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Pretherapy ^{18}F-FDG PET/CT in Predicting Disease Relapse in Patients With Immunoglobulin G4-Related Disease: A Prospective Study

Mei-Fang Cheng[1,2], Yue Leon Guo[2,3], Ruoh-Fang Yen[1], Yen-Wen Wu[4,5], Hsiu-Po Wang[6]

[1]Department of Nuclear Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan
[2]Institute of Environmental and Occupational Health Sciences, National Taiwan University, Taipei, Taiwan
[3]Department of Environmental and Occupational Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan
[4]Department of Nuclear Medicine, Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei, Taiwan
[5]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan
[6]Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, Taipei, Taiwan

Objective: To investigate whether the levels of inflammation detected by 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) can predict disease relapse in immunoglobulin G4-related disease (IgG4-RD) patients receiving standard induction steroid therapy.

Materials and Methods: This prospective study analyzed pretherapy FDG PET/CT images from 48 patients (mean age, 63 ± 12.9 years; 45 males and 3 females) diagnosed with IgG4-RD between September 2008 and February 2018, who subsequently received standard induction steroid therapy as the first-line treatment. Multivariable Cox proportional hazards models were used to identify the potential prognostic factors associated with relapse-free survival (RFS).

Results: The median follow-up time for the entire cohort was 1913 days (interquartile range [IQR], 803–2929 days). Relapse occurred in 81.3% (39/48) patients during the follow-up period. The median time to relapse was 210 days (IQR, 140–308 days) after completion of standardized induction steroid therapy. Among the 17 parameters analyzed, Cox proportional hazard analysis identified whole-body total lesion glycolysis (WTLG) > 600 on FDG-PET as an independent risk factor for disease relapse (median RFS, 175 vs. 308 days; adjusted hazard ratio, 2.196 [95% confidence interval: 1.080–4.374]; P = 0.030).

Conclusion: WTLG on pretherapy FDG PET/CT was the only significant factor associated with RFS in IgG-RD patients receiving standard steroid induction therapy.

Keywords: ^{18}F-fluorodeoxyglucose; PET/CT; IgG4-RD; Relapse-free survival; Therapy

INTRODUCTION

Systemic immunoglobulin G4-related disease (IgG4-RD) is an inflammatory disease affecting virtually any organ in the body. Previous studies have described the utility of whole-body positron emission tomography (PET)/computed tomography (CT) using ^{18}F-fluorodeoxyglucose (FDG) to determine the extent of disease involvement in IgG4-RD [1-3], and to highlight the involvement of critical organs. Over 50% of patients diagnosed with autoimmune pancreatitis or IgG4-RD pancreatitis fail to achieve sustained remission after initial steroid therapy [4]. The clinical features involved in disease relapse after initial steroid therapy are unclear, although some patients respond better to rituximab [5]. Whether specific organs are less responsive to steroid treatment warrants further investigation. Whole-body screening using FDG PET/CT can be used to evaluate the degree of inflammation in the involved organs before therapy is administered. Therefore, this study aimed to determine the utility of FDG PET/CT for predicting

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Corresponding author: Hsiu-Po Wang, MD, Department of Internal Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan.
• E-mail: wanghp@ntu.edu.tw

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relapse in patients diagnosed with IgG4-RD before initiating steroid induction therapy.

MATERIALS AND METHODS

Patient Selection and Study Criteria

The National Taiwan University Hospital (NTUH) Ethics Committee approved this prospective study (No. 200812155R) and all participants provided informed consent before participating in the study. From September 2008 to February 2018, 48 patients (45 males, 3 females; mean age ± standard deviation [SD], 63 ± 12.9 years) who met the 2011 International Consensus Diagnostic Criteria for IgG4-RD and received standard induction therapy were included in this analysis (Table 1). Each patient underwent a conventional diagnostic workup, including a physical examination, serum biomarkers (including carbohydrate antigen 19-9 and IgG4 levels), abdominal sonography, abdominal CT, magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP), or endoscopy. All FDG PET/CT procedures were performed within one week prior to the initiation of steroid therapy. Elevated serum IgG4 levels (≥ 135 mg/dL) were found in 47 of the 48 patients (median, 720 ng/mL; interquartile range [IQR], 331–1420 ng/mL), and 62.5% (30/48) of them had diabetes mellitus. When enrollment began in 2008, no standardized steroid treatment regimen or consensus was available on the dose and duration of steroid induction or maintenance schedules for IgG4-RD patients. Therefore, we followed the consensus treatment guidelines for autoimmune pancreatitis published by the Japanese Society of Gastroenterology, because our patients had initially presented with abdominal pain and had been referred by gastroenterologists [6]. Oral prednisolone was administered at an initial dose of 30 mg/day (or 0.6 mg/kg/day) for 4 weeks, then gradually tapered to 5–10 mg/day over 2 months, and finally continued as a low-dose maintenance therapy (5 mg/day) for the subsequent 3–6 months [7,8]. Only patients who adhered to this steroid protocol were included in the analysis; patients who used immunomodulatory drugs were excluded. In addition, only patients exhibiting disease remission, defined as the disappearance of symptoms and signs and resolution of IgG4-RD foci on prior conventional imaging during steroid treatment, were included in the analysis. All patients were followed-up at outpatient clinics every month for 3 months, every 3 months for 9 months after the initiation of steroid therapy, and every 3–6 months thereafter or until they were lost to follow-up. Laboratory tests, abdominal ultrasound, and CT or MRI were arranged every 3–6 months during the follow-up. Disease relapse was defined as the reappearance or new development of symptoms and signs; abnormal laboratory tests reflecting IgG4-RD activity within specific organs; or the appearance of new inflammatory lesions on follow-up imaging, including abdominal sonography, CT, MRI, or MRCP. By the time of the analysis, four of the 48 (8.3%) patients had died without recurrence (Supplementary Table 1), and 39 (81.3%) relapsed within the observation period (median follow-up time, 1913 days; IQR, 803–2929 days).

Table 1. Characteristics of Enrolled Patients (n = 48)

Characteristic	Values
Age, yr	63 ± 12.9
Gender (M:F)	45:3
BMI, kg/m^2	22 ± 4
Diabetes mellitus	30 (62.5)
Initial presentation	
Dry mouth/eyes	8 (16.7)
Arthralgia	2 (4.2)
Dyspnea	1 (2.1)
Abdominal fullness	27 (56.3)
Jaundice	21 (43.8)
Diarrhea	1 (2.1)
Number of organs	3.4 ± 1.7
Multi-organ disease	
≥ 3 organs	30 (62.5)
≥ 5 organs	10 (20.8)
Pretherapy serum IgG4 level, median (IQR), n/mL	720 (331–1420)
PET to initiation of steroid therapy, day	13.7 ± 12.7
Follow-up time of the entire cohort, median (IQR), day	1913 (803–2929)
Time to relapse, median (IQR), day	210 (140–308)

Values are presented as mean ± standard deviation or n (%) unless otherwise indicated. M = male, F = female, BMI = body mass index, IgG4 = immunoglobulin G4, IQR = interquartile range, PET = positron emission tomography

FDG PET/CT Imaging

All patients were required to fast for at least 4 h to maintain a serum glucose concentration below 180 mg/dL before the intravenous injection of 5–6 MBq/kg FDG. Whole-body PET scans were performed using PET/CT scanners routinely used at the NTUH PET center (Discovery LS or Discovery 710; GE Medical Systems). Image acquisition started 60 min after tracer injection, at 3 min per bed position from the mid-thigh to the head, in 2 or 3-dimensional mode, as described in our previous study

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[2] and according to the institutional and international guidelines provided by the Society of Nuclear Medicine. PET images were reconstructed iteratively using an Ordered Subset Expectation Maximization (OSEM) algorithm with segmented correction for attenuation using low-dose CT. Low-dose CT without contrast was performed for attenuation correction and anatomical coregistration. PET and CT images were fused using the Xeleris software (GE Medical Systems) and presented in axial sagittal and coronal views.

PET/CT Image Interpretation

Reconstructed PET images were independently reviewed by two board-certified nuclear medicine physicians (MF Cheng and RF Yen) with > 15 years of experience in reading PET/CT using the built-in software (eNTEGRA, GE Medical Systems) in different imaging sessions. The nuclear medicine specialist was blinded to the patient's clinical condition, other imaging findings, or clinical outcomes. Diverging interpretations were resolved after a joint review by immunological experts to achieve consensus on IgG4-RD organ involvement.

All IgG4-RD lesions were evaluated visually and semi-quantitatively. The sites of involvement were grouped into the following eight organs: the pituitary gland, lacrimal and salivary glands, lymph nodes, lungs, pleurae/pericardium, pancreas, biliary tract, retroperitoneum (including kidneys), and vessels. Prostate gland involvement was excluded from the analysis in order to avoid sex-related differences. The number of IgG4-RD lesion sites was counted in each patient. The patients were then grouped into two categories: those with the involvement of ≥ 3 FDG-avid organs and those with < 3 lesion sites.

For semiquantitative evaluation, IgG4-RD lesions with abnormally increased metabolism not associated with normal structures or artifacts in the FDG-PET slices were contoured using built-in software with an automatic threshold set at 40% of the maximum standardized uptake value (SUVmax) [2]. SUVs were automatically calculated as tissue concentration · Injected dose-1 · Body weight-1. Automatic contouring was manually corrected if non-lesion areas were incorrectly included within the volume of interest, using information from the corresponding low-dose CT. The metabolic volume (MTV), which represents the volume of lesions with upregulated glucose metabolism, was computed automatically [9]. We only included lesions with MTV greater than 5 mL in the final analysis to avoid partial volume effects [10]. IgG4-RD lesions with the highest SUVmax and SUVmean were selected for analysis in patients with multi-organ involvement [11]. The total lesion glycolysis (TLG) was calculated for each quantified uptake as the product of the MTV and mean SUV of the lesion, effectively combining both metabolic and volumetric information. Therefore, whole-body total lesion glycolysis (WTLG) is the sum of all TLG lesion values and represents a quantitative biomarker of the total disease burden in the patient [11].

Statistical Analysis

Numerical data were presented as mean ± SD, median ± IQR, or number (%). The cutoff values used to group the semi-quantitative PET parameters were calculated using the Youden method. In univariable analysis, all parameters (including clinical and PET parameters) were examined for their association with relapse-free survival (RFS) using the Cox proportional hazard model. We compared one parameter at a time in the univariable analysis; only variables with significant relationships ($P < 0.05$) were used for the multivariable analysis to identify the clinical and PET parameters independently associated with RFS. Predictors were expressed as hazard ratio (HR) with 95% confidence interval (CI). The Kaplan-Meier method was used to plot survival curves. Pearson's correlation coefficient was calculated between pretherapy serum IgG4 levels and WTLG to determine whether there was a linear relationship between the two parameters. All statistical analyses were performed using JMP®, version 10 statistical software package (SAS Institute Inc.), and a two-tailed *P*-value less than 0.05 was considered to be statistically significant.

RESULTS

The cumulative relapse rates were 67.9%, 75.3%, and 85.6% at 12, 36, and 60 months, respectively, and the median time to relapse was 210 days (IQR, 140–308 days). Among the 39 patients with disease relapse, the reappearance of previous symptoms and signs (19/39, 48.7%) was the most common, followed by new development of symptoms and signs (8/39, 20.5%), elevated hepatic and biliary enzymes or pancreatic enzymes reflecting IgG4-RD activity (6/39, 15.4%), and the appearance of new inflammatory lesions seen on follow-up abdominal echo and MRI (6/39, 15.4%). The mean number of involved organs detected by PET per patient was 3.4 ± 1.7 before the initiation of steroid therapy (Table 1). Thirty of the 48 patients (62.5%) had multi-organ disease (≥ 3 sites of involvement) (Supplementary Fig. 1) and 20.8% (10/48) had ≥ 5 organ involvement. The number

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of patients involved in each organ site is described in detail in Supplementary Table 2. The distribution of SUVmean in the different organs of the entire cohort is illustrated in Supplementary Fig. 2. The pretherapy median serum IgG4 level was 720 mg/dL (IQR, 331–1420 mg/dL), and the mean number of days between baseline PET scan and initiation of steroid therapy was 13.7 ± 12.7 (Table 1). The mean duration of low-dose steroid maintenance therapy was 4.1 ± 3.0 months. The parameters used in the analysis are listed in Table 2.

Univariable and Multivariable Analyses

Three parameters were found to be associated with RFS ($P < 0.05$) in the univariable analysis (Table 2): retroperitoneal involvement, lesion SUVmax > 6.0, and WTLG > 600. Even though vessel involvement and ≥ 5 organ involvement (data not shown) showed trend of increased risk of relapse after steroid treatment, both did not reach statistical significance in the univariable analysis.

In the forward selection model, which considered all significant univariable predictors of relapse, only WTLG > 600 remained significantly associated with RFS (adjusted HR, 2.196; 95% CI: 1.080–4.374, $P = 0.03$) (Table 2). The median RFS values for patients with WTLG ≤ 600 vs. > 600 days were 308 days and 175 days, respectively (Figs. 1–3).

Pearson's Correlation between Serum IgG4 Level and WTLG

The correlation between pretherapy serum IgG4 levels and WTLG was moderate. A coefficient correlation of 0.56 (95% CI, 0.32–0.73) was observed, indicating a positive linear correlation between pretherapy serum IgG4 level and WTLG found in the pretherapy PET scan.

DISCUSSION

Steroid therapy is the first-line treatment for patients diagnosed with IgG4-RD [12]. Although most patients reportedly respond initially to steroid therapy, the relapse rate ranges from 10.66% to 60% in different cohorts,

Table 2. Univariable and Multivariable Analyses of the Association with Relapse-free Survival

Variables	Univariable		Multivariable	
	HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age, yr†	1.016 (0.990–1.044)	0.257	NA	NA
BMI (≥ 25 vs. < 25 kg/m²)*	0.987 (0.398–2.123)	0.974	NA	NA
Diabetes mellitus (present vs. absent)*	1.217 (0.636–2.417)	0.661	NA	NA
Pretherapy IgG4, mg/dL†	1.000 (0.999–1.001)	0.316	NA	NA
PET parameters				
Visual interpretation				
Multi-organ disease (≥ 3 vs. < 3 organs)*	1.400 (0.728–2.829)	0.319	NA	NA
Site of organ involvement (present vs. absent)*				
Biliary tracts	1.615 (0.817–3.416)	0.233	NA	NA
Lacrimal/salivary glands	1.076 (0.559–2.152)	0.772	NA	NA
Lungs/pleurae	2.128 (0.843–4.701)	0.104	NA	NA
Lymph nodes	1.443 (0.742–2.972)	0.245	NA	NA
Pancreas	1.307 (0.599–2.634)	0.524	NA	NA
Pituitary gland	2.435 (0.719–6.244)	0.147	NA	NA
Retroperitoneum (including kidneys)	2.593 (1.136–5.402)	0.025	1.520 (0.544–4.357)	0.422
Vessels	2.099 (0.956–4.263)	0.064	NA	NA
Semi-quantitation				
SUVmax (> 6.0 vs. ≤ 6.0)*	2.215 (1.072–4.321)	0.033	1.380 (0.552–3.079)	0.468
SUVmean (> 3.5 vs. ≤ 3.5)*	2.509 (0.581–5.247)	0.438	NA	NA
Whole body MTV (> 200 vs. ≤ 200)*	1.543 (0.780–2.962)	0.262	NA	NA
Whole body TLG (> 600 vs. ≤ 600)*	2.252 (1.133–4.419)	0.021	2.196 (1.080–4.374)	0.030

*For categorical variables with categories in parentheses, the former was compared with the latter (the reference) to calculate hazard ratio (HR) and 95% confidence interval (CI) with the Cox regression analysis, †For continuous variables, an increase by 1 considered when calculating HR and 95% CI. BMI = body mass index, IgG4 = immunoglobulin G4, PET = positron emission tomography, SUVmax = maximum standardized uptake value, SUVmean = mean standardized uptake value, NA = non-applicable, MTV = metabolic tumor volume, TLG = total lesion glycolysis

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depending on whether low-dose steroid maintenance therapy is used [7,13–17]. This study was one of the first to investigate whether the levels of inflammation detected by pretherapy FDG PET could predict RFS in patients diagnosed with IgG4-RD who were receiving standard induction steroid therapy. Our results revealed that: 1) WTLG, an indicator of systemic inflammation, on pretherapy FDG-PET could predict RFS in patients receiving steroid induction therapy; 2) although patients with retroperitoneum, vessel involvement, or SUVmax > 6.0 exhibited trends of shorter RFS in univariable analysis, none were statistically significant in multivariable analysis.

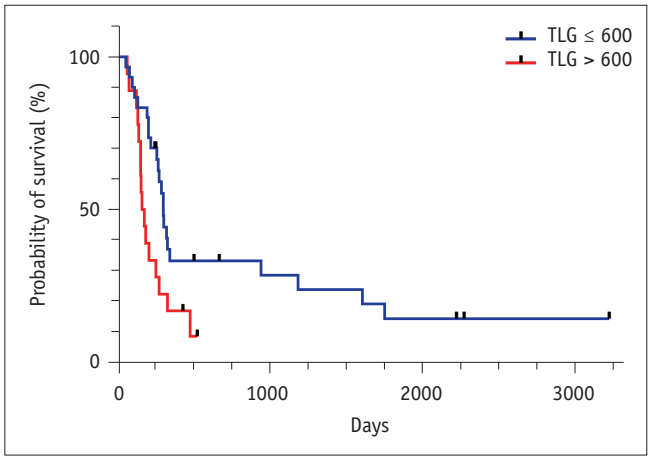

Fig. 1. Kaplan-Meier curves show the relapse-free survival (RFS) rates of patients with whole-body total lesion glycolysis (WTLG) ≤ 600 (median RFS: 308 days, blue curve) compared to those of individuals with WTLG > 600 (median RFS: 175 days, red curve). The difference was statistically significant, with an adjusted hazard ratio of 2.196 (95% confidence interval: 1.080–4.374, P = 0.030) in the group with WTLG > 600. TLG = total lesion glycolysis

A Japanese survey of autoimmune pancreatitis showed that maintenance steroid therapy could reduce relapse rates [14]. However, in our cohort, the duration of maintenance steroid therapy was not associated with the time to disease relapse (HR, 0998; 95% CI: 0.993–1.005, P = 0.60). Peng et al. [17] reported cumulative relapse rates of 10.66%, 22.95%, and 27.87% at 12, 24, and 36 months, respectively, in a cohort of 122 IgG4-RD patients who were followed-up for at least three years. A higher relapse rate was observed in our patients, with a relapse rate as high as 67.9% during the first year. The high relapse rate in our cohort could be secondary to referral bias, as patients with more severe presentations at initial diagnosis were referred for FDG-PET imaging to better evaluate their systemic inflammatory status. Approximately 60% of our patients had multi-organ disease (≥ 3 organs), as revealed via FDG PET/CT. Moreover, Kamisawa et al. [18] reported that patients with multi-

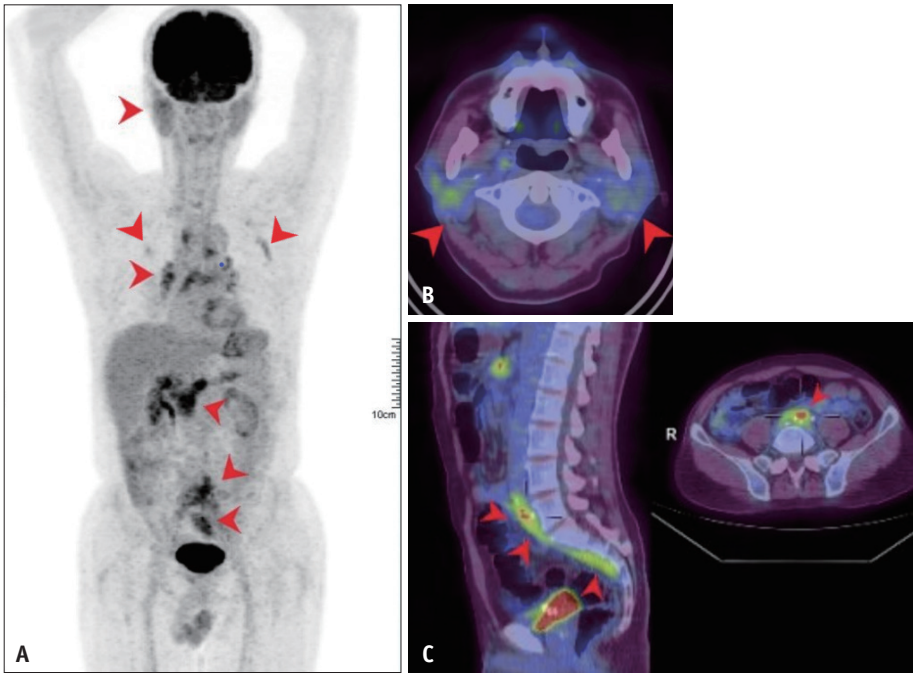

Fig. 2. Whole-body total lesion glycolysis measurement in a 58-year-old male diagnosed with immunoglobulin G4-related disease (IgG4-RD). Maximum intensity projection image **(A)** and cross-sectional images **(B, C)** show IgG4-RD lesions (arrowheads) in the parotid glands, mediastinal and left axillary lymph nodes, pleurae, pancreas (head to tail), and retroperitoneum. The patient's whole-body total lesion glycolysis was 1162.0 before steroid therapy. Relapse occurred shortly (160 days) after steroid withdrawal.

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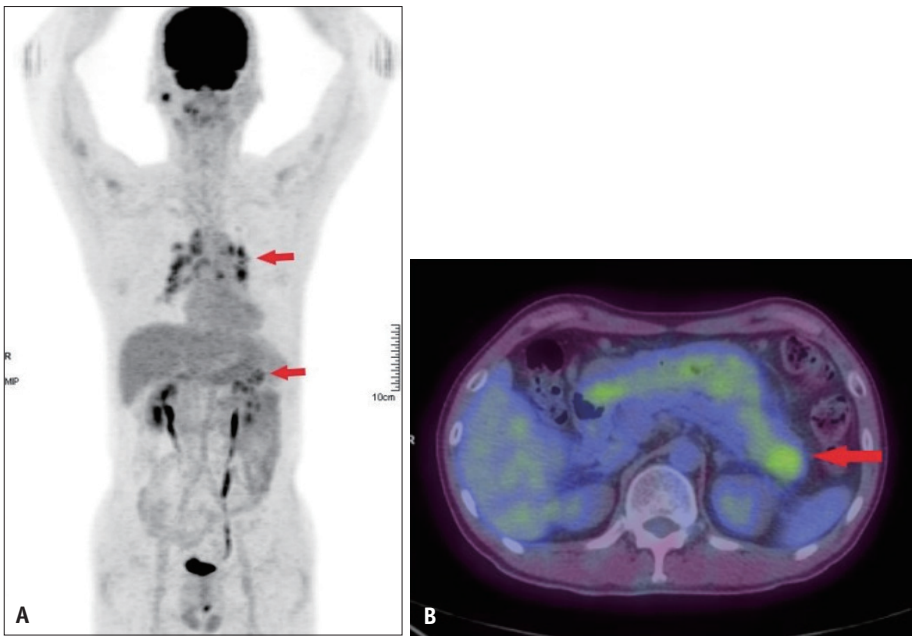

Fig. 3. Whole-body total lesion glycolysis (WTLG) measurement in a 56-year-old male who had immunoglobulin G4-related disease (IgG4-RD) lesions. Maximum intensity projection image **(A)** and cross-sectional images **(B)** show IgG4-RD lesions (arrows) in the pancreatic tail and mediastinal lymph nodes. The WTLG was 505.6 (< 600). The patient remained relapse-free for 1757 days. R = right, MIP = maximum intensity projection

organ disease, higher serum IgG4 levels, and proximal extrahepatic/intrahepatic biliary strictures correlated with an increased risk of relapse. Nonetheless, multi-organ disease (≥ 3 organs) in our study was not a significant predictor of initial disease relapse in univariable analysis, despite the higher WTLG observed in this group of patients compared to that in participants with < 3 organs of involvement (Supplementary Fig. 1). Retroperitoneal involvement was a significant predictor of relapse in the univariable analysis (HR, 2.458; 95% CI: 1.033–5.242, P = 0.043) in our study cohort. Similar findings were reported by Miki et al. [19], who found that the presence of retroperitoneal fibrosis at disease onset was an independent risk factor for relapse. Additionally, Peng et al. [17] reported that higher IgG4 responder index scores and elevated eosinophil levels were associated with disease relapse. The authors concluded that these patients may benefit from maintenance therapy, and recommended steroid doses > 6.25 mg/day during the maintenance period [17]. Most patients received a dose of 5 mg/day, which might have contributed to the high relapse rates in our cohort. Moreover, the duration of steroid maintenance in our patients was relatively short (≤ 6 months) compared with that of the patients in another cohort study in which maintenance steroid therapy was administered for 3 years [20]. This study began in 2008, when the duration of steroid maintenance had not reached a consensus. Moreover, elderly patients are prone to steroid-related complications, making long-term steroid maintenance therapy challenging [18]. The addition of immunomodulatory drugs and rituximab has been indicated in patients with persistently active disease undergoing steroid therapy [4,5,21]. The indications for a longer duration of steroid maintenance therapy or the addition of other immunomodulatory therapies to reduce the relapse rate may vary in individual patients according to clinical predictors [7]. For example, elevated serum IgG4 levels prior to therapy have reportedly increased the risk of relapse in several studies [18,22], but not in others [7,20], as in our study.

Although the lesion SUVmax > 6.0 on FDG PET was a significant predictor of RFS in univariable analysis, it did not reach statistical significance in multivariable analysis. SUVmax is the most commonly used semi-quantitative tool for quantifying tumor metabolic activity; however, it is a single value reflecting only the highest pixel activity with the volume of interest in the selected lesion [23]. SUVmax is easily influenced by various factors, is affected by noise, and cannot represent true values in lesions exhibiting heterogenous hypermetabolism [24]. Conversely, TLG is the product of SUVmean and MTV, which incorporates both the average whole-lesion metabolic activity and the volume of lesions with metabolically active uptake [23,24]. TLG reportedly correlates better than SUVmax with the

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histopathological response in malignancies [24]. In this study, we summed all TLG lesion values to obtain the WTLG [11], which is a measure of global disease activity [23]. Likewise, Nakatsuka et al. [25] reported that WTLG significantly correlated with soluble IL-2 receptors in 17 patients before the initiation or re-administration of immunosuppressive therapy, suggesting WTLG as a potential disease marker. Whole-body screening using FDG PET/CT has the advantage of determining the extent of IgG4-RD involvement before therapy [1,2,26]. As WTLG is the sum of all TLG values in the body, it represents a volumetric index of all metabolically active cells involved in the disease [27]. Our results suggest that baseline WTLG obtained from FDG PET has implications for the management of disease relapse in IgG4-RD patients. In patients with high baseline WTLG levels (> 600)—reflecting higher disease activity—may benefit from a more aggressive strategy, such as combining glucocorticoids and immunosuppressants or immunomodulators, rather than steroid monotherapy alone. Alternatively, a longer duration of steroid maintenance of at least 3 years should be instituted in these high-risk patients.

This study had several limitations. First, the patients were enrolled from a single center, was as a potential bias could have resulted from enrolling patients with a more severe disease phenotype. Therefore, our results do not reflect the entire cohort of relapse patients but rather patients with more severe illness at presentation. However, these patients were more likely to require prompt treatment and pretherapy FDG PET/CT. Nonetheless, approximately half of our patients were initially diagnosed with IgG4-RD involving the pancreas based only on diagnostic CT, but showed more extensive disease after FDG PET/CT. Based on these observations, we suggest a whole-body survey of inflammatory foci using FDG-PET in patients diagnosed with IgG4-RD before therapy to better delineate the extent of the disease and predict the risk of relapse. Second, relapse was defined as the identification of the reappearance of symptoms, signs, or inflammatory lesions in the follow-up images; however, these factors could also have been caused by a flare-up of the residual disease rather than a true relapse after complete remission. This may explain the high relapse rate in our cohort; nonetheless, our study highlights the need for a whole-body survey of inflammatory foci using FDG PET to predict disease flare-up or relapse prior to receiving first-line steroid therapy. Although the use of TLG as a clinical parameter to assess clinical outcomes is applied more frequently in lymphoma, our results reveal that this quantitative PET index can also assess the actual metabolic disease burden in IgG4-RD patients. Nevertheless, we assessed a limited number of patients, and further trials with a larger number of patients are warranted to validate the generalizability of our observations and their application in the risk stratification of IgG4-RD patients.

In conclusion, our study highlights the use of FDG-PET/CT to stratify the risk of recurrence in IgG4-RD patients before they receive first-line steroid therapy. The quantitative PET index, WTLG, obtained from pretherapy FDG-PET can predict disease relapse.

Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2022.0576.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Mei-Fang Cheng, Hsiu-Po Wang. Formal analysis: Mei-Fang Cheng, Yue Leon Guo, Ruoh-Fang Yen. Funding acquisition: Mei-Fang Cheng, Hsiu-Po Wang. Investigation: Mei-Fang Cheng, Hsiu-Po Wang. Methodology: Mei-Fang Cheng, Yen-Wen Wu, Hsiu-Po Wang. Project administration: Hsiu-Po Wang. Resources: Mei-Fang Cheng, Hsiu-Po Wang. Supervision: Hsiu-Po Wang. Validation: Ruoh-Fang Yen, Yen-Wen Wu. Visualization: Yue Leon Guo, Ruoh-Fang Yen. Writing—original draft: Mei-Fang Cheng. Writing—review & editing: Yue Leon Guo, Hsiu-Po Wang.

ORCID iDs

Mei-Fang Cheng
https://orcid.org/0000-0002-9359-0606
Yue Leon Guo
https://orcid.org/0000-0002-8530-4809
Ruoh-Fang Yen
https://orcid.org/0000-0003-1648-6482
Yen-Wen Wu
https://orcid.org/0000-0003-1520-1166
Hsiu-Po Wang
https://orcid.org/0000-0002-7741-9315

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