CHAPTER 18

TESTICULAR GERM CELL TUMORS

Christoph Ong • Carsten Bokemeyer • Karin Oechsle

INTRODUCTION

Malignant testicular germ cell tumors (GCTs) are relatively rare types of cancer accounting for 1% to 3% of all cancers in caucasian males in Western countries. But, GCTs are the most common malignancy among young men in most European populations.1,2 The worldwide incidence of testicular tumors is increasing and has more than doubled over the past 40 years.3,4 In contrast, testicular cancer mortality has markedly declined in a number of European countries since the mid-1970s likely related to the introduction of platinum-based chemotherapy and best-practice tumor management schemes.1

GCTs account for more than 95% of all testicular malignancies.4 Histologically and clinically, GCTs are classified into seminomatous and nonseminomatous germ cell tumors (NSGCTs).5,6 The majority of seminomas are diagnosed among men aged 30 to 45, whereas most of the NSGCT patients are between the ages of 20 and 35.7 The cause of GCTs is unknown but established risk factors for GCT development are cryptorchidism or maldescended testes, a previous contralateral GCT, and a family history of testicular cancer, particularly among siblings and in case of affected first-degree relatives.8,9 Furthermore, the Klinefelter syndrome appears to be a predisposing factor for the development of tumors arising from the testis and mediastinum.10

HISTOLOGY OF GERM CELL TUMORS

GCTs comprise a heterogeneous group of neoplasms that originate from cells belonging to the germ cell lineage.6,11 Male GCTs commonly occur in the testes, and in different extragonadal sites along the midline of the body; the retroperitoneal and mediastinal regions, as well as the midline of the brain, that is the hypothalamus–pineal gland region.12 As stated, testicular germ cell tumors (TGCTs) can be divided into two main types: Seminomas and nonseminomas. The latter type may harbor one or more histologically different components of embryonal carcinoma, teratoma, polyembryoma, choriocarcinoma, or yolk sac tumor.13 Pure seminomas comprise about 50% of TGCTs, and nonseminomas account for 30% of cases. The remaining tumors consist of a mixture of cell types containing both seminomatous and nonseminomatous components.12

STAGING AND CLASSIFICATION OF GERM CELL TUMORS

The definition of the clinical stage (CS) of patients with gonadal GCT is based on the UICC TNM classification (Table 18.1).14 Patients are designated as having CS I disease if no lymphatic spread or distant metastases can be detected.15 Prognostic factors for stage I GCT differ between the two histologic subtypes. For CS I seminoma, tumor size ≥4 cm and infiltration of the rete testis have been proposed as independent predictors of an adverse outcome.16 Recently, this risk stratification model could not be validated in a multivariate analysis. Therefore, at the present time, no distinctive risk factors can be defined for early stage seminoma.16

In CS I nonseminoma, the presence of vascular invasion (VI), is the most important prognostic factor for occult metastatic disease. It is mandatory that it is assessed in every patient.17 Forty-eight percent of VI positive patients will develop metastases if adjuvant treatment is not administered.18,19

In advanced GCT, treatment decision is based on prognosis but not on the CS alone. In a cooperative retrospective database analysis including data of a total of 5,202 patients, independent adverse factors were the following: Mediastinal primary site; degree of serum tumor marker elevation (α-fetoprotein, AFP; beta-subunit of human chorionic gonadotropin, β-HCG; lactate dehydrogenase, LDH); and presence of nonpulmonary visceral metastases. For seminoma, the predominant adverse feature was the presence of nonpulmonary visceral metastases.20 Based on these risk factors, the International Germ Cell Cancer Collaborative group (IGCCCG) classification was established (Table 18.2).

TABLE 18.1

<table>
<thead>
<tr>
<th>CLINICAL STAGE OF GERM CELL TUMORS AT PRIMARY DIAGNOSIS</th>
<th>Seminoma (%)</th>
<th>Nonseminoma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage I</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>Clinical stage II</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Clinical stage III</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>


TABLE 18.2

<table>
<thead>
<tr>
<th>RISK STRATIFICATION ACCORDING TO THE INTERNATIONAL GERM CELL CANCER COLLABORATIVE GROUP CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognosis</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Good (5-y survival 90%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Intermediate (5-y survival 75%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Poor (5-y survival 50%)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>


241
In CS I NSGCT, there also exist three different treatment options following orchiectomy. These are active surveillance, one or two cycles of chemotherapy (BEP), or nerve-sparing retroperitoneal lymph node dissection (RPLND). For low-risk patients, active surveillance is the recommended treatment strategy. In contrast, high-risk patients defined by VI should preferably receive adjuvant chemotherapy.24-26

Detection of patients with CS IIA caused by retroperitoneal lymph nodes ≤2 cm is problematic, because of difficulties in predicting malignancy of a suspicious lymph node based on a CT scan. Nerve-sparing RPLND is an established option if tumor marker levels are normal, and offers the opportunity for accurate pathological staging. Patients with CS IIA/B and elevated tumor markers should be treated systemically with chemotherapy.26

Patients with seminomatous or nonseminomatous advanced disease require cisplatin-based combination chemotherapy potentially followed by secondary salvage surgery to resect residual masses. The chemotherapy regimen of choice depends on the risk category according to the IGCCCG risk stratification model.20 It is recommended that low-risk patients receive three cycles of BEP, or if bleomycin has to be abandoned, four cycles of PE, alternatively. All intermediate-risk or high-risk patients should primarily receive four cycles of BEP. Four cycles of cisplatin, etoposide, and ifosfamide (VIP) are equally effective but cause more acute myelotoxicity and are therefore not recommended as standard therapy.25-26 Furthermore, in two randomized phase III trials, a primary treatment approach including high-dose chemotherapy (HD-CTX) slightly improved treatment outcome among patients with metastatic poor-risk disease, but the improvement did not reach statistical significance. Estimation of serum marker decline during the first two cycles of induction chemotherapy has been shown to be valuable for predicting the outcome of primary treatment. Delayed tumor marker decline during induction therapy predicts for adverse outcome with a significantly shorter progression-free survival and overall survival.27,28 Therefore, HD-CTX is currently not recommended as part of primary treatment in all poor-risk GCT patients, but may be a valuable option for selected patients with special risk characteristics.

Salvage Treatment

In contrast to the primary treatment, salvage strategies after relapse are less well established. The majority of relapses occur within 2 years after completion of the initial treatment. Even in the salvage situation, an overall rate of 40% to 50% long-term remissions can be achieved.25,26 Chemotherapeutic treatment regimens in the salvage setting are the following combinations: VIP, or paclitaxel, and ifosfamide with or without cisplatin (TI or TIP) for second-line, as well as gemcitabine, oxaliplatin preferably together with paclitaxel (GOP) as third or further line option for truly refractory patients. In the absence of randomized trials, no salvage chemotherapy regimen has shown unequivocal superiority.26,30,31 In patients with poor prognosis, phase II trials have suggested an improvement in survival using HD-CTX with subsequent autologous stem cell transplantation but the role of HD-CTX remains to be defined by prospective phase III trials.

The results of a retrospective analysis of a large international database of approximately 1,600 patients who relapsed after platinum-based first-line treatment by Lorch et al. indicate a clear advantage of HD-CTX given as first salvage treatment. Patients have been allocated to five different prognostic categories according to the prognostic model previously identified by the International Prognostic Factors Study group. Of interest, the advantage of HD-CTX was significant for all categories, except for patients with low-risk factors.16,33 Thus, HD-CTX with subsequent autologous stem cell support seems to be a promising salvage treatment option, which needs further prospective validation particularly in the salvage setting.
Residual Masses Post Chemotherapy

In about 40% of GCT patients, indeterminate residual masses persist in CT scans after completion of chemotherapy and tumor marker normalization. In pure seminomatous GCTs, residual masses presenting after chemotherapy do not have to be resected necessarily, irrespective of their size but should be followed closely by radiographic imaging and determination of serum tumor markers. Residual masses, not larger than 3 cm in size should routinely be observed without any further local or systemic treatment as the risk for persistent viable tumor cells is only about 0% to 10%. In patients with residual lesions of >3 cm in size, the incidence of recurrence is approximately 25% to 30% and treatment decision should be based on 18F-fluoro-2-deoxy-D-glucose PET/CT.

After treatment of an NSGCT, there is an increased risk of residual mature teratoma, if teratomatous histology was present in the initial tumor orchietomy specimen. Mature teratoma is chemotherapy-resistant, can grow locally and might undergo malignant transformation into teratocarcinoma. After surgical resection of residual masses >1 cm in NSGCT patients, histologic examination shows necrosis and/or fibrosis in 40%, mature teratoma in 40% to 50% and persistent viable tumor tissue in 10% to 20% of cases. Therefore, surgical resection is generally recommended for all NSGCT residues >1 cm, if technically feasible.

Thus, approximately 40% of patients with persisting residual masses after chemotherapy unnecessarily undergo overtreatment by surgery. This could be avoided if viable residual tumors could be excluded noninvasively. Unfortunately, both routine radiologic imaging (e.g., CT and MRI), and serum tumor marker monitoring are unable to determine the viability of a residual tumor sufficiently. There are only a few distinct markers that allow the prediction of pure necrosis with almost 90% certainty in patients with retroperitoneal or pulmonary residual masses. These are combinations of tumor shrinkage measured radiographically, initial histology lacking mature teratoma, and normal tumor marker values (AFP and HCG) prior to chemotherapy.

FDG PET Evaluation of Residual Masses Post Chemotherapy

Seminoma

Management of postchemotherapy residual masses in seminoma patients remains a challenge, with the primary dilemma being whether to resect or simply observe these lesions. In patients with pure seminoma and residual lesions after completion of chemotherapy of >3 cm in size, the risk for persistent viable tumor cells is approximately 25% to 30%. In patients with persistent viable tumor cells, further chemotherapy or complete resection of all lesions is necessary. Conventional radiographic imaging (e.g., CT), however, does not distinguish between necrotic or fibrotic tissue and viable tumor remnants. A prospective multicenter German–Austrian trial (SEMPET) was conducted to determine the value of 18F-FDG PET for viability assessment of seminomatous GCT post-chemotherapy residues. In a total of 37 patients, 41 residual lesions >1 cm after completion of chemotherapy were identified by 18F-FDG PET scans. The results were compared to clinical outcome during follow-up. Nine patients underwent secondary surgery of the lesions so that direct comparison between 18F-FDG PET results and histology was possible. Viability of residual masses was correctly assessed by 18F-FDG PET in all 14 patients presenting with lesions sized >3 cm, and in 22 of 23 patients (96%) with lesions ≤3 cm. There was only one false-negative 18F-FDG PET result. In the SEMPET study, in patients with pure seminoma 18F-FDG PET had a sensitivity of 100% and a specificity of 89% for all residual lesions and 100% for lesions sized >3 cm. The positive and negative predictive values were 100% and 97%, respectively. Therefore, 18F-FDG PET was judged to be a clinically useful tool to identify viable tumors in postchemotherapy residues of pure seminoma, especially those bigger than 3 cm. In an update of this trial, 56 18F-FDG PET
patients with residual mass or recurrent seminoma. Therefore, higher than expected number of false-positive scans was reported, (Table 18.4).38 Based on these studies, 18F-FDG PET is the best predictor of viable residual tumor in postchemotherapy seminoma residues and is recommended as a standard diagnostic tool for clinical decision making in this patient group (Fig. 18.1).21,38

However, following the more frequent use of PET scans, a higher than expected number of false-negative scans was reported, for example, up to 45% in a small prospective trial including 20 patients with residual mass or recurrent seminoma.39 Therefore, a retrospective trial was conducted by the Austrian–German study group to evaluate the current PET recommendations in a larger patient cohort (SEMPET trial). A total of 125 seminoma patients were eligible. Thirty-seven patients (30%) underwent subsequent secondary surgery of residual masses. Viable tumor was found in 8 of 37 patients (22%) whereas relapse was detected on radiologic or clinical follow-up in 14% of the remaining patients. False-positive PET results were obtained in eight studies (15%) in lesions <3 cm, and in lesions sized ≥3 cm 11 false-positive results (15%) occurred (Table 18.5).39 As a result, in the SEMPECON trial, the high specificity, sensitivity, and negative predictive value of 18F-FDG PET to evaluate postchemotherapy seminoma residues was confirmed.39 Similar results have been obtained in a small retrospective series at Indiana University Hospital showing the association between a negative 18FDG PET scan and a low likelihood of persistent seminoma in a residual mass (Fig. 18.2).56

A smaller prospective study of 29 patients, however, was subsequently conducted at Indiana University Hospital. This study failed to confirm a benefit of 18FDG PET to detect viable tumor, both after first-line, and after salvage chemotherapy caused by an increased number of false-negative results in patients who subsequently relapsed. Four patients relapsed despite a negative PET scan result: One had a 3 cm residual mass, two had a residual mass <3 cm, and in one, the size was undetermined.60

Nevertheless, the current recommendation is that at 6 to 8 weeks after completion of chemotherapy, 18F-FDG PET is a valuable tool for clinical decision making that spares patients unnecessary additional therapy.59

**Nonseminoma**

In residual masses of NSGCT after first-line chemotherapy vital carcinoma and mature teratoma are present in 40% to 60% of patients despite normalization of tumor markers. CT scans and

### TABLE 18.4

**IMPACT OF 18F-FDG PET ON THE ASSESSMENT OF RESIDUAL MASSES IN SEMINOMA**

<table>
<thead>
<tr>
<th>Detection of Viable Tumor by 18F-FDG PET</th>
<th>Detection of Viable Tumor by Size (&lt;3 cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity (95% CI)</td>
<td>1 (0.92–1)</td>
</tr>
<tr>
<td>Sensitivity (95% CI)</td>
<td>0.80 (0.44–0.95)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.74 (0.58–0.85)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.90 (0.70–0.96)</td>
</tr>
</tbody>
</table>


### TABLE 18.5

**SIZE OF RESIDUAL MASSES OF SEMINOMA AND ITS IMPACT ON DIAGNOSTIC IMAGING**

<table>
<thead>
<tr>
<th>Mode</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All lesions</td>
<td>PET</td>
<td>0.67</td>
<td>0.82</td>
<td>0.42</td>
</tr>
<tr>
<td>Lesions</td>
<td>CT</td>
<td>0.67</td>
<td>0.44</td>
<td>0.19</td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>CT</td>
<td>0.81</td>
<td>0.83</td>
<td>0.50</td>
</tr>
<tr>
<td>≥3 cm</td>
<td>CT</td>
<td>1.00</td>
<td>1.00</td>
<td>—</td>
</tr>
</tbody>
</table>


**FIGURE 18.1.** PET of a 22-year-old male with refractory seminoma 4 months after finishing first-line chemotherapy with three cycles of cisplatin, etoposide, and bleomycin (PEB). Subsequently, the patient underwent salvage chemotherapy based on the shown PET/CT scan. A: Whole body PET signalling with enhanced signalling of brain, heart, bladder and a retroperitoneal refractory seminomatous tumor residue. B: PET/CT slices of the residual viable mass.
measurement of serum tumor markers do not sufficiently distinguish between the presence of necrotic or fibrotic tissue, viable tumor residues, and/or mature teratoma. In patients with NSGCT, therefore, complete resection of all residual masses >1 cm is recommended today. Consequently, approximately 45% of patients with necrotic residuals unnecessarily undergo secondary surgical resection after completion of chemotherapy. In the 1990s, several small studies evaluated 18F-FDG PET to detect viable tumor residues after completion of chemotherapy in NSGCT. Results were heterogeneous. Hence, reliable differentiation between vital undifferentiated tumors and teratomatous lesions remains challenging.

In a retrospective single-center analysis of 85 residual masses in 45 patients, Kollmannsberger et al. described additional information by applying 18F-FDG PET scans together with the standard follow-up CT and tumor markers after completion of chemotherapy in metastatic NSGCT. The 18F-FDG PET results were validated either by histologic examination of resected tumor or biopsy samples (n = 28 lesions), or 6-months clinical follow-up (n = 57 lesions). The results of 18F-FDG PET alone were correctly positive in 34%, false positive in 4%, correctly negative in 39%, and false negative in 23%. Assessed together, the results of PET, CT, and tumor markers indicated that 39 residual masses (43%) could be correctly defined as viable tumor/mature teratoma. The remaining 46 lesions were interpreted as necrotic or fibrotic tissue. This resulted in 14 false-negative cases (16% of all lesions). Excluding patients with mature teratoma from the analysis did not further improve the results.

In a subsequent trial including 60 residual tumors in 28 patients who had undergone HD-CTX because of primarily poor-risk advanced disease or relapse after first-line treatment, similar results were obtained. Positive 18F-FDG PET results were highly correlated with the presence of viable tumor, but residual masses with negative 18F-FDG PET findings still required secondary resection caused possibly by remaining mature teratoma. In cases of tumor progression diagnosed by CT and elevated tumor markers, 18F-FDG PET scans did not improve results.

In another retrospective trial, 38 18F-FDG PET scans (28 NSGCT patients, 10 seminoma patients) after completion of chemotherapy were validated by histology (20 patients) or clinical follow-up. 18F-FDG PET revealed true-positive results in 30% of patients and also 30% false-positive results in patients with mature teratoma and inflammatory components. Of interest, 11 of all 12 patients with a true-negative 18F-FDG PET result did not have mature teratoma in their primary tumor. Therefore, 18F-FDG PET was considered to be useful to predict fibrotic residual masses in NSGCT without mature teratoma in the primary histology. Based on the results mentioned above, 18F-FDG PET once was recommended to accompany both CT and tumor marker determination during follow-up of NSGCT.

Nonetheless, in subsequent years a prospective multicenter trial was thought to determine the value of 18F-FDG PET in NSGCT patients presenting with a residual mass >1 cm in size in a CT scan. In this trial, secondary surgery was mandatory to obtain histologic validation of PET results. After inclusion of 121 patients, an interim analysis revealed that the study did not achieve the primary objective anymore, which was to demonstrate an accuracy of 18F-FDG PET imaging of 80%. Consequently, the study was prematurely closed. The accuracy for the prediction of residual tumor histology of all three diagnostic methods was nearly identical, with 55% for CT and 56% for both 18F-FDG PET and serum tumor markers (Table 18.6).

The lack of specificity for CT in this study is explained by the positive CT scan in all patients as residual masses in CT scan represented the main study inclusion criterion. Direct comparison

![FIGURE 18.2. PET of a 36-year-old male with seminomatous germ cell tumor showing a PET-negative residual tumor in the retroperitoneum after chemotherapy with three cycles of cisplatin, etoposide, and bleomycin. A: Whole body PET signal without presentation of the residual mass. B: PET/CT of the PET-negative retroperitoneal tumor residue.](image)

### TABLE 18.6

<table>
<thead>
<tr>
<th></th>
<th>18F-FDG PET</th>
<th>CT</th>
<th>Serum Tumor Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.70</td>
<td>1</td>
<td>0.40</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.48</td>
<td>0</td>
<td>0.73</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>0.59</td>
<td>0.55</td>
<td>0.61</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>0.51</td>
<td>0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

uptake was lower in GCTs as compared to 18F-FDG. PET-negative NSGCTs were caused by persisting inflammation at the time of histologic confirmation, 61% of false-positive residual lesions of be assumed that the combination of a negative PET scan at all sites in most of these studies in germ cell cancer patients. 18F-FDG is not demonstrated that 18FDG PET is unable to yield significant addi-
tional information compared to the standard diagnostic proce-
dures, CT and serum tumor markers, in the prediction of tumor viability in residual masses.44 The diagnostic value of 18FDG PET, however, was not worse than these methods either.

More recently, 18FLT PET has been used to evaluate the treat-
ment response of GCTs. Eleven patients (10 NSGCTs, 1 seminoma) were consecutively staged with both 18F-FDG and 18F-FLT PET prior to onset of treatment and after each chemotherapy cycle for metastatic GCT in addition to standard staging procedures. Seven patients underwent secondary salvage surgery, so that Ki-67 immunostaining was performed and compared to 18F-FLT PET result.45 The results are summarized in Table 18.7.

Both patients with teratomatous tumor components had negative PET results with both 18F-FDG and 18F-FLT. Furthermore, 18F-FLT uptake was lower in GCTs as compared to 18F-FDG. PET-negative residual masses post chemotherapy still require secondary surgical resection, because the low negative predictive value of 18F-FDG PET for viable tumor is not improved by application of 18F-FLT.44 False-positive PET results post chemotherapy have been shown in most of these studies in germ cell cancer patients. 18F-FDG is not a tumor-specific tracer. Accumulation in benign tissue frequently occurs if increased glucose metabolism is present (Fig. 18.3).

Extensive tracer uptake is caused by inflammatory and granu-
lomatous tissue with increased macrophage activity which is found in granulation tissue surrounding abscesses as well as non-
neoplastic cellular elements in the tumor mass. Furthermore, increased 18F-FDG uptake can be related to the effects of irradiation and chemotherapy.41,47,68 False-positive 18F-FDG PET results are caused by persisting inflammatory reaction with macrophage accumulation post chemotherapy.40 In the prospective trial with histologic confirmation, 61% of false-positive residual lesions of NSGCTs were caused by persisting inflammation at the time of histologic examination.66 Therefore, a minimal time interval of about 6 weeks after completion of chemotherapy is recommended for the evaluation of residual masses of a metastatic seminomatous GCT.21,24,25,66 In this study the rate of false-positive PET results was significantly higher in thoracic masses as opposed to abdominal residual tumors (41% versus 12%).66 Furthermore, for patients with multiple residual masses, it may be assumed that the combination of a negative PET scan at all sites and necrotic tissue found at the RPLND histology may identify a subgroup of patients who could be spared further surgery at other sites. This would be of interest, if surgical resection is not feasible to better predict a patient’s risk of relapse, as well as to guide decision making regarding the operative procedure in patients with lesions suitable for surgery.23 In this regard, Kolmmannsberger et al. found that if PET results were uniformly positive or negative for all lesions within a single patient, the clinical behavior of the multiple residual masses was uniform, which means remission or progression at all locations. Consequently, a uniformly positive 18FDG PET result was a strong predictor of viable GCT. Hartmann et al. found histology results to be different after secondary resection of multiple lesions at different anatomic localizations in approximately 30% of patients who underwent salvage surgery. In patients who underwent resection of a necrotic lesion at a single localization and who previously had PET-negative results uniformly for all lesions, the probability of necrosis at the remaining nonresected lesions clearly was >90% (negative predictive value of a quantitatively assessed PET was 67% in this study).64 Accordingly, a subgroup of patients with multiple residual lesions may benefit from PET scanning after incomplete resection by sparing them further, potentially harmful and dispensable surgery.

FDG PET for Evaluation of GCT at Relapse

Identification of recurrence after completion of prior treatment of testicular cancer remains a relevant problem in patients with continuously rising serum tumor markers but without morphologically correlating tumor in CT scan results.20,69 It is unclear if 18FDG PET scans add useful information in the early detection of relapse or the search of a tumor manifestation. As part of a retrospective analysis, 23 PET studies of patients with rising tumor markers during follow-up were evaluated. Among the patients with elevated markers but normal or long-term stable results on CT during follow-up, in three of four with a rapidly progressive relapse, the localization of relapse was identified by 18FDG PET scan. The positive predictive value of 18F-FDG PET in this cohort of patients at relapse was 92%, but the negative predictive value was only 50%.69

Another clinically relevant issue would be the identification of patients who are more likely to relapse after primary treatment for CS I NSGCT. In a study conducted by Lassen et al., in 46 patients with normal tumor markers and inconspicuous follow-up CT result after orchietomy for CS I GCT, 18F-FDG PET scans were performed within 1 month. Subsequently, patients were solely fol-
lowed by active surveillance even in cases with a positive PET result. 18FDG PET results were true positive in 70% of patients relapsing within 2 months. The negative predictive value of 18FDG PET in this study was 92%, implying that adjuvant treatment could be avoided in patients with CS I NSGCT, who have a negative PET scan during follow-up.22,51

### TABLE 18.7

<table>
<thead>
<tr>
<th>Timing of PET Imaging</th>
<th>PET Tracer</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After one cycle of CTX</td>
<td>18F-FDG</td>
<td>0.60</td>
<td>0.33</td>
<td>0.43</td>
<td>0.50</td>
</tr>
<tr>
<td>After one cycle of CTX</td>
<td>18F-FLT</td>
<td>0.60</td>
<td>0.80</td>
<td>0.75</td>
<td>0.67</td>
</tr>
<tr>
<td>After completion of CTX</td>
<td>18F-FDG</td>
<td>0.20</td>
<td>1</td>
<td>1</td>
<td>0.60</td>
</tr>
<tr>
<td>After completion of CTX</td>
<td>18F-FLT</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0.50</td>
</tr>
</tbody>
</table>

CTX, chemotherapy.

To confirm these findings in a larger patient cohort, a subsequent study of 111 patients with high-risk CS I NSGCT was performed by the MRC. After a median follow-up of 12 months, 33 of the 87 initially PET-negative patients on surveillance relapsed (1-year relapse-free rate 63%). For that reason, the trial was closed prematurely.\textsuperscript{53} In conclusion, \textsuperscript{18}F-FDG PET does not reliably detect CS I patients at risk of relapse, because even PET-negative results do not conclusively rule out an increased risk of relapse.

**FDG PET to Predict Treatment Outcome**

A large international database analysis found that patients with relapsed germ cell cancer receiving salvage HD-CTX may achieve an improved outcome compared to standard-dose chemotherapy. Treatment intensification, however, is potentially associated with higher toxicities.\textsuperscript{70} Therefore, it would be helpful to identify both responding and nonresponding patients at an early time point of treatment to avoid further toxic treatment or to potentially reduce the dose intensity in case of a very good response. In this regard, a prospective trial was conducted to evaluate whether \textsuperscript{18}F-FDG PET scans could add additional information to predict treatment outcome early in 23 patients with relapsed GCT who were scheduled to undergo salvage HD-CTX. Treatment consisted of three cycles standard-dose chemotherapy (TIP) followed by one cycle HD-CTX (thiotepa, etoposide, carboplatin) with subsequent autologous stem cell transplantation. \textsuperscript{18}F-FDG PET imaging was performed before the start of induction standard-dose chemotherapy and again within 8 days prior to HD-CTX. Baseline \textsuperscript{18}F-FDG PET prior to the start of chemotherapy was positive in all lesions evaluated in this study. Results of the second PET scan were correlated to the histologic findings of the residual mass if a secondary resection after completion of chemotherapy was done. If no resection was performed, the clinical course of the patient over the next 6 months was used for correlation. The clinical course of disease

**FIGURE 18.3.** PET of a 33-year-old male with nonseminomatous germ cell tumor showing a PET-positive residual tumor after first-line chemotherapy. The patient underwent subsequent surgical resection. The histologic examination revealed sarcoidosis in the tissue samples, which represents an interesting finding proving the difficulties in distinguishing tumors from otherwise metabolically active tissue by PET imaging alone. A: Whole body PET signaling showing several PET-positive nodular lesions of the mediastinum. B and C: PET/CT slices detecting multiple enlarged PET-positive mediastinal lymph nodes.
after HD-CTX was correctly predicted by \(^{18}\text{F-FDG PET}\) imaging during chemotherapy in 21 of the 23 patients (91%). Interestingly, none of the patients with negative \(^{18}\text{F-FDG PET}\) after induction chemotherapy relapsed after HD-CTX. Of the patients who still had a positive \(^{18}\text{F-FDG PET}\) prior to HD-CTX, 88% either relapsed within 6 months or the histology of the resected residual tumor mass after HD-CTX still revealed viable GCT components. Overall, the outcome of HD-CTX was correctly predicted by \(^{18}\text{F-FDG PET}\), CT scan, and tumor markers in 91%, 59%, and 48%, respectively. \(^{21}\)

Sensitivities and specificities to predict failure of HD-CTX are summarized in Table 18.8. \(^{18}\text{F-FDG PET}\) scans conducted early in the course of salvage treatment may help to identify patients with an overall unfavorable outcome despite intensified treatment (Fig. 18.4). \(^{21}\)

Moreover, a more reliable evaluation of tumor response during the course of chemotherapeutic treatment and thus the sensitivity to chemotherapy, for example, by the use of PET scanning, would be of great value to detect subgroups of patients, who may be applied a decreased dosage of chemotherapy while maintaining the excellent cure rate of GCTs. To elucidate this issue further prospective evaluation in clinical trials is necessary.

### Conclusion

\(^{18}\text{F-FDG PET}\) has been evaluated in different diagnostic settings in patients with TGCTs but an enduring impact of \(^{18}\text{F-FDG PET}\) was demonstrated in only a few indications. \(^{18}\text{F-FDG PET}\) has no relevant impact for primary staging of GCT and does not reliably detect CS I patients at risk of relapse. The most relevant clinical role of \(^{18}\text{F-FDG PET}\) is to detect viable tumor in postchemotherapy residual tumor masses in patients with pure seminoma. In patients with NSGCTs, a prospective trial with histologic confirmation demonstrated that \(^{18}\text{F-FDG PET}\) was not useful to identify viable tumor in postchemotherapy residues.

Patients with multiple residual lesions may benefit from \(^{18}\text{F-FDG PET}\) scans for staging because a negative PET result accompanied by necrosis or fibrosis in RPLND or single lesion histology may predict a low likelihood of relapse at other locations in a subgroup of NSGCT patients without a teratoma component in the primary tumor. \(^{18}\text{F-FDG PET}\) has a relevant positive predictive impact in the detection of recurrence in patients with rising serum tumor markers without tumor progression on CT scans but the negative predictive value is limited. Therefore, the use of \(^{18}\text{F-FDG PET}\) in this indication should be restricted to special questions on an individual patient basis. Furthermore, \(^{18}\text{F-FDG PET}\) scans early in the course of dose-intensified salvage chemotherapy in relapsed GCT patients identifies patients with worse prognosis. But, because HD-CTX does not represent a standard approach, this cannot be recommended as a standard diagnostic procedure.

### Table 18.8

<table>
<thead>
<tr>
<th>Early Prediction of HD-CTX Response by (^{18}\text{F-FDG PET}) versus Routine Staging Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{18}\text{F-FDG PET})</td>
</tr>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>Positive predictive value</td>
</tr>
<tr>
<td>Negative predictive value</td>
</tr>
</tbody>
</table>

Currently, there are no relevant data on the impact of any other nuclear medicine procedure in routine diagnostics or treatment of patients with malignant GCTs. Bone scintigraphy is only performed in patients with symptoms suspicious for bone metastases, but not part of routine diagnostics for any stage of GCT disease.

FUTURE CONSIDERATIONS

In the first years of the 21st century, preclinical and clinical trials had been conducted to evaluate the impact of 18F-FDG PET in several different diagnostic settings in patients with GCTs, for example, prediction of viable tumor in residual masses after completion of chemotherapy, the impact on primary diagnosis or early diagnosis of relapse or unfavorable prognosis. Unfortunately, the initial high level of enthusiasm among oncologists about 18F-FDG PET and PET/CT and the promising results of first retrospective studies and case series have been followed by disappointing results from larger and prospective analyses. Currently, prediction of residual viable tumor in postchemotherapy patients with pure seminoma remains the only diagnostic setting where 18F-FDG PET adds clinically relevant information.

To date, there are no clinically relevant studies ongoing regarding other nuclear medicine procedures in GCTs. But new PET tracers or other nuclear diagnostic tools such as PET/MRT may improve routine staging techniques. Aide et al.13 have succeeded in distinguishing mature teratoma from postchemotherapy necrotic masses in an NSGCT xenograft model in vivo. Imaging of αβ,3 integrin was performed on a micro-SPECT/CT after injection of the tracer [111In] 6-hydrazinonicotinic acid conjugated to cycloArg-Gly-Asp-D-Phe-Lys (HYNIC-RGD). αβ,3 imaging accurately distinguished mature teratoma (SPECT/CT positive) from necrosis following cisplatin-based chemotherapy. In conclusion, progress in developing other nuclear medicine procedures in GCTs. But new PET tracers or other nuclear diagnostic tools such as PET/MRT may improve routine staging techniques. Aide et al.13 have succeeded in distinguishing mature teratoma from postchemotherapy necrotic masses in an NSGCT xenograft model in vivo. Imaging of αβ,3 integrin was performed on a micro-SPECT/CT after injection of the tracer [111In] 6-hydrazinonicotinic acid conjugated to cycloArg-Gly-Asp-D-Phe-Lys (HYNIC-RGD). αβ,3 imaging accurately distinguishes mature teratoma (SPECT/CT positive) from necrosis following cisplatin-based chemotherapy. In conclusion, progress in distinguishing mature teratoma from postchemotherapy necrotic masses in an NSGCT xenograft model in vivo. Imaging of αβ,3 integrin was performed on a micro-SPECT/CT after injection of the tracer [111In] 6-hydrazinonicotinic acid conjugated to cycloArg-Gly-Asp-D-Phe-Lys (HYNIC-RGD). αβ,3 imaging accurately distinguishes mature teratoma (SPECT/CT positive) from necrosis following cisplatin-based chemotherapy.

REFERENCES

noma.

emission tomography (FDG-PET) for postchemotherapy seminoma residual masses in patients with bulky seminoma.


