Chapter 28

Positron Emission Tomography (PET) in Germ Cell Tumors (GCT)

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Introduction

Both the treatment and outcome of germ cell tumors (GCT) have changed with the implementation of cisplatin-based chemotherapy. High cure rates even in advanced tumor stages provide a unique scenario for young cancer survivors who look for optimal patient management with minimal acute and long-term morbidity and toxicity. Non-invasive staging tools like serum tumor marker assays and imaging studies such as computed tomography (CT) both made substantial contributions to this goal. Improved staging and response evaluation help to avoid unnecessary overtreatment by risk-adapted approaches precisely tailored to the individual patient.

However, conventional staging techniques still are prone to considerable over- and understaging attributable to their sensitivity and specificity [1–3].

Positron emission tomography (PET) is a more recent addition to the battery of clinical diagnostic tools. With this imaging technique, a non-invasive method for determining regional metabolic processes has become available. The use of PET in oncology is based on the well-founded assumption that the visualization of metabolic changes often precedes measurable morphologic alterations in neoplastic tissue [4–7]. Thus PET has added a new dimension, i.e., metabolic imaging, to current anatomy-derived imaging techniques.

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Physics

The principle underlying positron emission tomography (PET) is that when binding to electrons, positrons from positron-emitting radioisotopes release annihilation gamma rays. These consist of two photons of 511 keV each separating in diametrical directions and are detected by a ring of detectors with opposed scintillation crystals, which recognize coincident radiation events. PET produces both dynamic data like the movements in time of the injected tracer and its distribution in a circumscribed area and static data such as those obtained by whole body scans, which image the structures of interest in three dimensions (coronal, transverse, and sagittal) and are generally used for evaluating cancer patients. *S*tandard tracer *u*ptake *v*alues (SUVs) are being calculated in an attempt to quantify the intensity of local tracer uptake in the region of interest and to obtain results, which are easily compared with the results at another point in the course of the disease:

SUV = decay corrected maximal region of interest activity/injected dose / body weight

However, the usefulness and the reproducibility of SUVs compared to visual interpretation by an experienced nuclear physicist have repeatedly been questioned [8, 9].

Currently, the most sophisticated standard scanners, i.e., full-ring tomograph scanners [10], have a resolution of 4–5 mm. They detect volumes with positive tracer uptake down to 8–10 mL. The technology involved is complex and the costs incurred are high.

Tracers in GCT

In oncology, 2-^{18}fluoro-2-deoxy-D-glucose (FDG) is currently the most widely used tracer, because it selectively accumulates in cancer cells. On account of the regionally increased blood flow and the elevated activity of glucose transporters (GluT1) and intracellular hexokinase, cancer cells are avid glucose seekers. ^{18}F substitution at the C2

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of the glucose structure turns ^{18}FDG-6-phosphate into a polar molecule, which cannot be further metabolized and, as cancer cells contain little glucose-6-phosphatase, is trapped in them. These mechanisms contribute to distinguishing active tumor from non-neoplastic cells by its increased tracer uptake [11–13].

A few other tracers have been under investigation for GCTs, among them L-(1-carbon-11)tyrosine [14], which has, however, not been found to be suited for evaluating residual masses in GCT.

The following physiologic issues and limitations of FDG PET should be considered before clinical decision-making with the help of FDG PET:

Physiologic FDG Uptake

FDG also actively accumulates in normal tissues of the brain, the myocardium, the liver, the smooth muscles, and the bone marrow and is eliminated along renal and urinary pathways. Three-dimensional imaging and iterative reconstruction help to differentiate these superimposed structures from neoplastic tissue [15].

False Positive FDG PET Results

High FDG uptake is not totally tumor specific. It is well known that inflammatory and granulomatous tissue such as sarcoidosis show extensive tracer uptake caused by elevated macrophage activity [16–18]. This is also true for inflammatory reactions up to several months after irradiation [19, 20]. Active [^{18}F]FDG uptake by phagocytes within abscesses or by granulation tissue surrounding abscesses causes false positive results, whereas chemically sterile abscesses do not accumulate FDG [4]. Macrophage accumulation due to resorption of necrotic post-treatment tumor tissue will cause false positive FDG PET studies. Most importantly, there may be a metabolic flare within the first days after chemotherapy. Therefore, PET should not be performed too early in germ cell residual tumors after chemotherapy, i.e., within 2–4 weeks post-chemotherapy [17, 21, 22].

False Negative FDG PET Results

The timing of PET studies is of utmost importance. FDG uptake by neoplastic tissue may be reduced within 2 weeks of exposure to cytostatics [16]. This phenomenon is tumor- and treatment specific. In gastrointestinal stroma tumors (GIST), for instance, reduced uptake (true negative result) after exposure to imatinib mesylate has been described after only 24 h [23].

The size of the lesions to be evaluated is important as well. Due to the limited resolution we do not expect FDG PET to be positive in low-volume disease, e.g., lesions < 5 mm. But PET may detect extremely active lesions between 5 and 10 mm in size [5, 24–30].

PET for Non-invasive Tumor Staging

Consistent prospective data have established the clinical role of FDG PET in oncology particularly for staging non-small-cell lung cancer, colorectal cancer, and melanoma, for evaluating single pulmonary lesions, for detecting liver metastases, and for staging cancers with unknown primaries [11, 13, 31–35]. In Non-Hodgkin's lymphoma and Hodgkin's disease PET has become crucial for staging, treatment evaluation, early detection of relapse, and most recently for distinguishing aggressive and indolent disease [36–41].

FDG PET in Germ Cell Tumors (GCT)

Germ cell tumors as well as their secondaries are generally characterized by a high FDG uptake. Pure seminomas accumulate even more FDG than non-seminomatous lesions [5, 16, 42]. This very fact led numerous research teams to investigate the clinical role of FDG PET in GCT.

The following chapter will summarize the current state-of-the-art knowledge about the use of PET in different clinical situations during the treatment of germ cell tumors. Evidence derived from published trials and its consequences will be discussed. The pros and cons of PET scanning will be put into the context of crucial points in clinical decision-making. These include

- Staging at presentation
- Response evaluation
- Management of relapse

Staging at Presentation

Non-seminomatous and Seminomatous Germ Cell Tumors (NSGCT and SGCT)

Staging of GCT at presentation in clinical stages I and II with CT scans has a limited accuracy of about 70% [2, 30, 43, 44]. After staging by CT 20–30% of clinical stage II patients turn out to be stage I pathologically. On the other hand, CT underestimates the pathologic stage in up to 30% of patients

[43, 45]. The smaller the lymph nodes the higher the sensitivity, but the lower the specificity [2, 46, 47].

The role of FDG PET for initial staging in unselected NSGCT and SGCT patients was the subject of investigation in several trials [5, 16, 22, 24–29], two of which [22, 29] reported a higher sensitivity and a higher negative predictive value (NPV) for PET versus CT. The specificities of the two methods were comparable. No clinical consequences were drawn. Recently, a German group investigated the sensitivity, specificity, and accuracy of FDG PET in stage I/II NSGCT patients scheduled for primary retroperitoneal lymph node dissection (RPLND). There was no difference between CT and FDG PET in terms of false negative results, especially in small lesions [30].

In most of the studies PET failed to detect small (< 1 or < 0.5 cm) retroperitoneal lymph nodes [5, 24–30] and mature teratomas [24, 28]. One of the positive PET scans in one trial was attributable to sarcoidosis [16]. None of the trials unequivocally established a benefit of PET versus conventional staging with tumor markers and CT at presentation.

Summary

To date there is no proof of a benefit of PET for staging at presentation.

Clinical Stage I Non-seminomatous Germ Cell Tumors (NSGCT)

After orchiectomy about 30% of clinical stage I NSGCT patients staged with conventional techniques like (spiral-) CT scans will relapse within the first 2 years after the diagnosis.

The most accurate staging technique for the retroperitoneum, i.e., retroperitoneal lymphadenectomy, is very invasive for just a staging procedure, and its cure rate is no better than 10–15% [1, 47]. Systematic adjuvant short-term chemotherapy of high-risk clinical stage I patients in terms of risk-adapted treatment [48] is tantamount to overtreatment in as many as 50% of cases. Therefore, improved staging tools would be of utmost importance in clinical stage I GCT.

Three of four trials examining FDG PET for staging clinical stage I NSGCT patients with no more than a total of 27 patients correlated PET data with histopathology data obtained from subsequent (RPLND) [24, 27, 28]. In all three trials PET failed to improve clinical staging. Of 22 negative PET scans, seven proved to be false negative (NPV 68%): in six patients the histologically positive lymph nodes were smaller than 0.5 cm and in the remaining patient PET failed to detect a mature teratoma. PET (sensitivity 42%) correctly identified no more than 5 out of 12 metastasizing patients [24, 27, 28]. In the fourth study by Lassen et al. [49], PET data of 46 patients were compared to clinical follow-up data collected during surveillance. In this prospective trial, by contrast, 7 out of 10 relapses were correctly predicted (sensitivity 70%) and no more than 3 out of 39 negative PET scans proved to be false negative (NPV 92%). This prompted the authors to conclude that FDG PET had improved clinical staging in their patients. A CT review later on classified two patients to be stage II, who finally had to be removed from the analysis. After all, the sensitivity of FDG PET in this study fell to 50% [50]. Based on the initial results of this trial [49], the Medical Research Council initiated a prospective large-scale trial to investigate the role of FDG PET in high-risk clinical stage I NSGCT. PET-positive patients enrolled in this trial were subjected to adjuvant chemotherapy, while those with negative PET scans were put on surveillance. The study was closed early in 2005, after 33 out of 88 PET-negative patients had relapsed, with a 1 year relapse-free rate of 63.3% instead of the expected 2-year relapse-free rate of $> 90\%$ [51].

Summary

FDG PET has no role for staging or early detection of micrometastases in clinical stage I NSGCT.

Clinical Stage I Seminoma

Clinical stage I seminoma patients overall run a relapse risk of 18% [52] without further adjuvant treatment. Patients are usually offered adjuvant standard radiation therapy or are put on a surveillance protocol. Adjuvant chemotherapy with carboplatin has become a third option [53, 54], because randomized data still lack sufficient follow-up time and peer-reviewed publication. Any kind of adjuvant treatment in clinical stage I seminoma causes an overtreatment rate of about 80%.

So far, no scientific evidence is available for a positive role of PET in this clinical setting. Albers and Müller-Matheis [24, 27] described 31 clinical stage I seminoma patients, all of them with negative PET scans. But as all of them had undergone adjuvant radiotherapy, there is no way of telling whether the PET data was correct or not.

The role of PET in an adjuvant setting should be analyzed in patients under surveillance.

Summary

FDG PET has no advantage over CT in staging clinical stage I SGCT.

Clinical Stage II Disease/NSGCT

In clinical stage II, particularly in stage IIa disease, pathologic staging with RPLND shows that in up to 25% of cases patients are overstaged by CT [43]. FDG PET data for this clinical situation are contradictory: in a study by Albers et al. [24] CT staging was false positive in four out of nine clinical stage II NSGCT patients, while PET correctly staged all nine patients. Of the seven patients with clinical stage II disease contributed by Spermon et al. [28], all were correctly staged by CT, while PET failed to detect metastatic embryonic carcinoma in a retroperitoneal lymph node 1.2 cm in size and metastatic mature teratoma in another.

Summary

There is no evidence-based support for the use of FDG PET in stage II NSCGT.

Response Evaluation

Post-chemotherapy Residual Masses in NSGCT

After completion of cisplatin-based chemotherapy, one quarter to one third of all patients with metastases of NSGCT present with residual masses, although their tumor marker levels have returned to normal (marker-negative partial remissions; PRm-). These patients are candidates for residual tumor surgery. Multiple series of histological studies after RPLND show that only 40–45% of these residuals consist of necrotic/fibrotic tissue, while 10–20% harbor viable tumor and 30–45% mature teratoma [55, 56]. The latter two, viable tumor and mature teratoma, are the source of recurrences and therefore have to be removed. Complete resection of all residual NSGCT lesions is the only way of curing this group of patients [57, 58].

However, resection of mere necrosis/fibrosis only does not offer any therapeutic benefits. Neither retrospective trials nor predictive models [59] based on regression analyses have so far reliably predicted the histology of the residual masses. Therefore, several authors [16, 17, 27–29, 42, 60–63] evaluated FDG PET for its predictive potential in this clinical setting. Four of them were prospective trials [17, 27, 42, 61].

The authors unequivocally found that PET predicted viable tumor within the residual lesions with a high measure of diagnostic accuracy, except in very small residuals. Unfortunately, FDG PET failed to distinguish between mature teratoma and necrosis/fibrosis, because both accumulate very little or no FDG. Therefore, FDG PET does not help in deciding for or against surgery. Based on kinetic modeling, only Sugawara et al. [63] reported differences in the kinetic rate constants of FDG uptake between mature teratoma and necrosis/fibrosis, albeit in no more than six patients.

The German multicenter trial, first presented as an abstract in 2006, showed an accuracy of only 57% for FDG PET for predicting vital tumor and teratoma in 141 patients with post-chemotherapy residual tumors. There was also a high rate of false positive results. Interestingly, the PET scans had been performed at an average of only 8.5 days after chemotherapy [30].

The studies quoted provided two important messages for the proper use and interpretation of PET in post-chemotherapy patients: (1) In some of them [16, 17, 27–29] inflammatory reactions with abundant macrophages accompanying tumor necrosis seen histologically were the most common cause of false positive PET scans. (2) FDG PET studies done shortly after chemotherapy (within less than 2 weeks) may be false negative because of a putative suppression of tumor cell metabolic activity regardless of their final treatment response [16]. Both of these observations suggest that an interval of several weeks post-chemotherapy should be allowed for PET scans.

Summary

Current evidence does not support the use of FDG PET for post-chemotherapy evaluation of NSGCT lesions.

Post-chemotherapy Residual Masses in SGCT

Residual lesions after chemotherapy of bulky SGCT are expected to be present in 50–75% of patients. Overall, less than 20% of the resected residual masses harbor viable tumor. Therefore, the management of seminoma residuals is controversial. Trying to find risk factors for the presence of viable tumor within the residual lesions, some authors found that the likelihood rose with the residual tumor size [64, 65]. The cut-off was drawn at a size of 3 cm.

The pronounced desmoplastic reaction of the tissue surrounding residual seminoma masses makes their resection technically demanding. Consequently, some authors prefer surveillance and reserve surgery for patients with progressive lesions [66], while others only resect lesions larger than 3 cm in diameter [65]. The advantage of FDG PET in SGCT compared to its use in NSGCT is that the presence of mature teratoma is extremely rare in SGCTs [65]. FDG PET, on the other hand, reliably differentiates viable tumor from necrosis/fibrosis in residual NSGCT. Therefore, two research groups examined seminoma residuals with FDG

PET in prospective trials comparing the results with histologic data or the clinical outcome.

In the single-center Indiana University study [67], only 1 out of 29 patients undergoing PET scanning at arbitrary intervals post-chemotherapy was PET-positive. The authors concluded that FDG PET was not helpful in distinguishing necrosis from viable seminoma, because it was false positive in one and false negative in five cases. In the Austrian–German prospective multicenter trial, by contrast, an interval of at least 4 weeks post-chemotherapy was mandatory for PET scanning. Preliminary data from the first 37 PET scans showed the specificity and the positive predictive value (PPV) to be 100% at a sensitivity of 89% and a NPV of 97% [64]. The discrepancies between these data and those found in the Indiana University study prompted the Austrian–German researchers to continue the trial and to expand it to 51 patients with post-chemotherapy residual masses and 56 FDG PET scans: All residual lesions $>$ 3 cm and 95% of those $\leq$ 3 cm were correctly predicted by FDG PET. The specificity, sensitivity, PPV, and NPV of FDG PET was 100, 80, 100, and 96%, respectively (Fig. 28.1). This is clearly superior to CT. The authors concluded that FDG PET was the best predictor of viable residual tumor in post-chemotherapy seminoma residuals and should be used as a standard tool for clinical decision-making in this patient group. The main advantage of using FDG PET in this clinical setting is that, in patients with residual lesions $>$ 3 cm, even in very large lesions, surgery can be omitted safely, if PET scans are negative. PET-positive residual lesions, according to this data set, must be regarded as harboring viable tumor and should be resected, if technically possible [68].

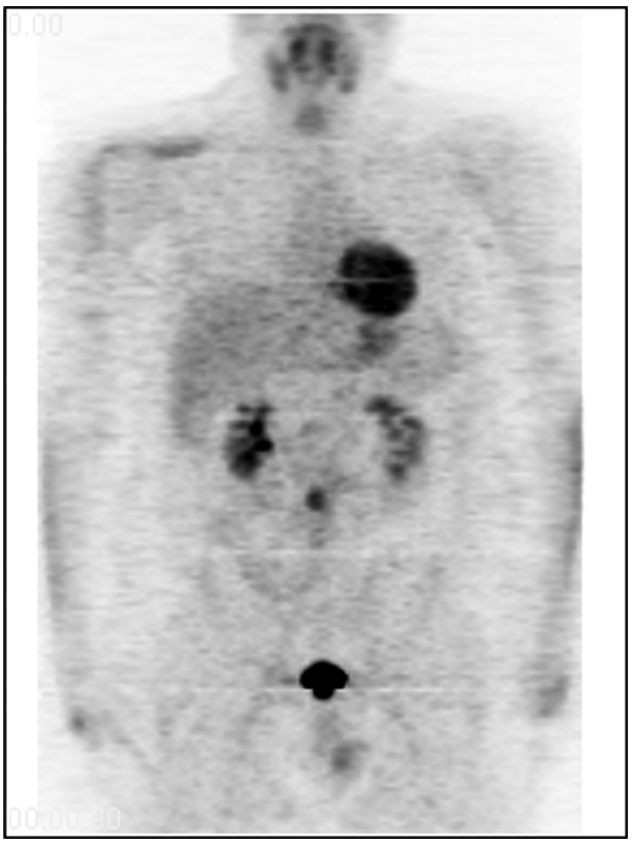

Fig. 28.1 FDG PET 6 weeks after chemotherapy for stage IIC SGCT. Histologically proven true positive residual lesion

Summary

FDG PET combined with CT studies for the evaluation of pure seminoma residuals can be regarded as a standard tool for clinical decision-making.

Early Prediction of Treatment Response to Salvage Chemotherapy

In some tumor entities FDG PET proved to be valuable for predicting treatment response non-invasively at an early point in time [23, 41, 69–71]. For first-line chemotherapy of germ cell tumors with a clear standard treatment and excellent cure rates, early response evaluation has no benefit. In patients with poor-prognosis GCT or germ cell tumors in relapse, however, strategies for a better and earlier response evaluation in order to modify ineffective but toxic chemotherapy regimens are warranted. Bokemeyer et al. [72] addressed this problem in 23 patients with relapsed germ cell cancer enrolled in a high-dose salvage chemotherapy program. FDG PET scans were recorded before conventional-dose induction and before high-dose treatment together with the usual tumor marker profiles and CT scans. The results were compared with the histologic response and/or the clinical course over 6 months following high-dose treatment (relapse versus freedom from progression). FDG PET showed a sensitivity, specificity, PPV, and NPV of 100, 78, 88 and 100%, respectively, and was superior to tumor marker assays, CT and both of them (Fig. 28.2). It therefore seemed to be a valuable addition to the established prognostic model for high-dose chemotherapy of germ cell tumors [73]. However, the authors cautioned that, at this point in time, it was not justified to derive treatment decisions from PET results alone. Larger studies are necessary to confirm this approach.

Summary

To date FDG PET has not been proven to be a reliable tool for changing treatment decisions in poor-risk or relapsed germ cell tumor patients.

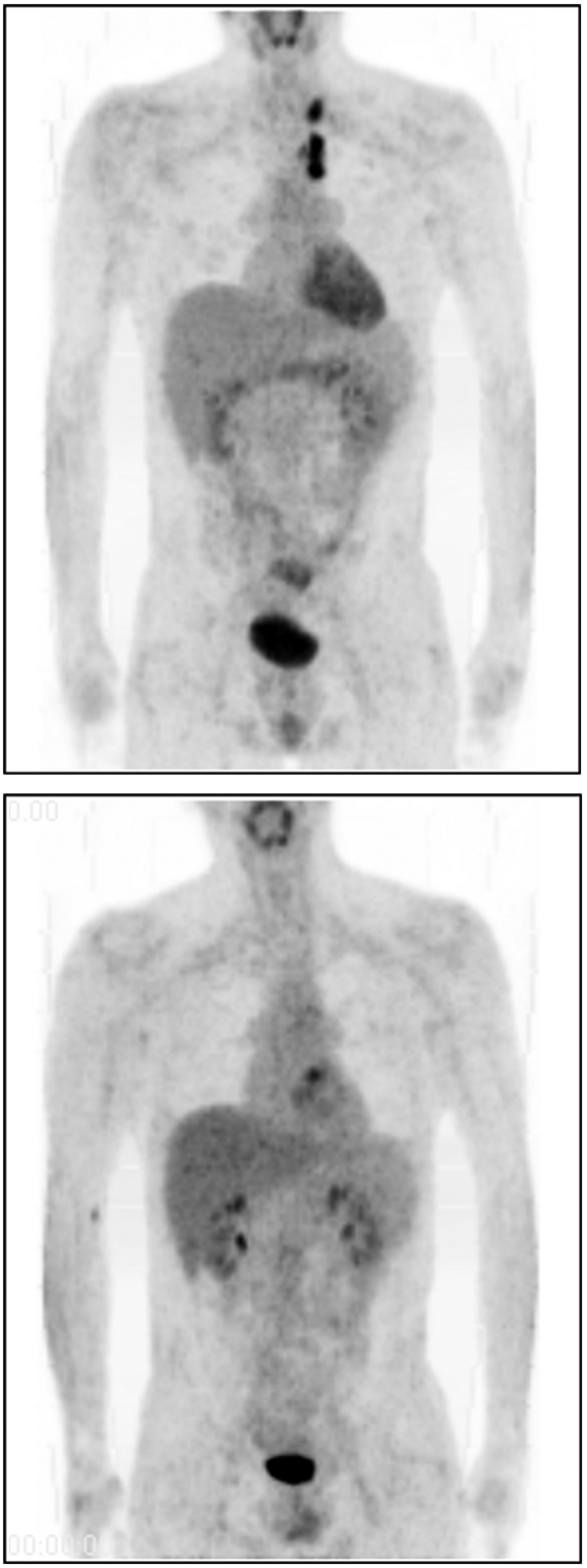

Fig. 28.2 a) Residual mediastinal lymph nodes, SGCT; true positive PET scan after completion of first line chemotherapy with clinical relapse 2 months later. b) True negative FDG PET in the same patient after first cycle of high dose chemotherapy. No residual tumor resection. Clinical follow-up and shrinkage of mediastinal residuals for >3 years

Relapse

Diagnosis of Relapse

About 20% of all patients with germ cell cancer relapse. Diagnostic evidence for this clinical situation is a rise in tumor marker levels and radiologic (rarely clinical) signs. For those who relapse with rising marker levels and unequivocal radiologic/clinical signs of progressive disease the guidelines for management are clear and well established: salvage chemotherapy, standard or high dose, followed by salvage surgery, or primary salvage surgery are the standard treatment options. For all other relapses FDG PET might be a valuable diagnostic tool. The key situations include

1. Rising tumor markers unmatched by clinical/radiologic abnormalities
2. Radiologic evidence of a new lesion or an increase in the volume of a pre-existing one unassociated with rising marker levels
3. Rising tumor marker levels in the presence of multiple residual lesions unchanged in size.

Although FDG PET appears to hold promise for answering these questions, only few reports on relapsing germ cell cancer patients, all of them retrospective or just case reports, are available [60, 62, 74].

Hain et al. [60] reported all 12 positive PET scans of 23 patients in marker-only relapse to be truly positive. PET clearly identified the site of the disease. However, 4 out of 11 scans were false negative. Subsequently, three of these PET scans turned positive and were the only imaging investigation to identify the site of the disease. In a report from France [74] FDG PET also was the only imaging study to identify the site of the disease in five out of seven patients with elevated markers. Sanchez et al. [62] found three true positive and two true negative FDG PET scans in patients with elevated markers and non-contributory CT scans and patients with normal marker levels and increasing lesions on CT, respectively, the latter mature teratoma by histologic evidence.

A patient reported by Reinhardt et al. [75] presented with negative markers and a negative FDG PET scan of a growing retroperitoneal bulk. Not surprisingly, this bulky disease proved to be a mature ”growing teratoma” on histology and therefore was true negative. In another case report FDG PET showed a contralateral testicular lesion in a clinically and sonographically normal testicle to be the underlying cause of an AFP rise [76].

Summary

FDG PET can be expected to be helpful for planning elective salvage surgery in chemoresistant patients and in those with multiple residual lesions to be removed. However, evidence from pertinent studies is not available.

Conclusions

In GCT, FDG PET is not superior to conventional staging tools for staging at presentation. It is not safe for detecting lesions less than 1 cm in size and mature teratoma.

FDG PET should be used as a standard diagnostic tool in patients with pure seminomatous residual lesions. It predicts the persistence of viable tumor in this clinical situation with a high diagnostic accuracy. FDG PET-negative SGCT residual lesions may be observed safely.

NSGCT patients with residual masses do not benefit from FDG PET. Residual mature teratoma, which is PET-negative, will be missed, and has to be resected at any rate, just like PET-positive residual lesions.

In relapsing patients with a mismatch between tumor marker levels and imaging data, FDG PET may be helpful in selected cases, particularly if salvage surgery is considered.

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