Rituximab as third line therapy in IgG4-Related Disease: experience from a multi-centre UK cohort

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1. BACKGROUND AND RATIONALE

- IgG4-RD is a multi-organ fibro-inflammatory B-cell mediated immune-mediated disorder
- Corticosteroids are first line therapy with 98% response. Relapse on steroid discontinuation is up to 60%. Leads to organ damage/failure.
- Rituximab (anti-CD20 chimeric monoclonal antibody) received UK NICE approval as third-line therapy for intolerance/relapse on steroids and immunomodulators.

2. AIMS AND OBJECTIVES

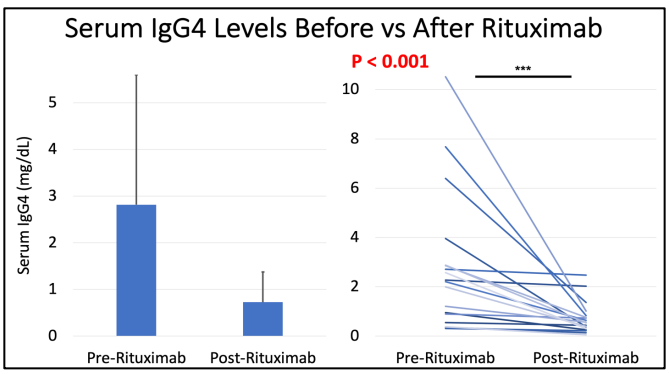
To assess the indications, clinical response and outcome to Rituximab in a multi-centre UK cohort of IgG4RD patients.

3. METHODS

- Retrospective data collected from five UK tertiary centres for IgG4RD patients that received Rituximab therapy
- Wilcoxon paired test was used for numerical variables.

4. RESULTS

52 patients received Rituximab for IgG4RD (see tables and figures). Serum IgG4 levels fell with Rituximab therapy (pre-treatment median 4.99g/L, post-treatment median 3.33g/L; p<0.001). The median number of cycles received was 1 pair (range 1-8). The majority had on-demand infusions (77%) and 10 (23%) received maintenance therapy.



Baseline characteristics N=52 from 5 centres	Mean (range)
Age at diagnosis (nearest year)	58 (19 to 79)
Age at Rituximab (nearest year)	64 (20 to 85)
Follow-up length (nearest month)	84 (19 to 184)
Duration between diagnosis and Rituximab (nearest month)	40 (1 to 148)

	N (%)
Male	39 (75%)
Raised serum IgG4 at diagnosis	39 (75%)
Multi-organ disease	40 (77%)

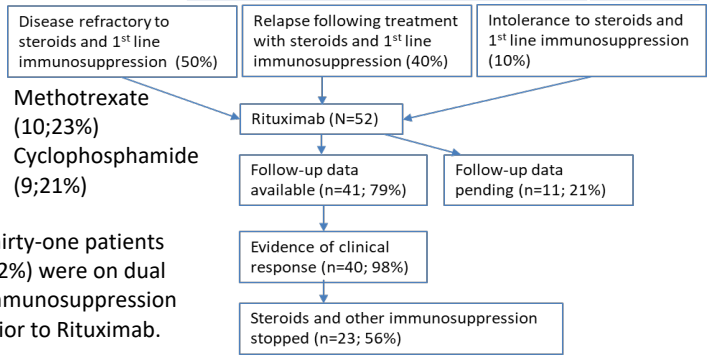
Disease phenotype	N (%)
Systemic	27 (52%)
Head and Neck	13 (25%)
Hepatopancreatobiliary	10 (19%)
Retroperitoneal and aorta	2 (4%)

Treatment preceding Rituximab included:

- Prednisolone (42; 81%)
- Azathioprine (20; 39%)
- Mycophenolate (17; 33%)
- Methotrexate (10;23%)
- Cyclophosphamide (9;21%)

Thirty-one patients (72%) were on dual immunosuppression prior to Rituximab.

Adverse effects	N (%)
None reported	35
Infection	4 (10%)
Hypogammaglobulinaemia (no rescue IV immunoglobulins required)	5 (12%)



CONCLUSION

Rituximab was safe and effective as third-line therapy for disease relapse in IgG4RD in this multi-centre prospective UK cohort, allowing discontinuation of steroid/conventional immunosuppression in the majority.

Quantitative MRCP metric to distinguish IgG4-sclerosing cholangitis from primary sclerosing cholangitis

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Background & Aim

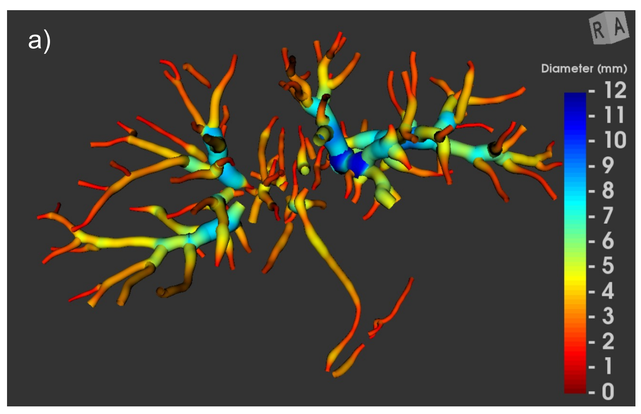
- Immunoglobulin G4-related sclerosing cholangitis (IgG4-SC) is often difficult to distinguish from primary sclerosing cholangitis (PSC) using traditional imaging assessments.
- We hypothesise that quantitative biliary tree assessments would enable stratification of patients with PSC and IgG4-SC.
- MRCP+ (Perspectum, Oxford, UK) is a quantitative imaging tool that uses artificial intelligence led technology to enhance MRCP images and create true 3D rendered models of enhanced data and metrics to facilitate visualisation and quantitative assessment of the biliary tree and pancreatic duct.

Methods

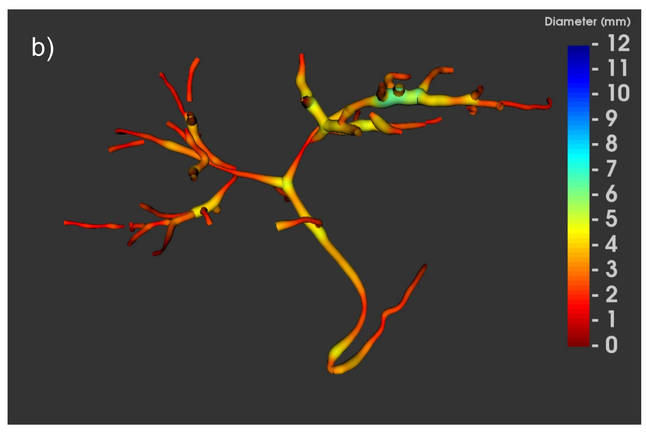
- We recruited 12 patients with histologically-confirmed IgG4-related disease (IgG4-RD). 6 males, median age 67 [range: 46–79] years, disease duration: 2 [range:1–9] years
- Disease phenotype: n=10 pancreatobiliary, n=9 active disease at recruitment
- Coronal T2-weighted 3D MRCP were prospectively performed on 1.5T Siemens scanner.
- MRCP data was processed using MRCP+ as described below to compute biliary tree metrics. MRCP+ metrics with good or excellent scan-rescan repeatability (ICC > 0.60) were included in analysis.
- One patient had MRCP and MRCP+ performed pre- and post-treatment (Figure 1)
- Age- and sex-matched large-duct PSC controls were selected from a previous study (REC: 18/SC/0367)
- The diagnostic performance of MRCP+ metrics with statistically significant differences between PSC and IgG4-SC, as well as serum IgG4 at a previously published threshold (>2.8 g/L)[1] were examined using ROC curve analyses
- AUC, sensitivity and specificity were recorded at the cut-off point that maximised the Youden index

Results

Figure 1: MRCP+-derived biliary tree model and corresponding biliary tree metrics in a 67 year old man with IgG4-sclerosing cholangitis a) pre-steroid; b) post-steroid for 6 weeks. The percentage of ducts with median diameter 3-5mm reduced from 39% to 26%.



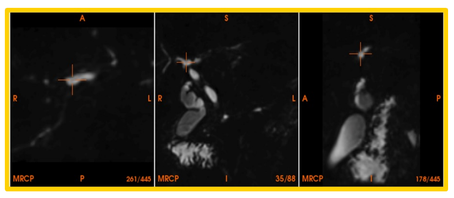
	Measured value	Reference interval
Biliary tree volume:[2]	29.0ml	(0 - 100ml)
Gallbladder volume:[2]	Not available	(1 - 99ml)
Percent of ducts with median width less than 3mm:	59%	(0 - 100%)
Percent of ducts with median width greater than 3mm up to 5mm:	39%	(1 - 99%)
Percent of ducts with median width greater than 5mm up to 7mm:	3%	(2 - 98%)
Percent of ducts with median width greater than 7mm:	0%	(3 - 97%)



	Measured value	Reference interval
Biliary tree volume:[2]	7.1ml	(0 - 100ml)
Gallbladder volume:[2]	7.1ml	(1 - 99ml)
Percent of ducts with median width less than 3mm:	74%	(0 - 100%)
Percent of ducts with median width greater than 3mm up to 5mm:	26%	(1 - 99%)
Percent of ducts with median width greater than 5mm up to 7mm:	0%	(2 - 98%)
Percent of ducts with median width greater than 7mm:	0%	(3 - 97%)

Figure 2: Differences in a) serum IgG4; b) percentage of bile ducts with median diameter 3–5mm between IgG4-sclerosing cholangitis (IgG4-SC; n=7) and primary sclerosing cholangitis (PSC; n=11).

Quantitative MRCP Analysis MRCP+



Non-contrast 3D MRCP images in axial, coronal and sagittal views

Step 1

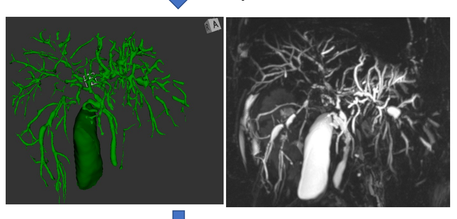
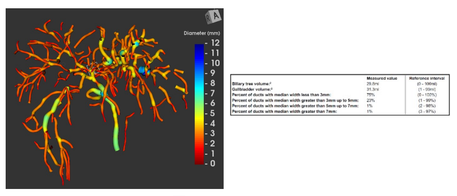


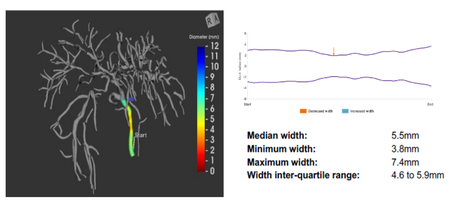
Image enhancement and segmentation of the biliary tree. Maximum intensity projection (MIP) image for comparison.

Step 2



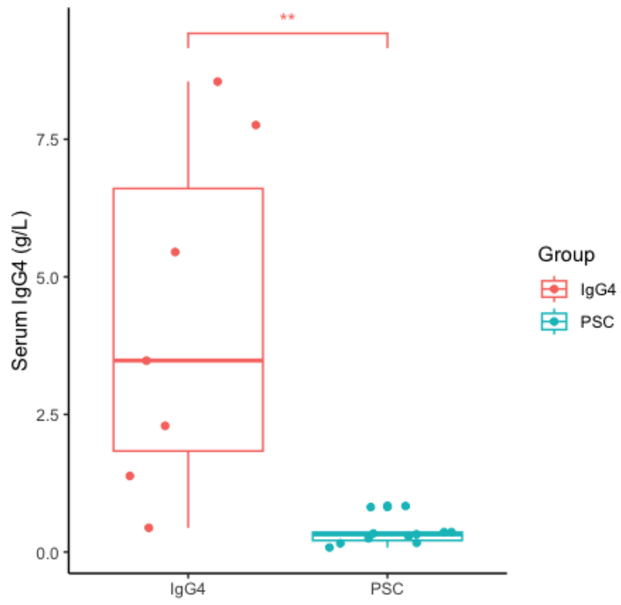
Automatic generation of a parametric model colour-coded according to duct width. Biliary tree metrics provided.

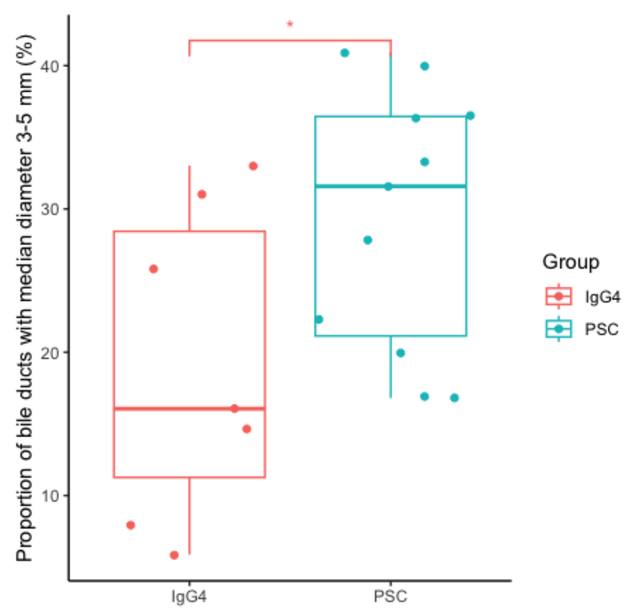
Step 3



Median width:	5.5mm
Minimum width:	3.8mm
Maximum width:	7.4mm
Width inter-quartile range:	4.6 to 5.9mm

Individual duct analysis and mathematical unfolding of the duct in 2D. Example of common bile duct (CBD) analysis.





- Median serum IgG4 was elevated in patients with IgG4-SC compared to PSC (IgG4-RD vs PSC: 2.29 [0.05–13.14] vs 0.32 [0.08–0.84] g/L, p = 0.001). It had 100% specificity for detecting patients with IgG4-SC but lower sensitivity (57%) at 2.8 g/L threshold.
- The percentage of ducts with median diameter 3–5 mm was lower in IgG4-SC than PSC (16 [11–28] vs 32 [21–36]; p=0.03). A cut-off value of 16.4% was able to differentiate the two conditions with AUC of 0.81 (0.58 – 1.00).
- Using serum IgG4 as a first line assessment and the percentage of ducts with median diameter 3–5 mm as a second line assessment in patients with low serum IgG4, maintained 100% specificity observed using serum IgG4 alone but increased the sensitivity of detection in this small cohort to 71%.

Conclusion

- **Quantitative MRCP metric may aid the differentiation of patients with IgG4-SC from those with PSC.**
- **The percentage of ducts with median diameter 3–5 mm has previously been shown to predict disease severity and transplant-free survival in patients with PSC[2,3], but further suitably powered study is needed to test its discriminatory value in differentiating IgG4-SC from PSC.**

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18F-FDG PET-CT identifies subclinical disease and disease activity in a prospective IgG4-related disease UK cohort.

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Introduction:

- The highly variable clinical range observed within multisystem fibro-inflammatory condition IgG4-related disease (IgG4-RD) presents an ongoing diagnostic challenge.[1]
- [18F]-fluorodeoxyglucose (18F-FDG) PET-CT is increasingly used to assess organ involvement and treatment response in IgG4-RD by providing whole-body metabolic information.
- Indications and effectiveness of PET-CT are not fully characterised. Here, we aim to inform of the current

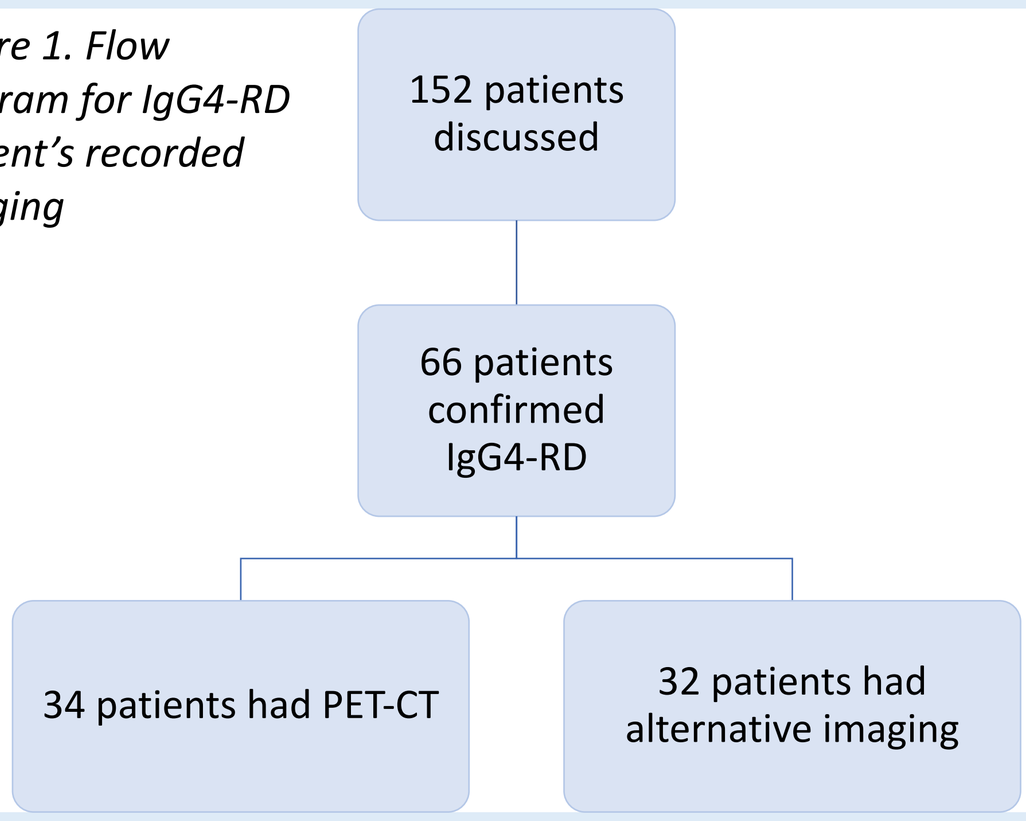
Materials and Methods

- Data was retrospectively collected from IgG4-RD patients discussed at Oxford University Hospital's specialist IgG4-RD MDT[2] over a 3 year period.
- Patients provided informed consent in accordance with Oxford ethics research council (10/h0604/51).
- Electronic patient records were used to search for: a confirmed diagnosis of IgG4-RD, record and indication of PET-CT, alternative imaging, and clinical actions following PET-CT.

Results:

1. Of 66 patients with confirmed IgG4-RD, 34 patients underwent a PET-CT scan. A total of 54 PET-CT scans were performed across these subjects (range=1-4).
2. PET-CT was most frequently used to assess for disease activity (51.8%), as well as use in diagnostic work up (27.8%), related to diagnoses other than IgG4-RD (12.9%), and to observe disease response to steroids (5.6%)
3. The action PET-CT results most commonly led to was a change in treatment (40.7%) followed by biopsy (22.2%), treatment continuation (16.7%), and follow up imaging (5.6%).

Figure 1. Flow diagram for IgG4-RD patient's recorded imaging



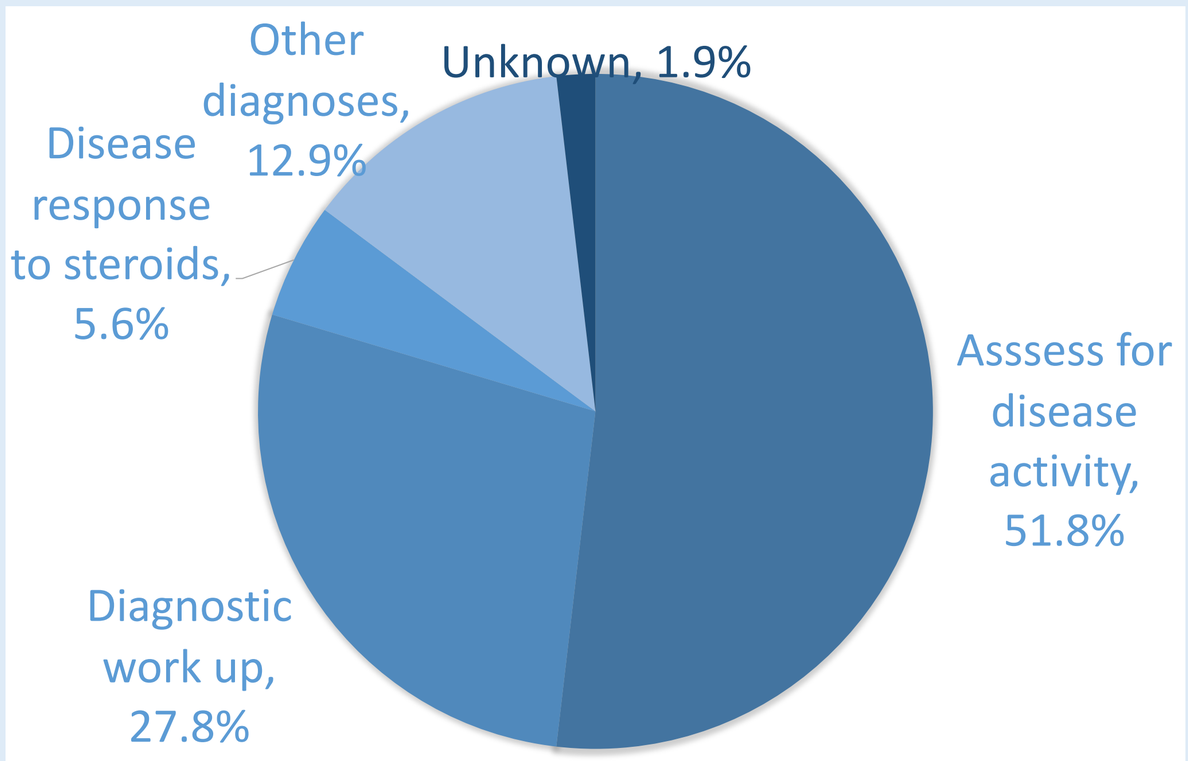


Figure 2. Clinical indication for PET-CT

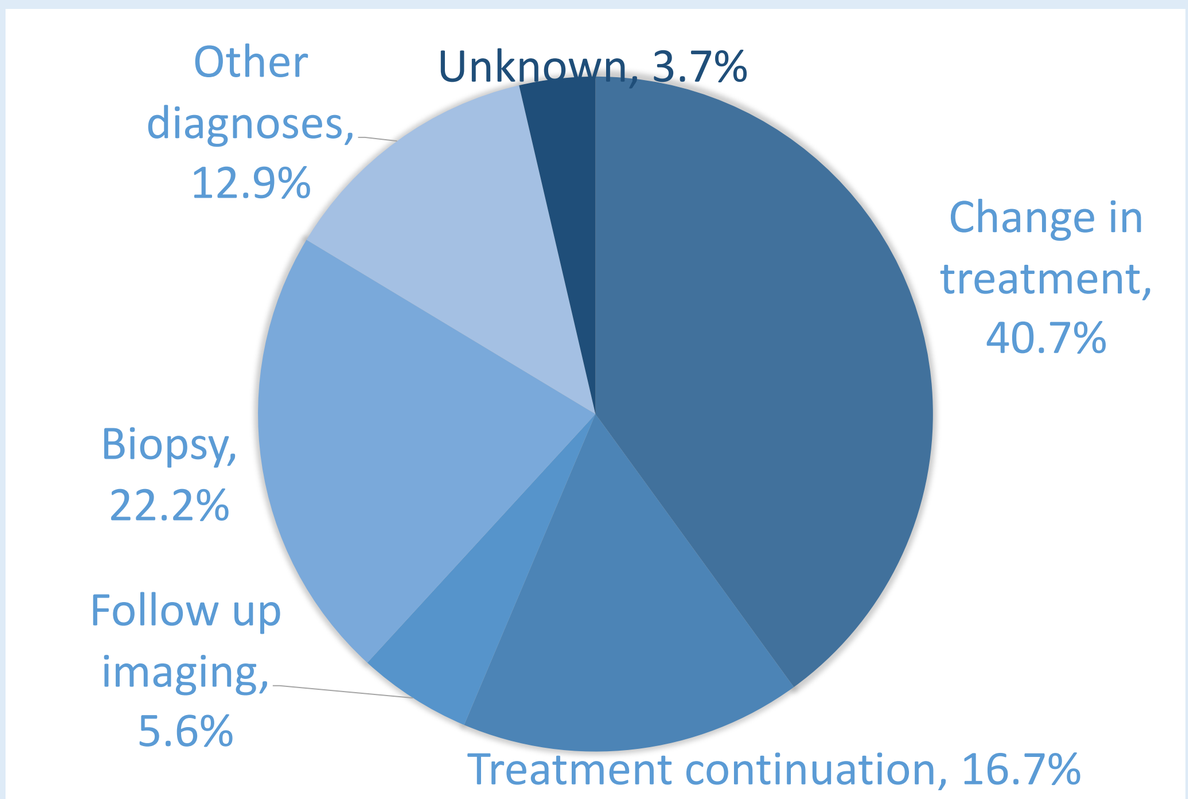


Figure 3. Clinical action following PET-CT

Discussion:

- PET-CT is used for assessment of acute flares and subclinical disease activity, by sensitive, and accurate whole-body imaging- especially important due to the widespread nature of this disease.
- These results are in line with previous work indicating PET-CT can be used for location of sites for biopsy, and for diagnosis of multi-organ disease[3].
- Here, PET-CT informed clinical action, especially important since the disease is often misdiagnosed, yet can be cured to remission with corticosteroid treatment[3].
- PET-CT monitoring may reduce unnecessary continuation of steroid treatment, and associated side effects, as well as screening for associated diseases.

Conclusion and limitations:

- 18FFDG PET-CT is used in practice for IgG4-RD diagnosis by determining extent of organ involvement, monitoring disease activity and influencing clinical decision making and therapeutics offered.
- Results are limited by availability/consistency of results on EPR, incorporation of deceased patient data, and influence of individual consultant preference.

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THE ROLE OF TRANSIENT ELASTOGRAPHY IN IgG4 RELATED HPB DISEASE

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Background & Aims

IgG4-Related Disease (RD) is associated with inflammation and fibrosis.
IgG4-Hepatobiliary (HPB) disease affects the liver, bile ducts and pancreas. Vibration controlled transient elastography (VCTE) for liver stiffness has a high-performance characteristic for detecting advance liver fibrosis in liver diseases such as metabolic, viral hepatitis, autoimmune and cholestatic liver diseases.
The role of VCTE in patients with IgG4-HPB disease to assess disease activity, damage and progression has not been addressed.

Methods

Descriptive single centre study; 85 IgG4-RD with VCTE readings by Fibroscan. Data was collected retrospectively from patient electronic health records.
Baseline and progression of liver stiffness readings, flair activity, organ involvement, serum biomarkers of activity were documented and studied.

Results

65 (76%) men, and the dominant phenotype was IgG4-HPB disease (79%).
Median value of liver stiffness was 5.5kPA; IgG4-HPB cohort median was 5.4kPA.

There was no difference in VCTE during an active flair or remission (Table 1). 30.6% of the patients had serial readings over a median of 4 years.

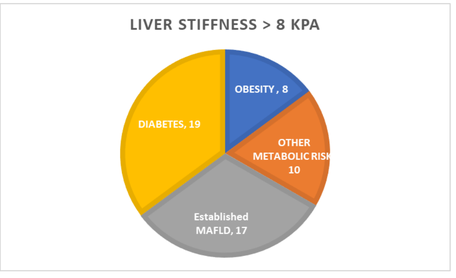
Significant difference between baseline (median 5kPA, IQR 4.2 – 6.5) and follow up readings (median 6.4kPA, IQR 4.6 – 8.7) (Z= 0.9, p=0.02, 97% CI 0.1 – 2.5).

25 (29%) patients had a liver stiffness reading ≥ 8kPA, with 8 (9%) having a reading > 12kPA. In this group 74% had a diagnosis of Metabolic Associated Fatty Liver Disease (MAFLD) with diabetes and obesity being the most significant risk factors. (76% and 32% respectively).

Table 1. Differences in liver stiffness measures (LSM) between patients with active disease and those in remission.

LSM in IgG4-HPB	Active disease (n = 21)	Remission (n = 56)	p-value
Liver stiffness (kPa), median (kPA)	5 (4.6 - 8.6)	6.1 (4.3 - 7.7)	0.94
Liver stiffness groups, n (%)			
LSM < 8 kPa	14 (66.7)	45 (82.1)	
LSM ≥ 8-12 kPa	4 (19)	9 (16.1)	0.33
LSM ≥ 12 kPa	3 (14.3)	2 (3.6)	

Figure 1. Comorbidities in patients with a LSM ≥ 8kPa



Conclusions

This is the first study to assess liver stiffness measurements with VCTE using Fibroscan in patients with IgG4-HPB and systemic disease.

Overall patients had a low liver stiffness reading suggesting low incidence of liver advanced fibrosis/cirrhosis. This is supported by clinical data showing low prevalence and rare progression to cirrhosis in IgG4-HPB disease.
Liver stiffness measurements increased over time, and this may be a means to track fibrosis progression in the disease.

High liver stiffness readings ≥ 8kPA were seen in majority of concomitant MAFLD patients. This is important as 50% of patients with IgG4-HPB disease will have exocrine diabetes mellitus and steroid-induced weight gain and worsening diabetes may be at additive risk factor for liver fibrosis.

Cardiovascular manifestations associated with IgG4-RD

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Background

Cardiovascular (CV) manifestations of IgG4-RD are poorly described. These range from arteritis and periarteritis of large and medium sized vessels (e.g., aorta and coronary arteries) to masses around the coronary arteries, constrictive pericarditis, cardiac pseudotumours and heart rhythm disturbances.

Aims

We assessed a cohort of patients with IgG4-RD for the occurrence of clinically meaningful CV abnormalities by imaging and electrophysiological studies.

Methods

Data was collected on 71 patients with IgG4-RD meeting the EULAR/ACR Classification Criteria.

Pre-defined findings considered important included ventricular systolic and diastolic dysfunction, ventricular dilatation, pericardial effusion or ≥ trivial valve disease; computed tomography (CT) evidence of aortic root, pericardial or coronary artery abnormality; or a clinical presentation with heart failure, cardiac conduction abnormality, or sequelae of coronary artery disease.

Electronic patient records including functional studies and imaging were analysed retrospectively.

Manifestation of cardiac disease		Frequency (% of total)
Echocardiography (n=14)	Valvular Regurgitation (≥ trivial)	13 (92.9)
	Diastolic Dysfunction	5 (35.7)
	Pericardial Effusion	3 (21.4)
CT Chest Imaging (n=41)	Coronary Artery Abnormality	4 (9.8)
	Pericardial Effusion	3 (7.3)
Clinical Presentation (n=58)	Heart Failure	5 (8.6)
	Conduction Abnormality	7 (12.1)
	Coronary Artery Disease	7 (12.1)

Table 1: Findings of cardiovascular imaging in patients with IgG4-RD.

Results

57 (80.3%) men, mean age at diagnosis was 62 .5 years (SD 13.5).
Duration of follow-up was 79.6 months (SD 44.1).
Transthoracic echocardiogram (TTE) and chest computed tomography (CT) were available for 15 (21.1%) and 41 (58%) patients respectively.

22 (31%) had CV abnormalities on TTE and/or CT.

Clinically meaningful valvar disease was present in 13 (18.3%), coronary artery disease in 7 (10%), conduction abnormalities in 7 (10%), heart failure in 5 (7%) patients (Table 1).
One patient presented a pseudotumour surrounding the left anterior descendent (LAD) coronary artery causing 25% stenosis of the vessel, which reduced with corticosteroids and rituximab therapy (Figure 1).

Conclusions

CV changes can occur in 1/3 of patients diagnosed with systemic IgG4-RD.
Studies have demonstrated the association of IgG4 antibodies and interleukins involved in the pathogenesis of IgG4-RD in the development of atherosclerosis and reduction of heart function.
We should expand this cohort to study the electrophysiological changes and functional imaging in active disease and post therapy to understand the role it plays in CV disease in this population.

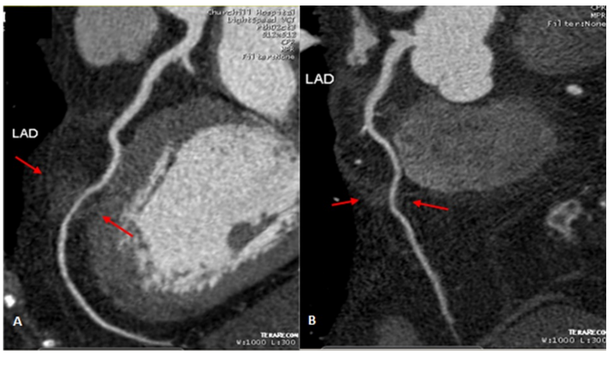

Figure 1. A) CT coronary angiogram imagie showing 15x15mm soft tisse mass enclosing LAD causing 25% stenosis. B) Reduction in size of the mass and relief of LAD stenosis following therapy.

Cardiac Manifestations of IgG4-Related Disease

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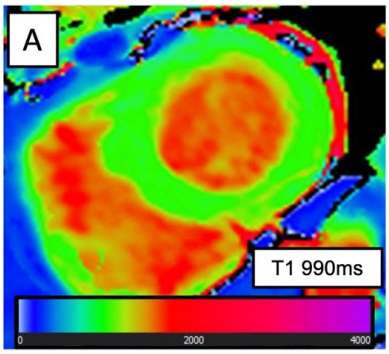
Introduction

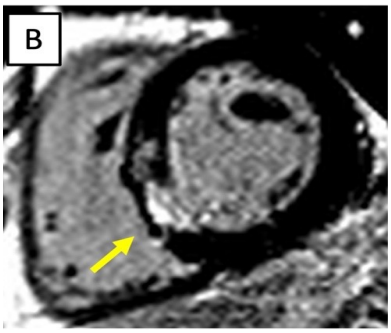
IgG4-related disease (IgG4-RD) is a relapsing-remitting immune-mediated condition that affects multiple organ systems. Case reports of suspected cardiovascular involvement in IgG4-RD have emerged though no study has systematically assessed the cardiovascular phenotype of IgG4-RD using cardiac magnetic resonance (CMR).

Methods

We recruited 11 patients with histologically-confirmed IgG4-RD (6 female, 61±11 years, 9 with active disease *(8 with pancreatic involvement, 3 parotid, 5 bile ducts, 5 kidneys and 3 cardiovascular)*). Patients underwent CMR at 1.5T including cine, myocardial tagging, native T1-mapping, late gadolinium enhancement (LGE) and extracellular volume (ECV). Results were compared to 10 healthy controls with no cardiac disease (50% female, 35±8 years). Results are presented as mean ± standard deviation (SD) unless otherwise stated.



Panel A – Myocardial T1 mapping in an individual with high native T1 values (990ms) with IgG4-RD



Panel B – Subendocardial LGE consistent with an infarct in a 48 y/o with IgG4-RD

Results

Patients with IgG4-RD had similar cardiac geometry to controls. No difference was observed in ejection fraction, however IgG4-RD patients showed significantly reduced global longitudinal strain (GLS). Male IgG4-RD patients (n=5) showed significantly higher myocardial T1 values, with 3/5 male patients having an abnormally high myocardial T1 (>2SD above limit of normal). Female IgG4-RD patients (n=6) had similar and normal myocardial T1 values to the reference group. Seven of the 11 IgG4-RD patients showed LGE, with 6 of these in a non-ischaemic pattern. ECV was not statistically different from reference values. Only 3 of the 11 patients had a completely normal CMR scan.

Conclusions

IgG4-RD patients show frequent cardiac abnormalities on advanced CMR phenotyping, including subclinical systolic dysfunction, ischaemic and non-ischaemic myocardial fibrosis, and elevated myocardial T1 times. These abnormalities have been described in inflammatory cardiovascular diseases, supporting a plausible pathophysiological link with IgG4-RD. Future work in larger and multicentre cohorts is warranted, to systematically define the novel cardiovascular phenotype of IgG4-RD.

	IgG4-RD (n=11)	Control Values† (n=10)	P value
LVEDV (ml)	144 (32)	153 (39)	0.595
RVEDV (ml)	150 (45)	148 (40)	0.926
RVEF (%)	59 (4)	60 (3)	0.574
LVEF (%)	60 (4)	60 (3)	0.955
Global Longitudinal Strain (%)	-16.8 (2.3)	-18.7 (1.6)	0.045
Male Global T1-mapping value (ms)	950 (33)‡	925 (18)†	0.036
Female Global T1-mapping value (ms)	962 (8)§	954 (21)†	0.247
Extracellular volume fraction (%)	29.5 (2.5)	27.9 (2.5)	0.192
Late gadolinium enhancement (n,%)	7/11 (64%)	0/10 (0%)	0.004

Table 1 – Cardiac Geometry, Function and Tissue Characterisation of patients with IgG4-RD and healthy controls

†reference group consisted of 10 controls, except for T1-mapping for which at least 15 healthy controls of each sex (15F and 17M) were used to establish sex-specific local normal ranges as per current guidelines; ‡based on 5 IgG4-RD males; §based on 6 IgG4-RD females

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The ACR/EULAR Classification Criteria for IgG4-related disease: A real world experience

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Introduction

The 2019 ACR/EULAR Classification Criteria for IgG4-related disease (IgG4-RD)[1] were developed and validated in a large international cohort and reported to have excellent diagnostic specificity. We sought to evaluate the performance of the classification criteria in real-world clinical practice through our supra-regional Oxford-London IgG4-RD multi-disciplinary meeting (MDM).

"ACR/EULAR Classification Criteria have excellent specificity for IgG4-related disease diagnosis."

Methods

We prospectively collected data on 153 patients referred to our IgG4-RD MDM over 4-years with suspected IgG4-RD. Each was classified as definite, possible or not IgG4-RD based on existing diagnostic criteria (HISORt, CDC, Boston Histopathology) and speciality experience. We retrospectively applied the ACR-EULAR classification criteria to this cohort to assess concordance with MDM outcomes.

Results

The ACR/EULAR classification criteria appropriately excluded all cases considered not IgG4-RD at the MDM (n=52) (Fig. 1). Sensitivity for IgG4-RD diagnosis was between 50.9% and 61.9% (Table 1). Of those considered definite IgG4-RD (n=63) in the MDM, only half (33;52%) met ACR/EULAR criteria. In those considered to have definite hepato-pancreato-biliary (HPB) involvement (n=48) at the MDM, just over half (27;56%) met ACR-EULAR criteria. Most of the IgG4-HPB patients not meeting ACR/EULAR criteria scored insufficient diagnostic points (n=17). This was due to the classification criteria's reliance on stringent pancreatic imaging characteristics; diffuse swelling and pseudocapsule; with no points awarded for cholangiopathy without pancreatic involvement, atrophy, or focal enlargement of the gland. Additional challenges to patients meeting the classification criteria were small and unrepresentative biopsies and specific exclusions including the absence of glucocorticoid response in advanced (fibrotic) cholangiopathy, and the presence of Crohn's disease or ulcerative colitis in otherwise isolated IgG4-HPB disease.

Figure 1. IgG4-RD MDM Diagnoses

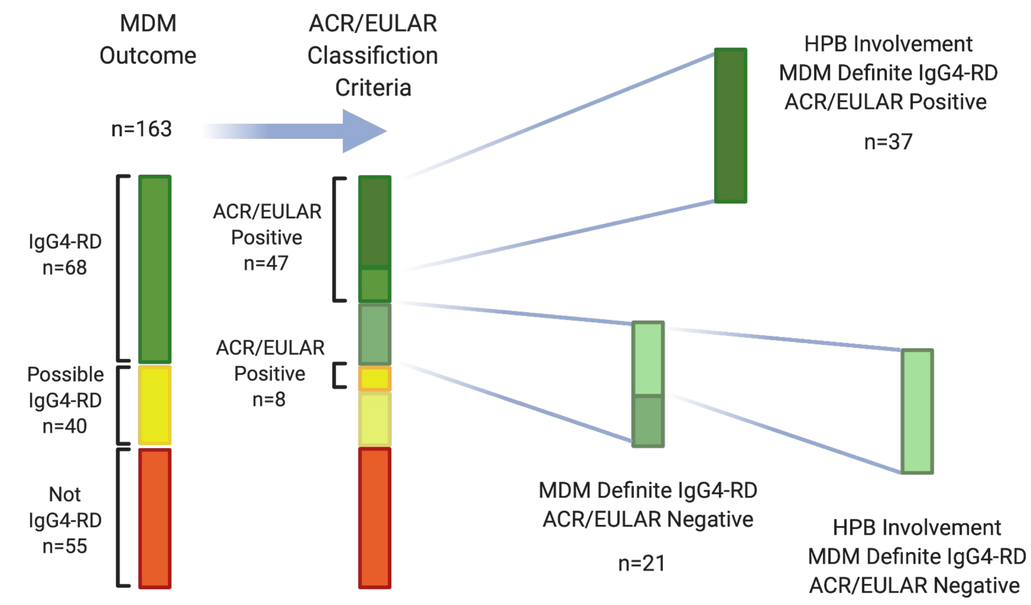

Table 1. ACR/EULAR Classification Criteria Performance

	Possibles Excluded	Possibles As Definites	Possibles As Not IgG4-RD
Sensitivity	69.1%	50.9%	69.1%
Specificity	100%	100%	91.6%
PPV	1.0	1.0	0.85
NPV	0.72	0.51	0.81

ACR/EULAR Classification Criteria performance assessed against MDM decision. Test performance characteristics calculated for all the potential permutations for those patients characterised as 'Possible IgG4-RD' (n=40) at the MDM.

"The classification criteria lack sensitivity in isolated biliary disease and pancreatic atrophy."

Conclusions

The ACR-EULAR classification demonstrated excellent specificity (100%) and will be a useful tool for clinical trials. Much of the disparity between diagnosis according to our IgG4-RD MDM and the ACR/EULAR criteria are explained by specific pancreatic imaging characteristics, absence of cholangiopathy/hepatopathy as a unique entity, and the necessity for steroid responsiveness even if presenting with advanced cholangiopathy.

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Referrals:

New referrals to the IgG4-RD MDM are welcomed, see https://igg4-rd.ndm.ox.ac.uk for a referral form and email ouh-tr.igg4MDT@nhs.net or uclh.hpbmedicine@nhs.net

Lymphoma and IgG4-related disease: Is there a link?

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Background

We have previously observed an increased risk of malignancy[1] associated with Immunoglobulin G4-Related Disease (IgG4-RD). Recent case reports have suggested a close relationship between IgG4-RD and lymphoma.[2] We therefore sought to identify evidence for a similar relationship in our large cohort of patients with IgG4-RD.

"We demonstrate a striking incidence of non-hodgkin's lymphoma in our IgG4-RD cohort."

Methods

We reviewed records for IgG4-RD patients discussed at the monthly Oxford IgG4-RD multi-disciplinary meeting over a period of 58 months, November 2016 to September 2021, to identify cancer diagnoses. In all cases IgG4-RD was confirmed by established diagnostic criteria (HISORt, CDC or Boston histopathological consensus) and cancer diagnosis was confirmed at the relevant cancer MDM. Using publicly available UK national cancer registry data[3] we were able to determine age and gender standardised incidence ratios (SIR) for malignancy and non-hodgkin's lymphoma (NHL) in our IgG4-RD cohort.

Results

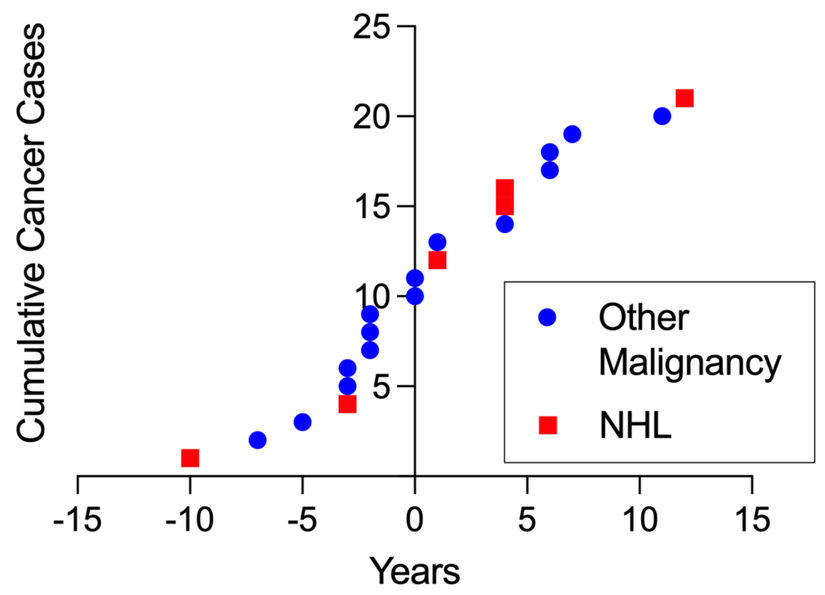
Of 105 patients, median age – 67 years (IQR 56-76) and Male:Female ratio of 2.4:1, 21 patients developed malignancies over their lifetimes with an SIR of 13.5 (95%CI 8.5-20.2) (**Fig.1**). 7/21 had lymphoma of which 6 were NHL B cell lymphomas SIR 93.6 (95%CI 34.2 – 203.7) (**Table 1**). 3 patients with lymphoma had IgG4 sclerosing cholangitis, 3 had head and neck IgG4-RD and 1 had IgG4 related renal disease. 4 lymphoma cases were diagnosed after their IgG4-RD diagnosis. The median time of lymphoma from IgG4 diagnosis was 4.35 years (range 0.6 – 11.8 years). Of these, 1 patient received a long-term (>3 months) immunomodulator, azathioprine. 3 patients were diagnosed with IgG4-RD after their diagnosis of lymphoma. The median time of lymphoma to IgG4 diagnosis was 7.4 years (range 2.6 – 9.5 years). All 3 patients were commenced on mycophenolate mofetil once diagnosed with IgG4-RD.

Conclusions

Our data demonstrates an increased incidence of cancer in our IgG4-RD cohort with a striking incidence of NHL. Though our results should not be used to infer causality they argue strongly for efforts to validate in other cohorts and further research into possible mechanisms for such an association. We question the rationale for the common off-label use of azathioprine,[4] a drug known to increase lymphoma risk, when it lacks prospective randomised efficacy data in IgG4-RD.

Figure 1.

Cancer Cases Relative to IgG4-RD Diagnosis



"Given the known association of Azathioprine and lymphoma we should be aware of this increased risk "

Table 1.

Cancers observed in the Oxford IgG4-RD Cohort

Primary Cancer	Observed cases
Lymphoma	7
Renal	2
Gastric	1
Biliary	2
Breast	1
Oesophagus	1
Thyroid	1
Pancreas	1
Prostate	2
Colon	2
Ovarian	1

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