의학석사 학위논문

종격동 생식세포종의 ^{18}F-fluorodeoxyglucose 양전자단층촬영/전산화단층촬영에서의 영상 특성 및 병리학적 아형에 따른 구별적 특징

^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography characteristics and discriminative features of primary mediastinal germ cell tumor according to pathologic subtypes

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이 논문을 의학석사 학위 논문으로 제출함

2022 년 2 월

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Abstract

Abstract

Purpose: Primary mediastinal germ cell tumor (MGCT) is a rare disease, which represents about 2%–4% of all germ cell tumors (GCT). We aimed to retrospectively review the distinctive visual characteristic and quantitative parameters of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) image for primary MGCT according to pathologic subtypes.

Methods: We retrospectively evaluated primary MGCT patients who underwent pre-operative ^{18}F-FDG PET/CT between 2010 and 2020 at Asan medical center. MGCTs included four histologic types and were divided into two groups (benign and malignant) for analysis. Visual assessment was performed by categorizing the uptake intensity (as grade 0-3), uptake pattern (as equivocal/homogenous/heterogeneous), and contour (as round/lobulated/infiltrative) of the primary mass. ^{18}F-FDG PET/CT quantitative parameters including maximum standardized uptake value (SUVmax), tumor-to-background ratio (TBR), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and maximum diameter values were compared between benign versus malignant MGCT. Receiver operating characteristic curve (ROC) analysis was used to evaluate the diagnostic performance of PET/CT variables in differentiating malignant from benign MGCT. In addition, subgroup analysis between seminoma versus nonseminomatous germ cell tumor (NSGCT) and according to high versus low level of tumor markers was performed.

Results: A total of 35 patients with 24 mature teratomas, 4 seminomas, 5 yolk cell tumors, and 2 mixed germ cell tumors were included. When compared with the benign MGCT group, the malignant group showed a significantly younger age distribution. In visual analysis, all 6 cases of grade 0 among 35 patients were teratomas but none of the teratomas showed grade 3 uptake. All the malignant GCT groups showed uptake with either grade 2 or 3. Most of the MGCT showed a heterogeneous uptake pattern. In quantitative analysis, all the PET/CT parameters

including SUVmax, TBR, MTV, and TLG showed significantly higher value in the malignant MGCT group than those in the benign MGCT group. In ROC curve analysis, SUVmax (Area Under Curve [AUC] = 0.947, $p < 0.0001$), TBR (AUC = 0.917, $p < 0.0001$), MTV (AUC = 0.727, $p = 0.0198$), and TLG (AUC = 0.920, $p < 0.0001$) showed excellent diagnostic performance in discriminating between benign and malignant MGCT. Especially, SUVmax demonstrated a significantly higher diagnostic value compared to MTV and maximum diameter ($p = 0.0254$ and 0.0114, respectively). With an optimal cut-off value of SUVmax 4.54, sensitivity and specificity for differentiating malignant from benign MGCT were 81.8% and 100%, respectively. In the subgroup analysis of differentiating between seminoma and NSGCT among malignant MGCTs, SUVmax, TBR, and maximum diameter showed significance ($p = 0.042$, 0.042, and 0.012, respectively). A high level of alpha fetoprotein (AFP) was correlated with a higher value of SUVmax, TBR, maximum diameter ($p = 0.012$, 0.034, 0.044, respectively), and no significant difference was found according to human chorionic gonadotrophin level.

Conclusions: Visual assessment of MGCT on ^{18}F-FDG PET/CT showed discriminative findings between benign and malignant MGCT. ^{18}F-FDG PET/CT quantitative parameters give additional information in differentiating benign versus malignant MGCT and seminoma versus NSGCTs.

Keywords: Mediastinal germ cell tumor; Fluorodeoxyglucose F18; Positron emission tomography

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Introduction

Mediastinal mass includes a wide spectrum of disease entities and accordingly a uniform approach is not appropriate. Primary mediastinal germ cell tumor (MGCT) is very rare and represent about 2%–4% of all germ cell tumors (GCTs) but should be considered in young males with markedly elevated tumor markers such as alpha fetoprotein (APF) or human chorionic gonadotrophin (HCG) [1-3]. Different entities of GCTs include mature and immature teratoma, seminoma, yolk sac tumor, choriocarcinoma, and embryonal carcinoma. Among GCTs, immature teratoma, seminoma, yolk sac tumor, choriocarcinoma, and embryonal carcinoma are considered malignant, and malignant MGCTs can be broadly subdivided into seminoma and nonseminomatous GCT (NSGCT) [4, 5]. Although MGCTs share similar histology with gonadal GCTs, the prognosis of MGCT is generally worse than that of gonadal GCT, and studies have shown that patients with seminomas show a more favorable prognosis compared with NSGCTs [3].

Due to its rare nature, so far there are no prospective studies to define a diagnostic approach, prognostic stratification, or different treatment strategies for MGCT and only a few retrospective studies and case series exist [6]. Therefore, treatment and management of this disease is challenging and requires a multidisciplinary approach and currently, MGCT is recommended to be treated like other gonadal GCTs. Tumor location, extension, serum tumor markers, and histopathological type are critical information for treatment planning and diagnosis of GCT [6, 7].

Recently, the role of 18F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) has been widely investigated for the diagnosis and prognostic stratification of cancer. However, ^{18}F-FDG PET/CT-related studies on primary MGCT are rare and mainly are comprised of case reports or series. Even a few reports that studied the role of ^{18}F-FDG PET/CT in gonadal GCTs do not recommend to be routinely performed in the initial staging of gonadal GCT [8, 9]. These few studies report that ^{18}F-FDG PET/CT has the additional value

of detecting distant metastasis or recurrence after chemotherapy, has a positive relationship with tumor markers such as AFP and HCG, and PET/CT quantitative parameters show a significant difference in worse prognosis group or NSGCT groups [10, 11]. In another preliminary study, the tumor to mediastinal ratio of ^{18}F-FDG PET/CT was significantly correlated with the expression of Glut1, HIF-1 EGFR, p-Akt, and p-S6K in primary non thymic neoplasm [12]. However, a structured study with visual assessment or quantitative PET/CT parameters of MCGT is yet to be reported.

Therefore, in this study, we aimed to retrospectively review the distinctive visual characteristic and quantitative parameters of ^{18}F-FDG PET/CT image for primary MGCT according to pathologic subtypes. In addition, we also investigated the relationship of serum tumor markers with quantitative PET/CT parameters.

Materials and methods

Study design and subjects

We retrospectively reviewed the medical records of patients who underwent surgery for MGCT in the Asan Medical Center from January 2010 to December 2020. Among these patients, those who underwent ^{18}F-FDG PET/CT within 4 months prior to biopsy or surgery were included. A total of 40 patients who underwent ^{18}F-FDG PET/CT before surgery who were pathologically diagnosed as primary MGCT with excisional biopsy or surgical resection were included in the study. Among these patients, 5 patients who performed PET/CT from outside the hospital who did not have information that was needed for quantification of ^{18}F-FDG PET/CT data (i.e., radiotracer injection dose, injection to scan time) were excluded from this study. This study was approved by the Institutional Review Board (IRB no. S2021-2042-0001) and the need for informed consent was waived due to the study's retrospective nature.

PET/CT image acquisition

All the study patients fasted at least 6 hours before ^{18}F- FDG PET/CT image acquisition and venous blood glucose level were controlled under 150 mg/dl. Patients were positioned in the scanners with their arms above their heads. ^{18}F-FDG PET/CT was performed using one of the following 4 PET/CT scanners; Biograph TruePoint 40 (Siemens, Erlangen, Germany), Discovery 690 (GE Healthcare, Milwaukee, WI, USA), Discovery 710 (GE Healthcare, Milwaukee, WI, USA), or Discovery 690 Elite (GE Healthcare, Milwaukee, WI, USA). The patients were intravenously administered 5.2 MBq/kg of ^{18}F-FDG and PET emission images were obtained 1 hour after the injection of ^{18}F-FDG with 5–6 bed positions covering from skull base to upper thigh, 2.5 min/bed, 168 × 168 matrix size (Biograph TruePoint 40) or 2 min/bed, 192 × 192 matrix size (Discovery series) in 3D acquisition mode. CT acquisition parameters were 120 kVp,10 mA, 5 mm slice thickness (Biograph TruePoint 40) or 140 kVp, Auto mA,

3.75 mm slice thickness (Discovery series). PET images were reconstructed using a three-dimensional ordered-subset expectation maximization algorithm with attenuation correction based on the CT data. Normalization and calibration of each scanner was conducted on daily basis (Biograph TruePoint 40) or quarterly basis (Discovery series). Cross-calibration against the dose calibrators was performed on at least an annual basis and SUV for the phantom were within the acceptable range of 90–110 %.

PET/CT image analysis

Both visual assessment and quantitative analysis were performed by one experienced nuclear medicine physician (K.L.) blindly. Visual assessment of PET/CT image was performed and each case was categorized according to ^{18}F-FDG uptake intensity grade, uptake pattern, and contour of the primary mass. For interpretation, uptake intensity grade was defined as follows: grade 0, lower or similar to mediastinal uptake; grade 1, greater than mediastinum but lower or similar to liver uptake; grade 2, greater than liver uptake; grade 3, markedly greater than liver uptake (Figure 1). Uptake pattern was defined as equivocal (neither heterogeneous nor homogenous, mostly not assessable due to very low metabolic uptake), homogenous (uniform uptake), and heterogeneous (uneven uptake) (Figure 2). Contour was defined as round (similar width and length with smooth margin), lobulated (lobulated with smooth margin), and infiltrative (irregular margin) (Figure 3). All three categories were evaluated based on PET/CT fusion images or with only PET images. Representative cases of visual assessment categorization are shown in figure 4.

For quantitative analysis of PET/CT images, we included data from four different scanners, we equalized the SUV among all scanners. We estimated the recovery coefficients (i.e., relative SUV ratios in relation to the ideal SUV of 2.5) using American College of Radiology-approved Esser phantom (Data Spectrum, Hillsborough, NC, USA) filled with ^{18}F-FDG water solution to set the hot cylinders SUV at 2.5 and background SUV at 1.0. The SUVs of different hot

cylinders with varying diameters were measured and recovery coefficient plots that allowed the estimation of the optimal smoothing kernel size for each matched different recovery coefficients were generated. After harmonization, the Volume-of-interest (VOI) of the anterior mediastinal tumor was drawn on PET/CT fusion image which allowed the VOI to be drawn within the mass shown on combined CT data. All of the PET/CT parameters from Biograph TruePoint 40 were calculated by drawing one VOI at the single workstation using Mirada DBX (version 1.2.0.59; Mirada Medical Ltd, Oxford, UK). Harmonized SUV values from the Discovery series were measured in our in-house software termed AMC NM Toolkit for Image Quantification of Excellence (ANTIQUE) using manually traced VOIs [13-15].

Maximum standardized uptake value (SUVmax) was the highest pixel uptake in anterior mediastinal mass and tumor-to-background ratio (TBR) and was calculated as the SUVmax of a mediastinal mass divided by the mean SUV (SUVmean) of the aorta with the same VOI. The volumetric parameter metabolic tumor volume (MTV) was segmented with a threshold of the relative value of more than 50% of SUVmax by VOI, and total lesion glycolysis (TLG) was calculated as SUV mean multiplied by MTV. The maximum diameter of the tumor was measured on a combined CT axial plane image.

Statistical Analysis

Demographic data (age) was expressed as means ± standard deviation (SD). Patient characteristics including time interval between biopsy or surgery and PET/CT, tumor markers were expressed as median and range. Quantitative data for statistical variables were expressed as median and range. Continuous variables were analyzed with one-way analysis of variance (ANOVA) or Kruskal-Wallis test with a post-hoc Dunn's test. Receiver operating characteristic (ROC) curve analysis was employed to show the diagnostic performance between benign and malignant MGCTs. DeLong’s method was used for comparing AUC values and their 95% confidence interval (CI). The optimal cutoff values were the exploratory cutoff value with the

highest accuracy. All statistical analyses were performed using SPSS software version 17 (SPSS, Chicago, IL) and MedCalc version 19.2.3 (MedCalc Software Ltd, Ostend, Belgium).

Results

Patient characteristics

A total of 35 consecutive patients (16 female and 18 male) were included in the analysis. The patient's mean age at the time of PET/CT image acquisition was 33.1 years. The median time interval between biopsy or surgery and PET/CT was 13 days (range 0-134 days). They were finally diagnosed as MGCT pathologically through excisional biopsy (n = 24) or resective surgery (n = 11). Of these patients, 24 patients were benign mature teratoma and 11 malignant lesions which included 4 seminomas, 5 yolk cell tumors, and 2 mixed GCT. The clinical and pathological characteristics of 35 patients are summarized in Table 1.

When compared with the benign MGCT group, the malignant group showed a significantly younger age distribution (Benign 38.2±18.0, malignant 21.9±4.0, *p*-value <0.001). All 11 patients in the malignant group were male. Time interval between biopsy or surgery and PET/CT did not significantly differ between the benign and malignant groups (*p*-value 0.221). Tumor markers AFP and HCG were examined in 26 patients among 35 patients and AFP was significantly higher in the malignant group whereas HGC was not (*p*-value 0.004 and 0.604, respectively) (Table 2).

Visual assessment

All 6 cases of grade 0 were teratomas and more than half of teratoma cases showed grade 2 uptake (58%, 14/24) but none of the teratomas showed grade 3 uptake. All of the malignant GCT groups showed uptake with either grade 2 (82%, 9/11) or 3 (18%, 2/11). Grade 3 cases were one seminoma and one mixed GCT. Most of the MGCT showed heterogeneous uptake patterns (83%, 29/35) and all the malignant MGCT showed heterogeneous uptake patterns (100%, 11/11). Most of the MGCT showed either round (74% 24/35) or lobulated contour

(23%, 8/35). Only one case of yolk cell tumor showed infiltrative contour and none of the MGCT cases showed homogenous uptake pattern (Table 3, figure 5).

Quantitative analysis of PET/ CT images

The median value of PET/CT parameters in total patients was SUV max 3.3, TBR 3.2 MTV 12.6, TLG 18.8, and maximum diameter 7.9. All the PET/CT parameters including SUVmax, TBR, MTV, and TLG showed significantly higher value in the malignant MGCT group compared with benign MGCT (p-value <0.001, <0.001, 0.033, and <0.001, respectively). Maximum diameter did not show a significant difference (p-value 0.115) between the two groups (Table 4).

In ROC curve analysis, SUVmax showed the highest AUC among all parameters (AUC 0.947) and showed significantly higher discriminative performance compared with MTV and maximum diameter between benign and malignant lesions. With the specific cutoff value of SUVmax 4.54, it showed a sensitivity of 81.82% and specificity of 100.00% in differentiating between benign and malignant MGCTs. TBR and TLG also showed excellent discriminative performance and did not show significant differences compared with SUVmax (AUC 0.917 and 0.920 respectively) (Table 5, figure 6).

Comparison of quantitative PET/ CT parameters between seminoma and NSGCT

Malignant lesions were subdivided into seminoma and NSGCT for further analysis. Among all parameters, SUVmax, TBR, and maximum diameter showed significant differences (p-value 0.042, 0.042, and 0.012 respectively) (Table 6).

Relationship between quantitative PET/ CT parameters and tumor markers

Patients were divided into two groups (high versus low) according to the threshold of the median value of each tumor marker (HCG = 1 and AFP = 2). Parameters SUVmax, TBR, and maximum diameter were significantly higher in the high AFP group (*p*-value 0.012, 0.034, and 0.044 respectively), whereas PET/CT parameters did not show a significant difference between high versus low HCG groups (Table 7).

Discussion

In this retrospective review of MGCT cases, visual assessment of ^{18}F-FDG PET/CT images showed some distinctive features. Particularly, teratomas (benign group) had a higher percentage of grade 0 cases compared with the malignant MGCT group which showed no case of grade 0. All the malignant MGCTs showed uptake greater than the liver. Also, interestingly all the uptake patterns were either equivocal or heterogeneous and no case showed a homogenous pattern. This is unique in comparison with other anterior mediastinal tumors reported such as thymic epithelial tumors or lymphoma cases that may show a homogeneous pattern. This factor could be useful in the initial diagnostic setting for differentiation with other anterior mediastinal malignancies.

Another notable finding of this study is with the information provided from the quantitative parameter of ^{18}F-FDG PET/CT which showed potential in discriminating benign MGCT from malignant MGCT. All the PET/CT parameters showed significantly higher values in malignant MGCT compared with those in benign mediastinal mature teratomas. Among all the parameters, SUVmax showed the highest AUC value and were significantly superior compared with MTV and maximum diameter. Additionally, SUVmax showed significantly higher value in the NSGCT group and high AFP group in further subgroup analysis. TBR also showed similar excellent results as SUVmax .

MGCT is a rare disease with heterogeneous entities. Although they share similar histopathologic features and tumor marker expression with gonadal GCT, they show different prognosis. According to the International Germ Cell Cancer Collaborative Group, NSGCTs have a worse prognosis compared with other primary GCTs. The role of ^{18}F-FDG PET/CT is not yet established in the initial diagnosis of MGCT and only a few studies exist at this point. ^{18}F-FDG PET/CT allows wholesome evaluation not only including nodal and distant metastasis but also the heterogeneity of the entire tumor, whereas biopsy can only evaluate the

obtained portion. In our study, SUVmax showed a higher AUC value compared with volumetric parameters like MTV or TLG. This could be explained by the heterogeneity of the tissue component that makes up the malignant MGCT. The second most common type of malignant MGCT is mixed germ cell tumor and even when seminoma is present as a component it is still considered as mixed germ cell tumor. In line with this pathologic differentiation, it suggests that the oncologic behavior of MGCT might be largely dependent on which malignant component of GCT histology is included rather than the whole volume of tumor cells.

Previous studies reported the additional value of ^{18}F-FDG PET/CT compared to CT alone in the assessment of GCTs. In one multicenter trial studying predictive values of ^{18}F-FDG PET in primary staging in patients with newly diagnosed gonadal NSGCT, they showed superior sensitivity (66% versus 41%, P = 0.038) and negative predictive value (78% versus 67%, *p*-value 0.05) compared with CT [9]. In testicular GCT, ^{18}F-FDG PET /CT is not routinely performed but is recommended for post-treatment evaluation of residual mass in seminoma patients [10]. A recent study by Aydos et al. reported that patients with elevated (at least two) tumor markers after surgery had a higher positive predictive value of ^{18}F-FDG PET in primary staging of testicular GCT. They also reported that MTV and TLG had significant positive correlations with HCG whereas AFP showed significant correlation only in the NSGCT patients. Our study also showed a correlation between tumor marker and quantitative parameters but only positive results in relation to AFP. This could be explained by the heterogenicity of patients included in each study. The disparity in the portion of subtypes comprising each study could have caused different results because seminomas seldom or rarely produce AFP but may have a variable amount of HCG whereas APF level in yolk cell tumor or HCG level in choriocarcinoma is almost always present and has a strong correlation with the whole tumor volume. LDH on the other hand, although less specific than AFP or HCG, is almost always elevated in malignant GCTs. Therefore, a further study with LDH lab data and

larger patient size to lessen the heterogeneity of this study is needed to verify the relationship between tumor markers and ^{18}F-FDG PET/CT data.

In one multicenter retrospective study, histology, high AFP, and HCG levels were identified as independent prognostic variables in GCTs patients [16]. In a few studies, NSGCT were reported to have a worse prognosis compared to seminoma. Aydos et al.'s study of testicular GCT reported that high MTV value and high tumor marker values were related to significantly to lower overall survival [10]. In our study, the NSGCT group and high AFP group were significantly associated with a higher value of SUVmax. Therefore, like the results from other studies, higher metabolic parameters combined with tumor markers may have a potential role in the prognosis prediction of MGCTs. Utilization of PET/CT combined with other prognostic factors could help identify the high-risk group of MGCT and thus have additional value in treatment and management planning in MGCT patients.

This study has a few limitations. This is a single-center retrospective study, and referral bias cannot be excluded due to the nature of the study. The impact of ^{18}F-FDG PET/CT in the evaluation of MGCT in the preoperative setting may be low because as shown in our study, imaging and clinical evaluation are not enough but pathologic confirmation with surgical resection is still necessary in PET-negative patients, due to some overlapping features between malignant and benign lesion. The sample size was small and thus additional prognostic assessment could not be performed. Also, some of the patients did not have tumor maker results and were excluded from the subgroup analysis. An additional study with a larger number of patients, tumor marker, and prognostic data is warranted in the future.

Conclusion

Visual assessment of MGCT on ^{18}F-FDG PET/CT showed discriminative findings between benign and malignant MGCT. ^{18}F-FDG PET/CT quantitative parameters give additional information in differentiating benign versus malignant MGCT and seminoma versus NSGCTs.

References

1. Bokemeyer C, Nichols CR, Droz J-P, Schmoll H-J, Horwich A, Gerl A, et al. Extragonadal Germ Cell Tumors of the Mediastinum and Retroperitoneum: Results From an International Analysis. 2002;20:1864-73. doi:10.1200/jco.2002.07.062.

2. Hainsworth JD, Greco FA. Extragonadal germ cell tumors and unrecognized germ cell tumors. Seminars in oncology. 1992;19:119-27.

3. Koizumi T, Kanda S, Nihonmatu R, Gomi D, Sekiguchi N, Noguchi T, et al. Primary mediastinal germ cell tumors - A retrospective analysis of >30 years of experience in a single institution. Thorac Cancer. 2021;12:807-13. doi:10.1111/1759-7714.13859.

4. Azizad S, Sannananja B, Restrepo CS. Solid Tumors of the Mediastinum in Adults. Semin Ultrasound CT MR. 2016;37:196-211. doi:10.1053/j.sult.2016.03.002.

5. Yang CJ, Cheng MS, Chou SH, Tsai KB, Huang MS. Primary germ cell tumors of the mediastinum: 10 years of experience in a tertiary teaching hospital. The Kaohsiung journal of medical sciences. 2005;21:395-400. doi:10.1016/s1607-551x(09)70140-8.

6. Kumar N, Madan R, Dracham CB, Chandran V, Elangovan A, Khosla D, et al. Primary mediastinal germ cell tumors: Survival outcomes and prognostic factors - 10 years experience from a tertiary care institute. Rare Tumors. 2020;12:2036361320972220. doi:10.1177/2036361320972220.

7. Mishra S, Das Majumdar SK, Sable M, Parida DK. Primary malignant mediastinal germ cell tumors: A single institutional experience. South Asian J Cancer. 2020;9:27-9. doi:10.4103/sajc.sajc_47_19.

8. De Giorgi U, Pupi A, Fiorentini G, Rosti G, Marangolo M. FDG-PET in the management of germ cell tumor. Ann Oncol. 2005;16 Suppl 4:iv90-4. doi:10.1093/annonc/mdi915.

9. de Wit M, Brenner W, Hartmann M, Kotzerke J, Hellwig D, Lehmann J, et al. [18F]-FDG-PET in clinical stage I/II non-seminomatous germ cell tumours: results of the German multicentre trial. Ann Oncol. 2008;19:1619-23. doi:10.1093/annonc/mdn170.

10. Aydos U, Tahtaci G, Ozgur Akdemir U, Ozet A. 18F-FDG PET/CT for primary staging of patients with testicular germ cell tumors: the predictors of 18F-FDG PET positivity and prognostic value of PET derived metabolic parameters. Nucl Med Commun. 2020;41:1199-209. doi:10.1097/MNM.0000000000001272.

11. Alongi P, Evangelista L, Caobelli F, Spallino M, Gianolli L, Midiri M, et al. Diagnostic and prognostic value of 18F-FDG PET/CT in recurrent germinal tumor carcinoma. Eur J Nucl Med Mol Imaging. 2018;45:85-94. doi:10.1007/s00259-017-3811-4.

12. Kaira K, Abe M, Nakagawa K, Ohde Y, Okumura T, Takahashi T, et al. 18F-FDG uptake on PET in primary mediastinal non-thymic neoplasm: a clinicopathological study. Eur J Radiol. 2012;81:2423-9. doi:10.1016/j.ejrad.2011.09.017.

13. Oh JS, Kang BC, Roh JL, Kim JS, Cho KJ, Lee SW, et al. Intratumor Textural Heterogeneity on Pretreatment (18)F-FDG PET Images Predicts Response and Survival After Chemoradiotherapy for Hypopharyngeal Cancer. Ann Surg Oncol. 2015;22:2746-54. doi:10.1245/s10434-014-4284-3.

14. Ha SC, Oh JS, Roh JL, Moon H, Kim JS, Cho KJ, et al. Pretreatment tumor SUVmax predicts disease-specific and overall survival in patients with head and neck soft tissue sarcoma. Eur J Nucl Med Mol Imaging. 2017;44:33-40. doi:10.1007/s00259-016-3456-8.

15. Kim JW, Oh JS, Roh JL, Kim JS, Choi SH, Nam SY, et al. Prognostic significance of standardized uptake value and metabolic tumour volume on (1)(8)F-FDG PET/CT in oropharyngeal squamous cell carcinoma. Eur J Nucl Med Mol Imaging. 2015;42:1353-61. doi:10.1007/s00259-015-3051-4.

16. International Prognostic Factors Study G, Lorch A, Beyer J, Bascoul-Mollevi C, Kramar A, Einhorn LH, et al. Prognostic factors in patients with metastatic germ cell tumors

who experienced treatment failure with cisplatin-based first-line chemotherapy. J Clin Oncol. 2010;28:4906-11. doi:10.1200/JCO.2009.26.8128.

Figures

Figure 1. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography images demonstrating uptake grade in visual assessment

Fusion PET/CT (positron emission tomography/computed tomography) and PET only images show four visual uptake grades of mediastinal germ cell tumors (arrows) of (A) grade 0 (lower or similar to mediastinal uptake), (B) grade 1 (greater than mediastinum but lower or similar to liver uptake), (C) grade 2 greater than liver uptake), and (D) grade 3 (markedly greater than liver uptake)

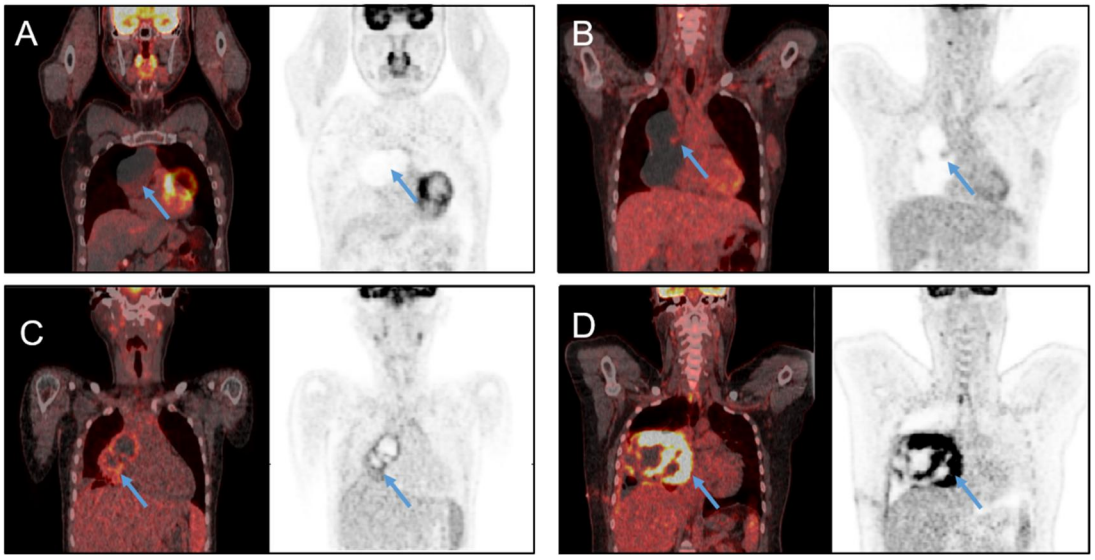


Figure 2. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography images demonstrating uptake pattern category

Fusion PET/CT (positron emission tomography/computed tomography) and PET only images showing two different uptake pattern categories the primary mediastinal mass (arrows): (A) equivocal, (B) heterogenous. Example of homogenous case is not shown due to lack of appropriate case in this study

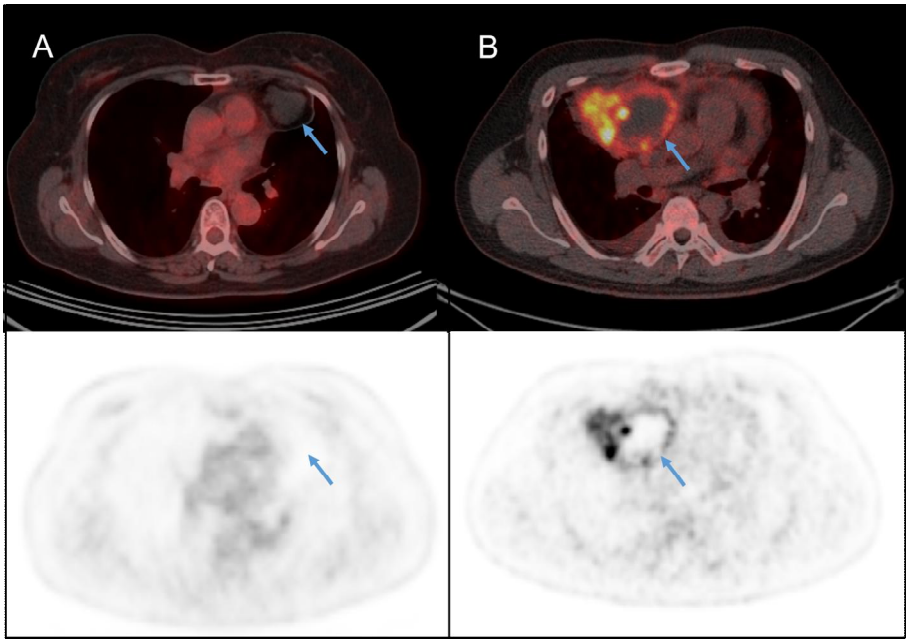


Figure 3. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography images demonstrating contour category

Fusion PET/CT (positron emission tomography/computed tomography) and PET only images showing three different contour categories of the primary mediastinal mass (arrows) : (A) round, (B) lobulating, and (C) infilatrative

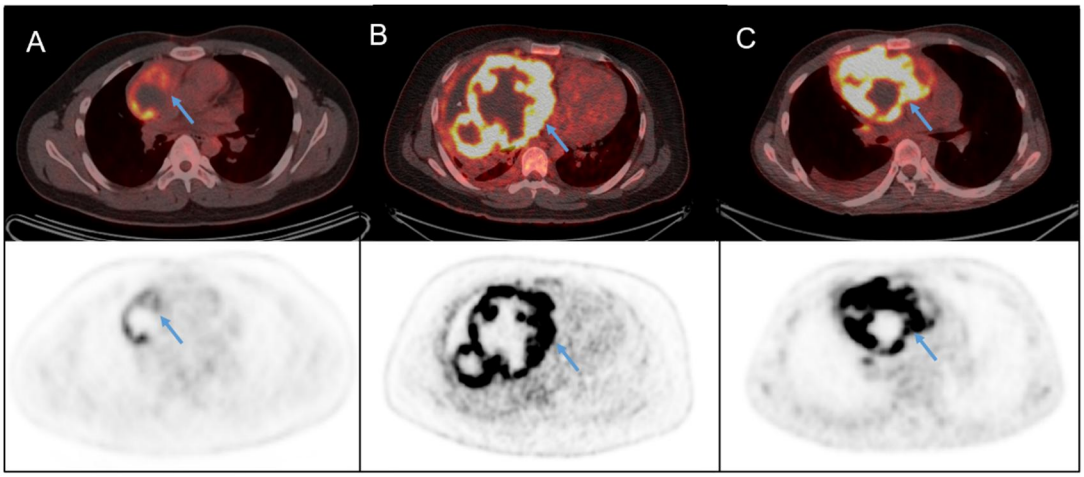


Figure 4. Representative cases of mediastinal germ cell tumor according to visual assessment categorization

Axial positron emission tomography/computed tomography fusion image of visual categorization examples, (A) 21 year-old male with benign mediastinal germ cell tumor (mature teratoma) shows category of grade 0 uptake, equivocal uptake pattern and round contour (SUVmax 1.87, arrow), (B) 31 year-old male with seminoma shows grade 3 uptake, heterogenous uptake pattern and lobulating contour (SUVmax 14.95, arrow), and (C) 22 year old male with yolk cell tumor show grade 4 uptake, heterogenous uptake pattern and linfiltrative contour (SUVmax 18.65, arrow) with anterior pleural Invasion, pleural effusion, and bone metastasis in the sternum (arrow head).

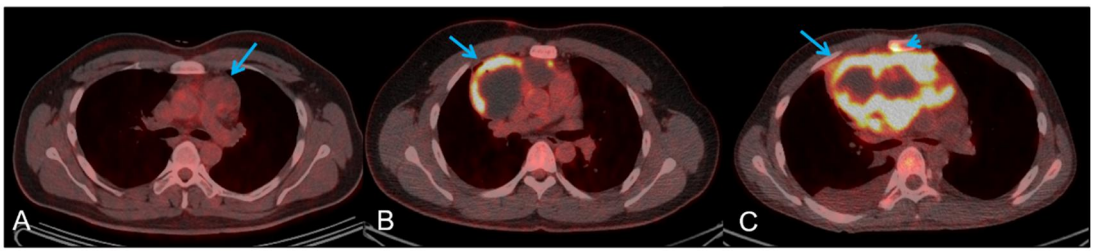


Figure 5. Comparsion of visual assessment results between benign and malignant mediastinal germ cell tumor group

Visual assessment between benign and malignant mediastinal germ cell tumor showed significant difference.

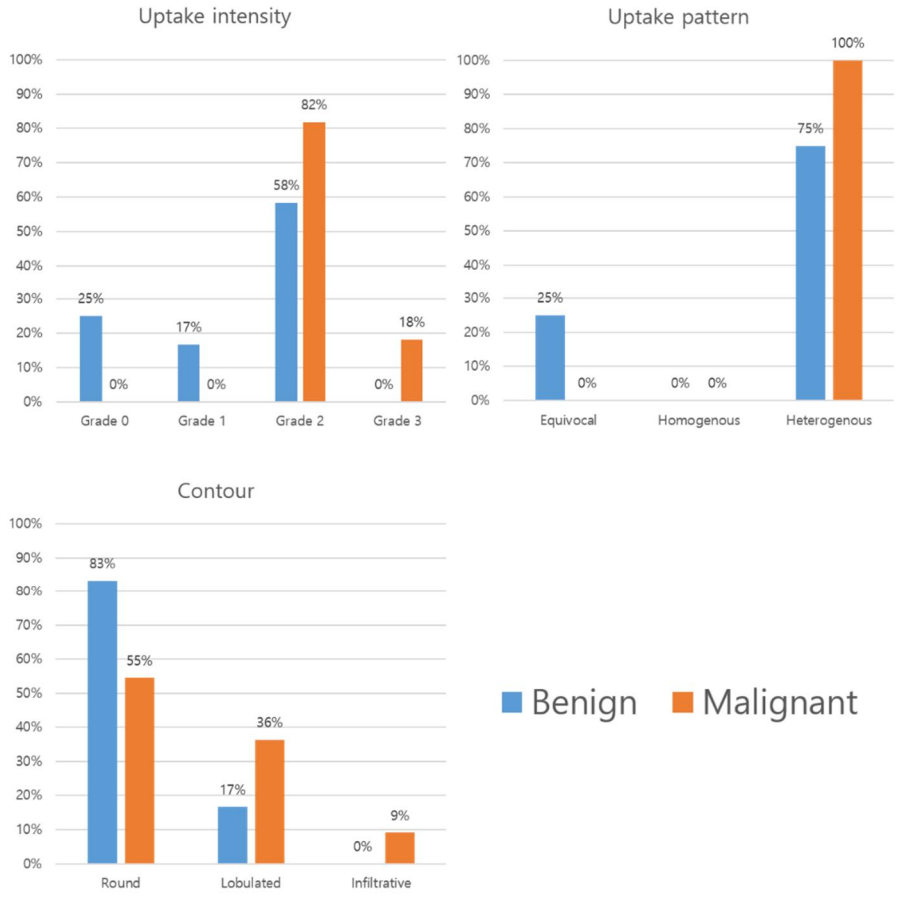
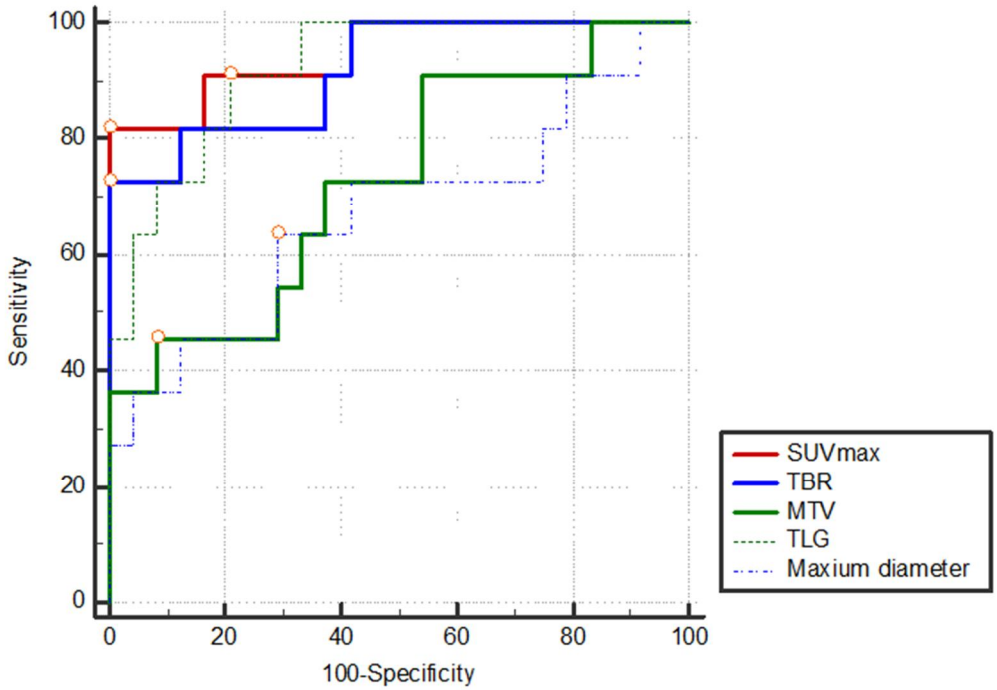


Figure 6. Receiver operating characteristic curve analysis of positron emission tomography/computed tomography parameters

On receiver operating characteristic curve analysis, all the positron emission tomography/computed tomography parameters show larger AUC than maximum diameter, and SUV max show the largest AUC of 0.947.



Tables

Table 1. Clinical and pathological characteristics

	Total
Number	35
Age (year, mean±SD)	33.1±16.8
Sex (F:M)	16:19
Time interval between biopsy or surgery and PET/CT (days)	13 (0-134)
AFP	1.9 (0.63-30800.0) [26†]
HCG	1.0 (1.0-197.0) [26†]
Surgical intent	
Excisional biopsy	24
Resective surgery	11
Clear resection margin	32
Lymph node metastasis	2
Pathologic diagnosis	
Mature teratoma	24
Seminoma	4
Yolk cell tumor	5
Mixed germ cell tumor	2

Continuous variables are expressed as median (range)

†Number of patients with tumor marker data that were included in the analysis

Table 2. Comparison of clinical and pathological characteristics between benign and malignant mediastinal germ cell tumor group

	Benign MGCT	Malignant MGCT	*p*–value
Number	24	11	
Age (year, mean±SD)	38.2±18.0	21.9±4.0	<0.001*
Sex (F:M)	16:8	0:11	
Time interval between biopsy or surgery and PET/CT (days)	16 (0-134)	10 (0-111)	0.221
AFP	1.0 (0.63-87.3) [15†]	16.8(1.1-3800.0) [11†]	0.004*
HCG	1.0 (1.0-197.0) [15†]	1.0(1.0-102.0) [11†]	0.604
Clear resection margin	24	9	
Lymph node metastasis	0	2	

Continuous variables are expressed as median (range)

P < 0.05*

†Number of patients with tumor marker data that were included in the analysis

MGCT, mediastinal germ cell tumors

Table 3. Visual assessment of mediastinal germ cell tumors according to type

		Total (N = 35)	Teratoma (N = 24)	Seminoma (N = 4)	Yolk cell tumor (N = 5)	Mixed GCT (N = 2)
Uptake intensity	Grade 0	6	6	0	0	0
	Grade 1	4	4	0	0	0
	Grade 2	23	14	3	5	1
	Grade 3	2	0	1	0	1
Uptake pattern	Equivocal	6	6	0	0	0
	Homogenous	0	0	0	0	0
	Heterogenous	29	18	4	5	2
Contour	Round	26	20	3	2	1
	Lobulated	8	4	1	2	1
	Infiltrative	1	0	0	1	0

Grade 0 ≤mediastinal; mediastinal < grade1 ≤ liver; liver< grade 2, grade 3≈ markedly greater than liver

GCT, germ cell tumor

Table 4. Comparison of positron emission tomography/computed tomography parameters between benign and malignant germ cell tumors

PET/CT parameters	Total (n = 35)	Benign MGCT (n = 24)	Malignant MGCT (n = 11)	*p*–value
SUVmax	3.3 (0.5-18.7)	2.5 (0.6–4.6)	10.7 (3.2–18.7)	<0.001*
TBR	3.2 (0.4-23.3)	2.4 (0.5–5.0)	9.7 (2.9–23.3)	<0.001*
MTV (ml)	12.6 (0.7-215.3)	10.6 (0.7–50.3)	16.3 (4.4–215.3)	0.033*
TLG (g)	18.8 (0.3-1862.7)	15.5 (0.3–107.1)	84.4 (18–1862.7)	<0.001*
Maximum diameter (cm)	7.9 (2.9-18.5)	7.6 (2.9–12.7)	9.5 (4.5–18.5)	0.115

P < 0.05*

Continuous variables are expressed as median (range)

PET/CT, positron emission tomography/computed tomography; MGCT, mediastinal germ cell tumors; SUV, standardized uptake value; TBR, tumor–to–background Ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis

Table 5. Receiver operating characteristic curve analysis curve analysis of positron emission tomography/computed tomography parameters in characterizing mediastinal germ cell tumor

PET/CT parameters	AUC	Cutoff value	*p*–value	Sensitivity (%)	Specificity (%)	AUC comparison with SUVmax
SUVmax*	0.947	> 4.54	< 0.0001	81.82	100.00	
TBR	0.917	> 4.91	< 0.0001	72.73	100.00	0.2215
MTV (ml)	0.727	> 20.26	0.0198	45.45	91.67	0.0254†
TLG (g)	0.920	> 24.59	< 0.0001	90.91	79.17	0.4844
Maximum diameter (cm)	0.670	> 8.75	0.1294	63.64	70.83	0.0114†

*Highest AUC, P < 0.05†

PET/CT, positron emission tomography/computed tomography; AUC, area under the receiver operating characteristic curve; SUV, standardized uptake value; TBR, tumor–to–background Ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis

Table 6. Subgroup analysis of positron emission tomography/computed tomography parameters between seminoma and malignant nonseminomatous germ cell tumor

PET/CT parameters	Seminoma (n = 4)	NSGCT (n = 7)	*p*–value
SUVmax	6.6 (3.2–9.2)	13.2 (3.7–18.7)	0.042*
TBR	5.6 (2.9–9)	10.3 (3.0–23.3)	0.042*
MTV (g/ml)	11.5 (7.7–14.6)	52.9 (4.4–215.3)	0.073
TLG (g cm³/ml)	45.9 (18–84.4)	408.1 (28.5–1862.7)	0.109
Maximum diameter (cm)	5.9 (4.5–9.5)	12.6 (7.9–18.5)	0.012*

P < 0.05*

Continuous variables are expressed as median (range)

PET/CT, positron emission tomography/computed tomography; NSGCT, nonseminomatous germ cell tumor; SUV, standardized uptake value; TBR, tumor–to–background Ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis

Table 7. Analysis of positron emission tomography/computed tomography parameters and tumor markers

PET/CT parameters	HCG≤1 (n = 18)	1<HCG (n = 8)	*p*– value	AFP<2 (n = 13)	2≤AFP (n = 13)	*p*– value
SUVmax	4.14 (1.3–18.7)	3.51 (1.5–13.2)	0.605	3.3 (1.3–4.6)	9.2 (1.5–18.7)	0.012*
TBR	4.54 (1.6–23.3)	3.19 (1.4–10.3)	0.807	3.6 (1.4–5)	9 (1.4–23.3)	0.034*
MTV (g/ml)	15.39 (4.3–215.3)	14.45 (5.1–71.3)	0.397	16.5 (4.3–50.3)	14.6 (4.4–215.3)	0.614
TLG (g cm³/ml)	36.4 (10.9–1862.7)	28 (6.3–546.9)	0.807	18.9 (8.9–107.1)	59.2 (6.3–1862.7)	0.081
Maximum diameter (cm)	9.71 (4.5–18.5)	7.36 (4.6–12.6)	0.144	8.8 (4.6–12.7)	9.5 (4.5–18.5)	0.044*

P < 0.05*

Continuous variables are expressed as median (range)

PET/CT, positron emission tomography/computed tomography; AFP, alphafetoprotein; HCG, human chorionic gonadotrophin; SUV, standardized uptake value; TBR, tumor–to–background Ratio; MTV, metabolic tumor volume; TLG, total lesion glycolysis

국문요약

목적: 원발성 종격동 생식세포종양(MGCT)은 전체 생식세포종양(GCT)의 약 2~4%를 차지하는 희귀질환이다. 본 연구는 이러한 MGCT 의 병리학적 유형별로 관찰되는 ^{18}F-fluorodeoxyglucose 양전자단층촬영/전산화단층촬영(^{18}F-FDG PET/CT)의 육안적 특성과 정량적 변수들의 특성들을 후향적으로 리뷰하였다.

방법: 본 연구는 2010 년에서 2020 년 사이 서울아산병원에서 수술 전 ^{18}F-FDG PET/CT 를 시행한 MGCT 환자를 후향적으로 평가하였다. MGCT 에는 4 가지 조직학적 유형이 포함되었으며 분석을 위해 두 그룹(양성 및 악성)으로 분류하였다. 육안적 평가는 섭취 정도(Grade 0-3), 섭취 패턴(모호한/균질한/비균질한)과 종양의 윤곽(원형/소엽성/침윤성)에 따라 분류하였다. 양성과 악성군 사이에서 maximum standardized uptake value (SUVmax), tumor-to-background ratio (TBR), metabolic tumor volume (MTV), total lesion glycolysis (TLG) 및 최대 직경을 포함한 PET/CT 변수들을 비교하고 수신자판단특성곡선분석(ROC)을 시행하여 각 변수들의 악성과 양성 종양 구별능을 평가하였다. 또한, 추가적으로 악성 MGCT 중 nonseminomatous germ cell tumor (NSGCT)와 seminoma 군, 그리고 종양 표지자가 높고 낮은 군간의 하위 그룹 분석을 하였다.

결과: 총 35 명의 환자에서 24 mature teratoma, 4 seminoma, 5 yolk cell tumor, and 2 mixed germ cell tumors 가 포함되었다. 6 개의 Grade 은 모두 mature teratoma 였으며 teratoma 중 grade 3 의 섭취 정도를 보이는 케이스는 없었다. 모든 악성 MGCT 들은 grade 2 혹은 3 의 섭취 정도를 보였다. 대부분의 MGCT 는 비균질한 섭취 패턴을 보였다. 모든 PET/CT parameter 들은 악성 MGCT 그룹에서

유의하게 높게 관찰되었다. ROC 분석에서 SUVmax (곡선 아래 면적[AUC]=0.947, P <0.0001), TBR (AUC=0.917, P <0.0001), MTV (AUC=0.727, P=0.0198) 및 TLG (AUC=0.920, P <0.001)가 양성과 악성 MGCT 를 구별하는데 유의한 진단 성능을 보였다. 특히 SUVmax 는 MTV 와 최대 직경에 비해 유의하게 높은 진단값을 보였으며 (P=0.0254, 0.0114). 4.54 의 값을 기준으로 악성과 양성 MGCT 를 감별하는 민감도와 특이도는 각각 81.82%와 100.00%였다. 악성 MGCT 중 seminoma 와 NSGCT 그룹간의 하위 분석에서는 SUVmax, TBR 및 최대 직경이 유의한 차이를 보였다 각 P=0.042, 0.042, 0.012). Alphafetoprotein 이 높은 그룹에서는 SUVmax, TBR, 최대 직경의 값들이 낮은 그룹에 비해 유의하게 높은 값을 보였으며(각각 P=0.012, 0.034, 0.044), human chorionic gonadotrophin 의 값이 높고 낮은 그룹간의 PET/CT 변수값들은 유의한 차이가 확인되지 않았다.

결론: ^{18}F-FDG PET/CT 에서 관찰되는 MGCT 의 육안적 특징들은 양성과 악성 그룹 사이에 유의한 차이를 보였다. ^{18}F-FDG PET/CT 정량적 변수들은 악성과 양성 혹은 NSGCT 와 seminoma 군을 구별하는데 유용한 정보를 제공하였다.

핵심용어: 원발성 종격동 생식세포종양; Fluorodeoxyglucose F18; 양전자방출단층촬영