the aortopulmonary space

relapse if surveillance alone is undertaken after orchiectomy, mostly within the first year. The treating clinician should discuss with the patients the advantages and disadvantages of each treatment option; surveillance is usually offered to non-risk compliant patients [14, 15].

First-line treatment of stage II or stage III TGCT depends on histology of the primary tumor and on prognostic groups (see Table 3). To date, the standard treatment of stage IIA/B seminoma has been radiotherapy, with reported recurrence rates of 9–24% [14, 15]. Alternatively, these patients may undergo three courses of chemotherapy with bleomycin, etoposide, and cisplatin (BEP) or four courses with etoposide with cisplatin. Stage IIA/B NSGCT with elevated tumor markers should receive chemotherapy followed by residual tumor resection if indicated. Stage IIA/B NSGCT patients without elevated tumor markers can be managed by primary retroperitoneal lymphadenectomy or surveillance. Chemotherapy is the standard treatment of

metastatic TGCTs with varying chemotherapy protocols according to histology and prognostic stratification [14, 15].

Assessing the Efficacy of Treatment(s)

[^{18}F]FDG PET/CT is especially useful for evaluation of post-chemotherapy residual masses and metastatic seminoma, an occurrence observed in an average 25% of cases [24, 25, 28]. Several studies have reported that [^{18}F]FDG PET is superior to CT in predicting viable tumor in seminoma residuals after chemotherapy, with accuracy greater than 90% [24, 25, 28, 44, 45].

When the residual lymph node mass is larger than 3 cm in its long axis, particularly in cases with pure seminomas, surgical treatment is usually recommended [46]. However, the prospective SEMPET study has suggested that [^{18}F]FDG PET/CT can confidently differentiate residual disease from fibrosis [44]. When [^{18}F]FDG PET is negative, then there is no need to perform surgery, and the patient is put under surveillance. False-positive [^{18}F]FDG PET scans are infrequent if scans are scheduled more than 2 months after chemotherapy [15]. A retrospective validation of the SEMPET trial including 127 patients yielded sensitivity, specificity, negative predictive value, and positive predictive values of [^{18}F]FDG PET at 50%, 77%, 91%, and 25%, respectively [47]. To reduce the post-chemotherapy false-positive cases, it is currently recommended to repeat the [^{18}F]FDG PET scan at least after six additional weeks. Repeating [^{18}F]FDG PET is a helpful strategy particularly if residual disease is considered unlikely from the clinical point of view; it is also helpful to guide biopsy in those patients who otherwise can also be falsely classified as negative. If the repeat scan is not performed, the residual mass must then be biopsied [15, 39, 41, 47, 48].

[^{18}F]FDG PET is not routinely indicated for post-chemotherapy staging in NSGCT [15]. Residual masses after completion of first-line chemotherapy are found in approximately 40% of patients, even after normalization of serum tumor markers [49]. Histology of the resected lesions reveals necrosis in 40%, vital carcinoma in 20%, and mature teratoma in 40% of cases [50]. Mature teratomas are completely chemoresistant; in addition, they carry the risk of subsequent malignant transformation, and as mentioned previously, they are usually not [^{18}F]FDG avid. Therefore, tumor resection is mandatory for all patients with residual masses >1.0 cm along the short axis on CT images [15]. In a prospective trial of 121 stage IIC or III NSGCT patients, [^{18}F]FDG PET was performed after completion of chemotherapy, and the results were correlated with histopathology, CT scan, and serum tumor markers [51]. Prediction of tumor viability with [^{18}F]FDG was correct in 56% of the cases, therefore, with an accuracy that was not better than CT (55%) or tumor markers (56%). Sensitivity and specificity of [^{18}F]FDG PET were 70% and 48%, respectively. The positive predictive values were not significantly different (55%, 61%, and 59% for CT, serum tumor markers, and PET, respectively). Judging only vital carcinoma as a true malignant finding, the negative predictive value increased to 83% for [^{18}F]FDG PET. As mentioned previously, the presence of vital carcinoma and mature teratoma is common in residual masses in patients with NSGCT; this prospective, histology controlled study demonstrated that [^{18}F]FDG PET does not yield a clear additional clinical benefit with respect to the standard diagnostic procedures (CT and serum tumor markers) for predicting tumor viability in residual masses [51]. [^{18}F]FDG PET, on the other hand, can be used to localize post-chemotherapy hypermetabolic tissue and therefore serve as a guide for biopsy or surgical intervention.

Surveillance in Seminomas

The National Comprehensive Cancer Network (NCCN) has recently published clinical practice guidelines in testicular cancer, describing in details surveillance of testicular cancer according to stage of disease, histopathological findings, and treatment plan. Since a detailed discussion of the

proposed surveillance plan is beyond the scope of this chapter, we summarize here the relevant recommendation particularly regarding seminomas, where [^{18}F]FDG PET plays a major role for clinical decision-making [14].

Pure Seminoma Stage IA and IB

The relapse rate seen in these patients is 15–20% at 5 years; the risk of relapse is highest in the first 2 years, and most of the relapses are first detected in infradiaphragmatic lymph nodes. Surveillance is considered as the preferred option for patients with pT1–pT3; if surveillance is not possible, adjuvant chemotherapy or radiotherapy should be considered.

Follow-Up During Active Surveillance

It includes a medical history and physical examination, with measurement of post-orchiectomy serum tumor markers every 3–6 months for the first year, every 6–12 months for years 2–3, and annually thereafter. There is controversy regarding how many imaging studies should be performed in patients during active surveillance. The NCCN Panel recommends abdominal/pelvic CT every 3, 6, and 12 months for the first year; every 6–12 months for years 2 and 3; and then every 12–24 months for years 4 and 5. No initial relapses in the lung have been reported for patients with stage I seminoma managed by active surveillance; therefore, according to the NCCN Panel, routine chest imaging during surveillance is only indicated for patients with thoracic symptoms.

Follow-Up After Adjuvant Treatment

The risk of recurrence 5 years after adjuvant treatment is $<0.3\%$ annually. Follow-up of patients treated with adjuvant therapy includes a history and physical examination, with measurement of post-orchiectomy serum tumor markers performed every 6–12 months for the first 2 years and annually thereafter. The NCCN Panel recommends performing abdominal and pelvic CT scans annually for 3 years in patients treated with radiotherapy or carboplatin. Chest x-rays should be obtained only when clinically indicated.

Pure Seminomas Stages IIA and IIB

Follow-Up for Stages IIA and Non-bulky IIB Pure Seminoma After Radiotherapy Treatment

The recommended follow-up after radiation therapy for patients with stage IIA and non-bulky IIB tumors includes a history and physical examination, with measurement of post-orchiectomy serum tumor markers performed every 3 months for year 1 and then every 6 months for years 2 through 5. Chest x-ray is recommended every 6 months for the first 2 years. An abdominal CT scan is recommended at 3 months, then at 6 and 12 months in year 1, and then annually for years 2 and 3 after radiotherapy and as clinically indicated thereafter.

Follow-Up of Bulky Stages II A, IIB, IIC, and III Treated with Chemotherapy

After chemotherapy these patients are evaluated with serum tumor markers and a CT scan of the chest, abdomen, and pelvis. Patients are then classified according to the presence or absence of a residual mass and the status of serum tumor markers. Patients with normal markers and either no residual mass or residual mass of 3 cm or less need no further treatment. They should undergo surveillance as pure seminoma bulky stage II and stage III after chemotherapy. In cases of residual tumor >3 cm and normal marker levels, the NCCN Panel recommends an [^{18}F]FDG PET scan in these patients approximately 6 weeks after chemotherapy in order to decide whether to continue with surveillance or resume treatment. If the PET scan is negative, no further treatment is needed; however, the patient should undergo follow-up as discussed in pure seminoma bulky stage II and stage III after chemotherapy. In cases with a positive [^{18}F]FDG PET scan, retroperitoneal lymph node dissection

(RPLND) may be considered if technically feasible; alternatively, second-line chemotherapy is indicated.

Follow-Up of Pure Seminoma Bulky Stage II and Stage III After Chemotherapy

The NCCN Panel recommends follow-up schedules for patients with bulky stage II or stage III disease *after* treatment with chemotherapy *and* either no or $\leq$3 cm residual mass and normal tumor markers, including history and physical examination plus measurement of post-orchiectomy serum tumor markers every 2 months for the first year, every 3 months for the second year, every 6 months for the third and fourth years, and annually for year 5. An abdominal/pelvic CT scan is recommended at 3 and 6 months and then as clinically indicated. The [^{18}F]FDG PET scan may be performed if clinically indicated. Chest x-ray is recommended every 2 months during the first year, every 3 months during the second year, and annually during years 3 through 5. Chest CT is preferred over chest x-ray in patients with thoracic symptoms.

The NCCN Panel notes that patients with PET-negative result and tumor residual mass measuring >3 cm after chemotherapy should undergo an abdominopelvic CT scan every 6 months for the first year and then annually for 5 years.

Surveillance in NSGCT

Follow-Up for Nonseminoma Stage IA

In the updated NCCN Guidelines, the long-term follow-up tests for stage IA patients electing primary surveillance, post-RPLND, or post-chemotherapy include serum marker assessment, chest x-ray, and an abdominal CT scan.

Follow-Up for Nonseminoma Stage IB

In the updated NCCN Guidelines, the long-term routine follow-up tests for the selected patients with T2 disease undergoing surveillance and for those who underwent chemotherapy include serum marker assessment, chest x-ray, and an abdominal/pelvic CT scan. The frequency of these tests varies depending on the adjuvant management strategy.

Follow-Up for Nonseminoma Stages IIA and IIB and Metastatic Nonseminoma

After primary treatment, the subsequent management depends on tumor marker levels and the residual masses detected on CT scan; lesions less than 1.0 cm may still harbor residual disease and therefore must be interpreted with caution. [^{18}F]FDG PET scans have limited negative predictive value in patients with residual masses, but still might be useful in guiding multimodality treatment [52].

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