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FDG-PET in the management of germ cell tumor

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Germ cell tumor is the most common malignancy in young men. The cure rate of these patients has tremendously increased in the cisplatin era, and recent results have indicated that the management of patients with GCT is still improving. The use of FDG-PET in the management of patients with GCT has been recently investigated. This report attempts to comprehensively review new advances and delineate the potential applications of FDG-PET in GCT.

Introduction

Germ cell tumor (GCT) is the most common malignancy in men aged 20–35 years [1]. Since the introduction of cisplatin as the basis of chemotherapy in the mid-1970s, the cure rate of these patients has tremendously increased [1]. Moreover, in the cisplatin era, the 10-year survival rate of patients with metastatic nonseminomatous GCT significantly increased from 76% during the period 1977–1986 to 88% during the period 1987–1996 [2]. In 1997, the staging system of the International Germ Cell Cancer Collaborative Group (IGCCCG), based on sites of disease and serum tumor marker levels aided to optimize the standard treatment of GCTs (Figure 1) [3]. These results indicate that the management of patients with GCT is still improving.

Positron emission tomography (PET) with the glucose analogue ^{18}F-fluorodeoxyglucose (FDG) has become an important innovation in cancer imaging. The success of this technology is based on the observation that many neoplasms have an enhanced metabolism of glucose when compared to normal tissue. FDG undergoes the same uptake as glucose, and is phosphorylated to FDG-6-PO4 by hexokinase. Unlike glucose-6-PO4, FDG-6-PO4 cannot be further metabolized in the glycolytic pathway and remains trapped and accumulated in the cells. The accumulation of labelled FDG in hypermetabolic cancer cells can be detected with high resolution by the PET scanners, allowing differentiation between cancer and the surrounding normal tissues [4]. The use of FDG-PET to improve the management of patients with GCT has been recently investigated. This report attempts to comprehensively review new advances and delineate the potential applications of FDG-PET in GCT.

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Initial staging and follow-up

Traditionally, staging and follow-up of GCT has involved clinical examination, determination of serum tumor markers alpha-fetoprotein (AFP), beta-human chorionic gonadotropin (beta-HCG) and lactate dehydrogenase (LDH), and standard anatomic imaging investigations [5]. Ultrasonography of the testes and computerized tomography (CT) of the chest, abdomen and pelvis are considered mandatory in the staging at initial presentation and in the follow-up strategy. Chest X-ray is considered as an alternative to chest CT at diagnosis in stage I seminoma, and in the follow-up in all stage I GCTs [5, 6]. Surveillance is one of the options proposed in the management of stage I nonseminomatous GCT when there is only a low risk of progression. The presence of recurrences in this population, which is at low risk of progression, accounts for the continuing research for more precise predictive factors of occult metastases. Although several studies appear to indicate a useful predictive value for some of these factors, their application in clinical practice still appears to be difficult [7]. It has been recognized that the use of anatomic imaging for GCT detection at diagnosis may be flawed since GCT cells may be present in normal sized lymph nodes [8]. Importantly, the optimum treatment strategy for GCT at presentation is conditioned by detection of sites of metastatic disease. However, there have been few reports that assessed the effect of FDG-PET in the initial staging of GCT patients. Results of preliminary experiences demonstrated FDG-PET to be a potentially useful diagnostic tool for initial staging in patients with stage I-II GCTs, even if FDG-PET was not able to identify mature teratoma [9–12]. In particular, FDG-PET might be helpful to identify stage IIA in clinical stage I non-seminomatous GCT. These preliminary results were considered sufficient to suggest that a large prospective study was mandatory. A Medical Research Council (MRC) trial has recently started to evaluate the role of FDG-PET in stage I nonseminomatous GCT [13].

Good Prognosis

Non-seminoma Testis/retroperitoneal primary and No non-pulmonary visceral metastases and AFP < 1000 ng/ml and HCG < 5000 U/l and LDH < 1.5 x upper limit of normal (N)	*Seminoma* Any primary site and No non-pulmonary visceral metastases and Normal AFP, anyHCG, any LDH

Intermediate Prognosis

Non-seminoma Testis/retroperitoneal primary and No non-pulmonary visceral metastases and AFP = 1000 and ≤10,000 ng/ml or HCG = 5000 and ≤ 50,000 U/l or LDH = 1.5 x N and ≤10 x N	*Seminoma* Any primary site and Non-pulmonary visceral metastases and Normal AFP, anyHCG, any LDH

Poor prognosis

Non-seminoma Mediastinal primary or Non-pulmonary visceral metastases or AFP > 10,000 ng/ml or HCG > 50,000 U/l or LDH > 10 x upper limit of normal	*Seminoma* No patients classified as poor prognosis

Figure 1. International Germ Cell Cancer Collaborative Group (IGCCCG) classification.

In the follow-up of GCT patients, the ability of FDG-PET to identify suspected recurrences was investigated mainly in a context of elevated circulating tumor markers, where there are two areas of difficulty. Firstly, in patients with no residual masses, where if anywhere is the malignancy located. Secondly, when there are multiple residual masses which if any contain malignant GCT [8]. Results of the largest reported experience showed that FDG-PET allowed the identification of the sites of disease in these patients [8]. Besides, other authors emphasize the diagnostic difficulties encountered with FDG-PET in these patients, mainly because of false-positives due to post-operative inflammatory changes [9, 14, 15]. The possible contribution of FDG-PET in this area should be evaluated in larger series of patients. To date, no study is yet available to define the real place of this technique in the follow-up strategy.

FDG-PET has the potential to detect active malignant disease and thereby could influence management of these patients. However, false-positive findings should be considered with FDG-PET, because malignant neoplasms may also be simulated by other diseases [16]. In the chest, tuberculosis, histoplasmosis, aspergillosis and sarcoidosis may mimic tumors [16, 17]. Especially sarcoidosis should be considered in the differential diagnosis of GCT relapse, as there is a demonstrated association between these two conditions [18]. Moreover, increased FDG uptake may be observed in inflammation in any tissue including the operative site, and in bone, for instance because of hyperplastic marrow including stimulation by growth factors. In addition, a high number of studies showed increased FDG uptake in the normal thymus, particularly in children and young adults [19]. It has been recently reported that thymic FDG uptake can be observed in the anterior mediastinum in nearly 20–25% of patients with lymphoma after 1 and 2 years of treatment [20]. Therefore, even in GCT patients special attention should be given to the FDG-PET evaluation of the anterior mediastinum to avoid misinterpreting normal thymic uptake as disease recurrence in the mediastinum. Recently new fluorinated tracers, more directly addressing protein or DNA synthesis, have been proposed to differentiate malignant from non malignant lesions [21]. It is possible that in a close future these new tracers will be easily commercially available.

Early prediction of treatment response

FDG-PET has demonstrated efficacy for monitoring therapeutic response in a wide range of cancers, including breast, esophageal, lung, head and neck, and lymphoma. Establishing new surrogate end points for monitoring response to treatment could be also useful to optimize treatment in patients with advanced GCT. In GCTs the prognostic relevance of the rate of decline of serum AFP and beta-HCG for patients with non-seminomatous GCT represents an easy tool in the therapeutic management of these patients [1, 22]. However, FDG-PET might be an additional useful biomarker for early treatment evaluation in poor prognosis GCT patients, but data are not yet available.

In patients with relapsed/refractory GCT, FDG-PET might provide additional information to anatomic imaging techniques and tumor marker evaluation such as assessing subclinical response. In a recent study, the role of FDG-PET has been compared with established means of tumor response assessment such as CT and serum tumor marker changes in 23 patients with relapsed GCT treated with salvage chemotherapy [23]. FDG-PET performed early in the course of salvage treatment has provided independent prognostic information [23]. In particular, FDG-PET could be useful when mismatch between tumor marker and CT changes occurs and salvage surgery could be considered as an option [23, 24]. However, larger trials are needed before drawing any firm conclusion.

Response to therapy is probably the best suited target for DNA-synthesis imaging with thymidine analogues labelled with ^{11}C or ^{18}F [25]. In the next future, the diffusion of this tracer will probably improve the impact of PET molecular imaging on pharmacological treatment planning of tumors. Currently, no report specifically deals with the use of thymidine PET scanning in GCT.

Post-chemotherapy residual disease

Seminoma

Testicular seminoma presents at a relatively early phase in its natural history, spreads systematically via lymphatics, only later hematogenously, and is exquisitely sensitive to chemotherapy and radiotherapy [1]. Long-term survivors of seminoma treated with retroperitoneal radiotherapy are at significant excess risk of death as a result of cardiac disease or second cancer [26, 27]. Management strategies that minimize these risks, and maintain the excellent observed cure rates need to be actively pursued.

In the late 1990s, the predictive potential of FDG-PET for detecting viable tumor tissue in residual postchemotherapy masses of seminoma patients was investigated in two prospective trials with controversial results [28, 29]. The Indiana University trial concluded that FDG-PET was not beneficial in distinguishing viable seminoma cells from necrosis [28]. Vice versa, De Santis et al. showed FDG PET to be a clinically useful predictor of viable seminoma in postchemotherapy residual lesions, especially those greater than 3 cm [29]. These conflicting results were explained by the small number of patients in both studies, the possible different timing between end of chemotherapy and FDG-PET scanning, the different criteria of response employed. Finally, in the last years, the technology of PET scanning has been tremendously improved, and this may have played a role in the results of the former trial from Indiana University [28, 29]. To better address this issue, De Santis et al. decided to continue their trial and extended the number of enrolled patients and the follow-up in order to achieve a larger-sized analysis [30]. Fifty-six FDG-PET scans of 51 patients were evaluated. All cases with residual lesions >3 cm, and 95% with residual lesions ≤3 cm were correctly predicted by FDG-PET. This investigation confirmed that FDG-PET is actually the best predictor of viable seminoma in postchemotherapy residual lesions [30]. Because of the relevant clinical implications, FDG-PET should be used as a standard tool for clinical decision making in this patient group.

Nonseminoma

Several studies showed that FDG-PET can be useful for detection of residual viable malignant disease following chemotherapy in nonseminomatous GCT patients with residual masses [29–38]. FDG-PET results were compared in a blinded analysis with CT scans and serum tumor marker changes as established methods of assessment in 85 residual lesions from 45 patients with nonseminomatous disease enrolled in a prospective study [34]. PET assessment demonstrated positive and negative predictive values of 91% and 62%, respectively, in differentiating tumor from non tumor lesions. Accordingly, PET offers additional information for the prediction of residual mass histology in patients with nonseminomatous GCT [31, 34]. FDG-PET results were highly correlated with the presence of viable tumor, but negative FDG-PET studies did not exclude the presence of disease, mainly because of the presence of teratoma. As consequence, residual masses with negative PET findings still require surgical resection. In cases of tumor progression diagnosed by CT and elevated tumor markers, additional FDG-PET examinations are without benefit. FDG-PET seems useful in patients with stable disease or partial remission in CT and normalized tumor markers as well as in marker-negative disease.

FDG-PET can provide important information in nonseminomatous GCT patients with postchemotherapy residual masses, which cannot be determinant in clinical decision making because it is still difficult to differentiate mature teratoma from necrosis or scar with conventional visual interpretation or semiquantitative analysis of FDG uptake. Sugawara et al. investigated the role of FDG-PET and kinetic modelling in differentiation of viable malignant nonseminoma, mature teratoma, and necrotic tissue in residual masses after chemotherapy [39]. Although both mature teratoma and necrosis or scar had low FDG uptake at the conventional static PET scanning at 60 min after injection, the generated kinetic parameter for FDG transport for mature teratoma was significantly higher than that for necrosis and scar. On the one hand, FDG-PET with kinetic analysis appears to be a promising method for management of disease in patients with GCT after treatment, but an efficient procedure for non-invasive arterial sampling is not yet assessed. Overall, these findings need to be confirmed in larger series. Future studies have to prove whether the combination of clinical prognostic factors and new advances of PET scanning will allow to spare subsets of patients from resection of residual masses.

Conclusions

Initial staging and early recurrence diagnosis are key parameters in the treatment and outcome of GCT. Conventional anatomic imaging modalities can miss node involvement

and are non-specific since enlargement does not ever rhyme with involvement. FDG-PET might be helpful in identifying stage IIA in clinical stage I non-seminomatous GCT. A large MRC study has been recently started to address this issue [13]. In the follow-up, FDG-PET could be able to identify the sites of suspected recurrences in a context of elevated circulating tumor markers. In patients with relapsed GCT, FDG-PET performed early in the course of salvage treatment may provide independent prognostic information. In particular, when a discrepancy between tumor marker and imaging changes is reported, FDG-PET appears to be useful whenever salvage surgery is considered. FDG-PET is the best predictor of viable residual tumor in postchemotherapy seminoma residuals and should be used as a standard tool for clinical decision making in this patient group. Besides, the clinical impact of FDG-PET in the evaluation of postchemotherapy nonseminomatous residual masses is low because of necessity of surgical resection still in PET-negative patients, due to the possible residual mature teratoma, which has low FDG uptake. Moroever, in all these cases, the possibility of false-positive FDG-PET findings due to inflammatory processes have to be considered.

Although preliminary studies have documented the possible role of FDG-PET for the detection and staging of GCT, the monitoring of therapy results, and the prediction of viable malignant cells in postchemotherapy residual masses in these patients, it is very important to assess the impact of this technique on patient outcome and to show cost-effectiveness from the societal viewpoint.

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