



Published in final edited form as:

Nat Rev Rheumatol. 2023 December ; 19(12): 805–817. doi:10.1038/s41584-023-01045-w.

* A list of authors and their affiliations appears at the end of the paper.

Corresponding Author: Rohit Aggarwal M.D., M.S., Professor of Medicine, Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, 3601 5th Avenue, Suite 2B, Pittsburgh, PA 15261, USA, Phone: 412-383-8100, Fax: 412-383-8864, aggarwalr@upmc.edu.

Competing interests

R.A. served as a consultant for Kezar, Csl Behring, AstraZeneca, Octapharma, BMS, Pfizer, Janssen, Mallinckrodt, Alexion, Q32, argenx, Boehringer-Ingelheim, Corbus, and EMD-Serono; and received research funding from Pfizer, BMS, Genentech, Kezar, Csl Behring, and Mallinckrodt.

L.C. (Lorinda Chung) receives funding from Boehringer Ingelheim; served on an advisory board for Eicos Sciences and Mitsubishi Tanabe; received consulting fees from Kyverna, Jasper, and Genentech.

P.M.M. received consulting/speaker's fees from Abbvie, BMS, Celgene, Eli Lilly, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche, and UCB, outside the submitted work.

R.A.V. received a research grant from Pfizer.

H.C. received research grants, travel grants, consultancy or speaker honoraria from AbbVie, Amgen, BMS, Biogen, Janssen, Lilly, Novartis, and UCB.

V.P.W. served as a consultant for Kezar, CSL Behring, AstraZeneca, Octapharma, Pfizer, Janssen, Neovacs, and Idera; and received research funding from Pfizer, CSL Behring, and Corbus.

L.A.O. received consulting/speaker's fees from Abbvie, BMS, Boehringer Ingelheim, Eli Lilly, Janssen, Novartis, Pfizer, and Roche, outside the submitted work.

J.P.C. owns stock in trust accounts in the following companies: Abbvie, Abbott Laboratories, Amgen, Allergan, Celgene, 3M, Merck, Johnson and Johnson, Procter and Gamble, Pfizer, Gilead, Walgreens and CVS. In addition, he served on a Safety Monitoring committee for Principia Biopharma and as an adjudicator for study entry for EMD Serono and Biogen.

C. C-S. has served as a consultant for Abbvie, Gilead, Octapharma, Pfizer, and Regeneron-Sanofi and has received research funding from Abbvie, Bristol-Myers Squibb, Octapharma, and Pfizer.

B.F.C. served as a consultant for Biogen Inc., Bristol Meyers Squibb, Horizon Therapeutics, EMD Serono, and Bristol Meyers Squibb, and received research funding from Daavlin Company. He is an investigator for Pfizer Inc. and Biogen Inc.

P.F.D. works for UpToDate, serves on an FDA Advisory committee, has received research grants in the past 3 years from Genentech and Bristol Myers, and was on an unpaid advisory group for Boehringer Ingelheim

L.P.D. received speaker honoraria from Boehringer Ingelheim and has served on a data safety monitoring board for Corbus Pharmaceuticals.

M.M.D. serves or recently served as a consultant for Abcuro, Amazentis, argenx, Catalyst, Cello, Covance/Labcorp, CSL-Behring, EcoR1, Janssen, Kezar, MDA, Medlink, Momenta, NuFactor, Octapharma, Priovant, RaPharma/UCB, Roivant Sciences Inc, Sanofi Genzyme, Shire Takeda, Scholar Rock, Spark Therapeutics, Abata/Third Rock, UCB Biopharma, and UpToDate. M.M.D. received research grants or contracts or educational grants from Alexion, Alnylam Pharmaceuticals, Amicus, Biomarin, Bristol-Myers Squibb, Catalyst, Corbus, CSL-Behring, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Kezar, Mitsubishi Tanabe Pharma, MDA, NIH, Novartis, Octapharma, Orphazyme, Ra Pharma/UCB, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics, The Myositis Association, UCB Biopharma/RaPharma, and Viromed/Healixmith.

F.E. has received research support and funding from Genentech and Octapharma.

D.F. received honoraria from Bristol-Meyers Squibb, Kyverna, Janssen, Amgen, UCB, Priovant, and Merck. D.F. received funding for contracted research from Pfizer and a research grant from Serono.

Z.G. received speaker honoraria from AbbVie, Eli Lilly, Novartis, and Roche and served on an advisory board for Octapharma.

A.J.vdK. served on an advisory board for argenx.

M.K. received research grants, travel grants, consultancy or speaker honoraria from AbbVie, argenx, Astellas, Boehringer Ingelheim, Chugai, Corbus, Horizon Therapeutics, Kissei, Medical & Biological Laboratories, Mochida, Ono, and Mitsubishi Tanabe.

I.E.L. has received consulting fees from Corbus Pharmaceuticals, Inc and research grants from Astra Zeneca; has been serving on the advisory board for Bristol Myers Squibb, Corbus Pharmaceutical, EMD Serono Research & Development Institute, argenx, Octapharma, Kezaar, Orphazyme, Pfizer and Janssen; has stock shares in Roche and Novartis.

C.A.M. served a consultant for Boehringer Ingelheim and for the National Vaccine Injury Compensation Program.

J.J.P. reports consultant fees from Alexion, Roivant, argenx, EMD-Serono, Pfizer, Kezar, and Guidepoint; clinical trial research support from Alexion, Pfizer, and Kezar.

J.R. received departmental research support from the Dutch Prinses Beatrix Spierfonds, Dutch ALS foundation, Marigold foundation, Prothya Biosolutions, argenx, and Health-Holland/Dutch Ministry of Economic Affairs.

L.G.R. served as an unpaid consultant for AstraZeneca, CSL Behring, Alexion, Boehringer Ingelheim, Argenx, Pfizer, and Horizon Therapeutics, and received research funding from BMS, Hope Pharmaceuticals, and Lilly.

J.V. received research grants, consultancy or speaker honoraria from Abbvie, argenx, Biogen, Boehringer Ingelheim, Eli Lilly, Gilead, Horizon, Kezar, Merck Sharp and Dohme, Octapharma, Pfizer, Takeda, UCB, and Werfen.

M.d.V served as a consultant for Novartis and Dynacure.

M.D. has I received honoraria and consultation fees from Biogen, CSL-Behring, Sanofi-Genzyme, Abcuro, and Roche.

International Guideline for Idiopathic Inflammatory Myopathy-Associated Cancer Screening:

An International Myositis Assessment and Clinical Studies Group (IMACS) Initiative

Alexander G.S. Oldroyd^{1,2,3,4}, Jeffrey P. Callen⁵, Hector Chinoy^{1,2,3}, Lorinda Chung^{6,7}, David Fiorentino⁸, Patrick Gordon⁹, Pedro Machado^{10,11,12,13}, Neil McHugh¹⁴, Albert Selva-O'Callaghan¹⁵, Jens Schmidt¹⁶, Sarah L. Tansley^{14,17}, Ruth Ann Vleugels^{18,19}, Victoria P. Werth^{20,21},

International Myositis Assessment and Clinical Studies Group Cancer Screening Expert Group*,

Rohit Aggarwal²²

¹National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, University of Manchester, Manchester, United Kingdom

²Department of Rheumatology, Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, Manchester Academic Health Science Centre, Salford, United Kingdom

³Centre for Musculoskeletal Research, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

⁴Centre for Epidemiology Versus Arthritis, University of Manchester, Manchester, United Kingdom

⁵Division of Dermatology, Department of Medicine, University of Louisville School of Medicine, Louisville, Kentucky, USA

⁶Division of Immunology and Rheumatology, Department of Medicine and Dermatology, Stanford University, Stanford, California, USA

⁷Palo Alto Health Care System, Palo Alto, California, USA

⁸Department of Dermatology, Stanford University School of Medicine, Redwood City, California, USA

⁹Department of Rheumatology, King's College Hospital NHS Foundation Trust, London, UK

¹⁰Centre for Rheumatology, Division of Medicine, University College London, London, UK

¹¹Department of Neuromuscular Diseases, Division of Medicine, University College London, London, UK

¹²National Institute for Health Research University College London Hospitals Biomedical Research Centre, University College London Hospitals National Health Service Trust, London, UK

¹³Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK

¹⁴Department of Life Sciences, University of Bath, Bath, UK

¹⁵Systemic Autoimmune Diseases Unit, Vall D'Hebron General Hospital, Medicine Department, Universitat Autònoma de Barcelona, Barcelona, Spain

¹⁶Department of Neurology, Neuromuscular Centre, University Medical Centre Göttingen, Göttingen, Germany

¹⁷Royal National Hospital for Rheumatic Diseases, Royal United Hospitals NHS Foundation Trust Bath, Bath, UK

¹⁸Harvard Medical School, Boston, Massachusetts, USA

¹⁹Department of Dermatology, Brigham and Women's Hospital, Boston, Massachusetts, USA

²⁰Department of Dermatology, University of Pennsylvania, Philadelphia, Pennsylvania, USA

²¹Division of Dermatology, Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania, USA

²²Myositis Center and Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Abstract

Adult-onset idiopathic inflammatory myopathy (IIM) is associated with an increased cancer risk within three years prior to or following IIM onset. Evidence and consensus-based recommendations for IIM-associated cancer screening can potentially improve outcomes.

Recommendations were formed via a modified Delphi approach using a series of online surveys completed by an international Expert Group.

In total, 18 recommendations were made. First, recommendations allow a patient's individual IIM-associated cancer risk (compared to overall IIM population, not the general population) to be stratified into standard, moderate, and high risk according to the IIM subtype, autoantibody status, and clinical features. Second, recommendations outline a "basic" screening panel (including chest radiography, preliminary laboratory blood tests) and an "enhanced" screening panel (including computed tomography [CT] and tumor markers). Third, recommendations advise on the timing and frequency of screening via basic and enhanced panels, according to standard/moderate/high risk status. Recommendations also advise consideration of upper/lower gastro-intestinal endoscopy, naso-endoscopy, and ¹⁸F-FDG PET/CT scanning in specific patient populations.

The International Guideline for IIM-Associated Cancer Screening provides recommendations addressing individual patient IIM-associated cancer risk stratification, cancer screening modalities, and screening frequency. These recommendations aim to facilitate earlier IIM-associated cancer detection, especially in those who are at high risk, thus potentially improving outcomes, including survival.

Introduction

Idiopathic inflammatory myopathy (IIM, commonly termed "myositis") is a chronic multisystem autoimmune condition with a range of manifestations, including muscle inflammation, skin involvement, and interstitial lung disease (ILD)^{1,2}.

Adult-onset IIM is associated with an increased risk of cancer, particularly within the three years prior to and after IIM onset³. Evidence suggests that up to one in four people with IIM are diagnosed with cancer within three years of IIM onset⁴. Various cancers have been reported, including lung, ovarian, colorectal, lymphoma, breast, and naso-pharyngeal among the most common⁵. Cancer remains the leading cause of death in adults with IIM^{4,6-8}, likely in part due to delayed diagnosis. IIM-associated cancers are overwhelmingly diagnosed at a late stage; a cohort study identified that 83% of IIM-associated cancers were stage three or four by the time of diagnosis and were associated with a cancer remission rate of only 17%⁵.

Early detection of cancer is key to improving outcomes. Consensus-based recommendations, based on available evidence, will inform screening for malignancy in patients with IIM, standardise practices across health systems, particularly for patients managed outside specialist IIM centres.

The International Myositis Assessment and Clinical Studies Group (IMACS), the largest international multi-disciplinary group for IIM scientific studies, sponsored a project to develop evidence and consensus-based cancer screening recommendations for patients with IIM. The first component of the project involved conducting a meta-analysis, which aimed to identify IIM-associated cancer risk factors, and a systematic review, which aimed to compile evidence on screening modalities⁹. The second component of work involved forming an international multidisciplinary “Expert Group” with expertise in IIM and cancer screening, with the aim of developing evidence-based consensus recommendations on screening for IIM-associated cancer, specifically addressing cancer risk stratification, screening modalities, and screening frequency. Herein, we present the methodology and consensus-based recommendations for IIM-associated cancer screening developed by the large multi-disciplinary international Expert Group derived from members of IMACS. These recommendations have been scientifically reviewed by the IMACS Scientific Committee and have been endorsed by the International Myositis Society. They will be revised and endorsed periodically.

Methods

The recommendation formation process was guided by a Steering Committee (N=14), formed by IIM specialists affiliated with IMACS, led by R.A and A.G.S.O.

Evidence collation was carried out via a systematic literature review (SLR), to update the recently published meta-analysis and systematic review⁹ using the same methodology (study selection, data extraction, quality assessment, data synthesis) and adhering to PRISMA guidelines¹⁰ (see acknowledgement section for details of individuals that provided input on the systematic literature review and meta-analysis). Evidence published prior to 1st April 2022 was included.

An international Expert Group, with expertise in IIM and cancer screening, was convened. Eligibility criteria for the Expert Group included: 1) clinical expertise in IIM with 10 or more years’ experience, or 2) one or more publications focused on clinically translational aspects of IIM-associated cancer, or 3) clinical/research expertise in non-IIM-associated

cancer screening. The Expert Group comprised a total of 75 individuals, including members of the Steering Committee, but excluding the process leads R. A. and A.G.S.O.. The Expert Group comprised a total of 46 rheumatologists, 12 neurologists, 9 dermatologists, three oncologists with expertise in cancer screening, two pulmonologists with a special interest in IIM, two researchers with expertise in cancer screening implementation, and one paediatric rheumatologist across a total of 22 countries and five continents (North America, South America, Europe, Asia, Australia) (see Supplementary material for composition of Expert Group by specialty and geographical location).

The recommendation formation process followed a modified Delphi Method approach using a series of online surveys. Expert Group members were advised to review evidence contained within the updated SLR and the published meta-analysis⁹ prior to completing the first survey. The first survey, created by A.G.S.O and R.A. and amended by the Steering Committee, aimed to identify the opinion of the Expert Group regarding IIM-associated cancer risk factors (i.e. factors that are associated with increased cancer risk), “protective factors” (i.e. factors that are associated with reduced cancer risk), and appropriate use of cancer screening modalities. See Supplementary Material for questions comprising the first survey. The Steering Committee created draft recommendations based on responses from the first survey.

Members of the Expert Group were asked to consider individualised cancer risk stratification in comparison to the wider IIM population only, not the general population.

Subsequent surveys asked members of the Expert Group to rate their level of agreement with each draft recommendation on a 1-9 numerical rating scale (1 = “complete disagreement”, 9 = “complete agreement”). The median vote rating for each draft recommendation was calculated and defined a priori as “disagreement” (median vote of 1-3), “uncertainty” (median vote of 4-6), and “consensus” (median vote of 7-9). Expert Group members were able to provide feedback to A.G.S.O. and R.A. on each recommendation. Draft recommendations were amended according to vote ratings and provided feedback, then re-presented to the Expert Group via an online survey. A total of three recommendation voting surveys, in addition to the preliminary survey, were carried out before consensus was reached.

Each recommendation was assigned a strength of recommendation (1 = strong, 2 = conditional); “strong” recommendations are made where the benefits are deemed to clearly outweigh risks, whereas “conditional” recommendations are made when benefits are more balanced with risks.

Each recommendation was assigned a quality of supporting evidence via the Scottish Intercollegiate Guidelines Network (SIGN)¹¹, thus summarising the quality of body of evidence for each recommendation: high (A), moderate (B), low (C), or very low (D), according to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology.

Three patient partners with adult-onset IIM provided written feedback on the acceptability of the final recommendations and co-authored the final manuscript (one chose to remain anonymous and not be included as a co-author).

The project and final manuscript was reviewed and approved by the IMACS Scientific Committee.

Results

A total of 18 final recommendations were formed, addressing IIM-associated cancer risk stratification (compared to the wider IIM population, not the general population), use of screening modalities, and screening frequency (see Table 1 for summary of recommendations). Regarding strength of recommendation, 13 recommendations were “strong” and five were “conditional”. Quality of supporting evidence was “moderate (B)” for 8 recommendations, “low (C)” for four, and “very low (D)” for three; three further recommendations had no corresponding evidence base and were formed via expert consensus only. No recommendation had “high (A)” quality of supporting evidence. See Supplementary Material for evidence corresponding to each recommendation.

Each recommendation is followed by details relating to: strength of recommendation (i.e. 1 = strong, 2 = conditional), quality of supporting evidence (GRADE level), the number of votes, and the median vote rating with the inter-quartile range (IQR).

1 - Screening for IIM-associated cancer is not routinely required in patients with juvenile-onset IIM

1, B, 62, 8 (8, 9)

Current evidence indicates that cancer risk is not increased in patients with juvenile-onset IIM¹²⁻¹⁸. Therefore, routine cancer screening was not deemed necessary by the Expert Group. Clinicians should, however, be vigilant for features suggestive of underlying cancer in patients with juvenile-onset IIM, including abnormal complete blood count, unexplained weight loss, fevers, and splenomegaly/lymphadenopathy.

2 - Screening for IIM-associated cancer is not routinely required in patients with verified inclusion body myositis

1, B, 62, 8 (7, 9)

Existing evidence indicates that inclusion body myositis (IBM) is not associated with an increased risk of cancer^{4,19}. In particular, a nationwide Norwegian-based cohort study by Dobloug et al calculated a cancer standardised incidence rate of 1.0 (95% confidence interval 0.6, 2.1) in 100 IBM cases, indicating a cancer risk similar to the general population⁴. However, emerging evidence suggests a potential association between IBM and T cell large granular lymphocytic leukaemia^{20,21}; ongoing research may further delineate this association and potentially inform the need for screening.

3 - All IIM patients, irrespective of cancer risk, should continue to participate in country/region-specific age and sex appropriate cancer screening programmes

1, B, 64, 9 (9, 9)

It is imperative that all IIM patients, including those with juvenile-onset IIM and IBM, continue to participate in population-level cancer screening programmes, such as mammography for breast cancer, pelvic exam/smear test for cervical cancer, and low radiation dose chest CT scanning for lung cancer, available in their country/region, according to their age and sex²². These recommendations aim to facilitate detection of IIM-associated cancers above and beyond the general population screening guidelines. Moreover, these recommendations are not tailored to detect cancers that may occur due to non-IIM-associated risk factors for which certain countries/regions may have instigated screening programmes.

4 - All adult patients with new onset IIM should be tested for myositis-specific autoantibodies and myositis-associated autoantibodies to assist stratification of cancer risk.

1, B, 64, 9 (8, 9)

Myositis-specific autoantibodies (MSA) can aid risk stratification for IIM-associated cancer, diagnosis, prediction of clinical manifestations, and aid management decisions. A variety of methods are available for MSA detection and clinicians should interpret results in the context of potential limitations, especially false positivity/negativity.

5 - Underlying cancer risk of adult IIM patients should be stratified according to subtype, autoantibody status, and clinical features in the following manner:

High risk -

- a. Dermatomyositis (DM)
- b. Anti-transcriptional intermediary factor 1 gamma (anti-TIF1-gamma) positivity
- c. Anti-NXP2 positivity
- d. Age >40 years at the time of onset
- e. Features of persistent high disease activity despite immunosuppressive therapy (including relapse of previously controlled disease)
- f. Dysphagia (moderate to severe)
- g. Cutaneous necrosis/ulceration

Intermediate risk -

- a. Clinically amyopathic dermatomyositis
- b. Polymyositis (PM)
- c. Immune-mediated necrotising myopathy (IMNM)
- d. Anti-small ubiquitin-like modifier-1 activating enzyme (anti-SAE1) positivity

- e. Anti-3-hydroxy 3-methylglutaryl coenzyme A reductase (anti-HMGCR) positivity
- f. Anti-Mi2 positivity
- g. Anti-melanoma differentiation-associated gene 5 (anti-MDA5) positivity
- h. Male sex

Low risk -

- a. Anti-synthetase syndrome (ASSD)
- b. Overlap IIM/connective tissue disease-associated myositis
- c. Anti-signal recognition particle (anti-SRP) positivity
- d. Anti-Jo1 positivity
- e. Non-Jo1 ASSD antibody positivity
- f. Myositis-associated antibody positivity (PM-Scl, Ku, anti-ribonucleoprotein [anti-RNP], Ro/La [SSA/B])
- g. Raynaud's phenomenon
- h. Inflammatory arthropathy
- i. ILD

1, B, 52, 8 (7, 9)

6 - Adult IIM patients with two or more “high risk” factors (subtype, autoantibody, or clinical feature) should be considered to have a “high risk for IIM-related cancer”.

1, B, 67, 8 (8, 9)

7 - Adult IIM patients with two or more “intermediate risk” factors (subtype, autoantibody, or clinical feature) or only one “high risk” factor (subtype, autoantibody, or clinical feature) should be considered to have an “moderate risk for IIM-related cancer”.

1, B, 67, 7 (7, 9)

8 - Adult IIM patients that do not fulfil the “high” or “moderate risk” definitions should be considered to have “standard risk for IIM-related cancer”.

1, B, 67, 8 (7, 9)

Recommendations have been formed that allow clinicians to stratify an individual patient's risk of IIM-associated cancer. The Expert Group formed an initial recommendation that identifies IIM subtypes, autoantibodies, and clinical features associated with “high”, “intermediate”, and “low” risk of IIM associated cancer. The Expert Group also formed three subsequent recommendations that allow clinicians to assign an individual patient as having “high”, “moderate”, or “standard” overall risk of IIM-associated cancer, based on their IIM subtype, autoantibody status, and clinical features. It is important to note that these risk categories are in comparison to the overall IIM population, not the general population;

indeed, those with “standard” risk of IIM-associated cancer will likely have a higher risk compared to the general population. Empirical comparison of cancer risk between the standard risk group and the general population has not yet been carried out and is clearly warranted.

Seven high risk factors (one subtype, two autoantibodies, four clinical features) were identified by the Expert Group. Dermatomyositis (DM) is consistently associated with the highest cancer risk, compared to other subtypes; our recent meta-analysis identified a risk ratio (RR) of 2.21 (95% CI 1.78, 2.77), indicating that DM cancer risk is more than double that of other IIM subtypes. A large number of observational studies exist that detail cancer risk for each IIM subtype. A large body of evidence has characterised the high cancer risk associated with anti-TIF1-gamma positivity, hence inclusion as a high risk factor with a RR of 4.68, indicating that risk of cancer is over four times higher for adults with anti-TIF1-gamma positive IIM, compared to those that are anti-TIF1-gamma negative. Anti-NXP2 positivity has also been associated with increased risk of cancer, however it is considered lower risk than that of anti-TIF1-gamma. It is important to note that a number of studies associating anti-NXP2 positivity with increased risk of cancer employed the general population, not an IIM cohort, as a comparator group^{23,24}. Our meta-analysis, which employed the wider IIM cohort as a comparator group, identified no association of anti-NXP2 positivity with cancer (RR 1.16, 95% CI 0.73, 1.87)⁹. However, the Expert Group deemed the available evidence sufficient to categorise anti-NXP2 positivity as a high risk factor. Older age at time of IIM onset is associated with increased cancer risk. Selection of a specific age threshold is challenging due to the probable incremental risk that older age of IIM-onset confers; a threshold of 40 years was chosen due to the clear age cut-off for cancer development identified in studies of anti-TIF1-gamma positive adults^{25,26}. It is important to note that no clear age cut-off has been established in the context of other autoantibody profiles and an incremental risk with increasing age is likely, however the 40 year threshold was selected for clarity across all patients regardless of clinical features and autoantibody status. The accuracy of this age threshold will be assessed in future research into the utility of the guideline. Features of persistent high disease activity despite immunosuppressive therapy was deemed by the Expert Group to be associated with a high risk of cancer. Evidence exists to support the relationship between persistent high disease activity, including myositis and skin involvement²⁷⁻²⁹, and increased cancer risk, especially when associated with anti-TIF1-gamma positivity; however overall the body of evidence is limited. Dysphagia, especially when treatment-refractory, has been associated with cancer, hence being deemed a high risk factor by the Expert Group. The mechanism between dysphagia and increased IIM-associated cancer risk is not clear, however may represent a manifestation of persistent high disease activity. Finally, cutaneous necrosis/ulceration, which has been associated with increased risk of cancer, potentially due to the association with severe refractory DM, was deemed a high risk factor by the Expert Group.

Eight intermediate risk factors (three subtypes, four autoantibodies, one clinical feature) were identified by the Expert Group. The subtypes clinically amyopathic DM (CADM), polymyositis (PM), and immune-mediated necrotising myopathy (IMNM) were assigned as being associated with intermediate cancer risk; evidence suggests that the risk of cancer in these IIM subtypes is lower than that of DM, but higher than that of anti-synthetase

syndrome (ASSD) and “overlap IIM”. Definition of PM is challenging with recent studies indicating patients may be more appropriately classified as other IIM subtypes such as IBM, IMNM, and ASSD^{30,31}. PM is still a commonly diagnosed condition however, therefore the Expert Group agreed its inclusion as an intermediate cancer risk factor. CADM is less commonly associated with cancer, compared to DM, however the evidence base is limited. Overall, IMNM was classified as an intermediate cancer risk factor by the Expert Group. Recognising the results of a study by Allenbach et al³², the Expert Group deemed it appropriate to distinguish cancer risk for IMNM patients according to MSA positivity, with anti-HMGCR positivity assigned as an “intermediate” risk factor and anti-SRP positivity a “low” risk factor. The study by Allenbach et al, however, identified different cancer risks for anti-SRP, anti-HMGCR, and autoantibody negative IMNM cohorts using the general population, not an IIM cohort, as a comparator group. Male sex, anti-MDA5, anti-Mi2, and anti-SAE1 positivity were assigned as “intermediate” risk factors by the Expert Group in light of the results of our meta-analysis. In particular, anti-MDA5, anti-Mi2, and anti-SAE1 positivity were assigned as intermediate risk factors due to their non-significant association with cancer in the meta-analysis and in comparison to the significantly reduced cancer risk associated with anti-Jo1.

Nine low risk factors (two subtypes, four autoantibodies, three clinical feature) were identified by the Expert Group. Our meta-analysis and other evidence indicates a low risk of cancer for patients with ASSD, ASSD-associated clinical features (i.e. ILD, inflammatory arthropathy, and Raynaud’s phenomenon), and MSAs (i.e. anti-Jo1), and patients with overlap/CTD-associated IIM.

Three recommendations address estimation of risk of IIM-associated cancer according to combination of IIM subtype, clinical features, and MSAs: patients with two high risk factors are deemed to have high risk, patients with one high risk factor or two intermediate risk factors are deemed to have moderate risk, and the remainder have standard risk. It is important to note that this combination is based on expert opinion and available observational evidence, rather than empirical evidence quantifying cancer risk according to each combination. Examples of individual patient IIM-associated cancer risk stratification below illustrate the implementation of these recommendations:

Example 1:

A 70 year old female with anti-NXP2 positive DM who initially developed symptoms 6 months previously would be classified as having “high” risk, due to fulfilment of three individual high risk factors (DM, anti-NXP2 positivity, age >40 years at the time of onset).

Example 2:

A 52 year old female with anti-HMGCR positive IMNM who developed symptoms three months previously would be classified as having “moderate” risk, due to fulfilment of two individual intermediate risk factors (IMNM, anti-HMGCR positivity).

Example 3:

A 26 year old male with anti-Jo1 positive ASSD who developed. symptoms two months previously would be classified as having “standard” risk, due to non-fulfilment of moderate or high risk criteria.

9 - “Basic cancer screening” should include the following investigations (in addition to country/region-specific age and sex appropriate cancer screening programmes for the general population):

- a. Comprehensive history
- b. Comprehensive physical examination
- c. Complete blood count
- d. Serum liver function tests
- e. Serum erythrocyte sedimentation rate/plasma viscosity
- f. Serum C-reactive protein
- g. Serum protein electrophoresis and free light chains measurement
- h. Urinalysis
- i. Plain chest X-ray radiograph (CXR)

1, C, 50, 7 (6, 8)

10 - “Enhanced cancer screening” should include the following investigations:

- a. Computed tomography (CT) scan of the neck, thorax, abdomen, and pelvis
- b. Cervical screening (i.e. smear test)*
- c. Mammography*
- d. Prostate-specific antigen (PSA) blood test*
- e. CA-125 blood test
- f. Pelvic/trans-vaginal ultra sound scan (USS) for ovarian cancer
- g. Faecal occult blood*

*If not already part of country/region-specific age and sex appropriate screening programmes.

1, C, 51, 8 (7, 8)

11 - Adult IIM patients at “standard risk of IIM-related cancer” should undergo “basic cancer screening” at the time of IIM diagnosis. This is in addition to country/region-specific age and sex appropriate screening programmes for the general population.

1, NA, 67, 8 (7, 9)

12 - Adult IIM patients at “moderate risk of IIM-related cancer” should undergo “basic screening” and “enhanced screening” at the time of IIM diagnosis.

1, NA, 66, 8 (7, 9)

13 - Adult IIM patients at “high risk of IIM-related cancer” should undergo “enhanced screening” and “basic screening” at the time of diagnosis and “basic screening” annually for three years.

1, NA, 67, 8 (7, 9)

The Expert Group deemed it appropriate to form two “panels” of screening approaches/modalities - basic and enhanced, beyond age and gender based general population screening. The basic screening panel aims to facilitate clinicians’ ability to identify clinical features potentially consistent with IIM-associated cancer, such as iron deficiency anaemia indicating colon cancer, monoclonal gammopathy indicating multiple myeloma, and CXR-visible lung cancer.

The enhanced screening panel was formulated to facilitate the identification of the most common IIM-associated cancers, such as breast, lung, and ovarian cancer. Patients may have undergone a number tests as part of country/region-specific age and sex appropriate screening programmes, such as mammography or prostate-specific antigen (PSA) level measurement; clinicians should balance the benefits of repeating such investigations against risks on an individual patient basis in the context of cancer risk. Clinicians should also consider the potential increased cancer risk due to investigations that involve radiation exposure, such as CT-based investigations.

The Expert Group formed recommendations relating to the timing and frequency of carrying out basic and enhanced screening according to IIM-associated cancer risk category (see Figure 1 for flowchart detailing risk stratification). Screening should be carried out for patients diagnosed within three years after IIM symptom onset; recommendations therefore do not apply to those diagnosed after this time period. These recommendations are based on expert opinion only; no study has empirically investigated the utility of the timing and frequency of these specific panels of basic and enhanced screening, hence the inability to ascribe an evidence quality grading.

Recommendations apply only to adult patients diagnosed with IIM within the three year period after symptom onset

14 - Clinicians should consider carrying out an ^{18}F -FDG PET/CT scan for adult IIM patients at “high risk of IIM-related cancer” where underlying cancer has not been detected by investigations at the time of IIM diagnosis.

2, C, 67, 8 (7, 9)

15 - Clinicians should consider carrying out an ^{18}F -FDG PET/CT scan as a single screening investigation for anti-TIF1-gamma positive DM patients with disease onset >40 years with ≥ 1 additional high risk clinical feature.

2, C, 67, 8 (7, 9)

A growing body of evidence demonstrates the utility of ^{18}F -FDG PET/CT as a screening modality for IIM-associated cancer³³⁻³⁷. The Expert Group deemed it appropriate to form a conditional recommendation relating to the use of ^{18}F -FDG PET/CT scanning as a screening method only in those with “high” risk of cancer where basic and enhanced panels have not identified a cancer, especially if lymphoma is suspected. Evidence has also shown that ^{18}F -FDG PET/CT can identify cancers at a comparable rate to a large number of conventional screening investigations, including complete physical examination, laboratory tests (complete blood count and serum chemistry panel), thoraco-abdominal CT scan, tumour markers (CA125, CA19-9, CEA, PSA), gynaecological examination, ovarian ultrasonography and mammography³⁴. The Expert Group therefore agreed that ^{18}F -FDG PET/CT could be considered as a single screening method in patients with DM onset >40 years with anti-TIF1-gamma positivity and ≥ 1 additional high risk clinical feature, thus potentially facilitating an earlier diagnosis and the need for fewer investigations. Clinicians should, however, balance the increased cancer risk attributed to ^{18}F -FDG PET/CT-related radiation exposure against the benefit of potential cancer detection. The Expert Group also acknowledged that ^{18}F -FDG PET/CT may not be available in all healthcare systems.

16 - Clinicians should consider carrying out upper and lower gastro-intestinal endoscopy for adult IIM patients at “high risk of IIM-related cancer” where underlying cancer has not been detected by investigations at the time of IIM diagnosis.

2, D, 67, 8 (7, 9)

The gastro-intestinal (GI) tract is a common site of cancer in people with IIM-associated cancer. Evidence relating to the utility of upper and lower GI endoscopy as a cancer screening modality in patients with IIM is limited and confers potential risks (e.g. bowel perforation), thus resulting in the Expert Group forming a conditional recommendation^{33,38,39}. Upper and lower GI endoscopy should be considered after other cancer screening investigations, including basic and enhanced screening panels, have been carried out in adult IIM patients at high risk of IIM-related cancer. The Expert Group recognised that upper and/or lower GI endoscopy may be carried out as part of country/region-specific age and sex appropriate cancer screening programmes.

17 - Clinicians should consider carrying out naso-endoscopy at the time of diagnosis in adult IIM patients in geographical regions where risk of nasopharyngeal carcinoma is increased.

2, D, 67, 8 (7, 9)

Nasopharyngeal cancer is a leading site of IIM-associated cancer in certain populations, especially those of East Asian and South-East Asian heritage; a recent meta-analysis estimated nasopharyngeal cancer prevalence in adults with DM of 37% in Hong Kong, 28% in Malaysia, and 12% in Singapore⁴⁰. Consideration of naso-endoscopy is therefore advocated as a cancer screening modality for patients at high risk of nasopharyngeal cancer.

18 - Clinicians should consider cancer screening in all IIM patients with the following “red-flag” symptoms/clinical features, regardless of risk category:

- Unintentional weight loss

- Family history of cancer
- Smoking
- Unexplained fever
- Night sweats

2, D, 66, 9 (7, 9)

The Expert Group recognised that identification of certain “red-flag” symptoms/clinical features may aid clinicians in identifying patients with underlying IIM-associated cancer. Clinicians should identify organ-specific features of cancer during the comprehensive history and examination (recommendation 9), such as haemoptysis (i.e. lung cancer) and dysphagia (i.e. oesophageal cancer).

Discussion

The International Guideline for IIM-Associated Cancer Screening provides, for the first time, evidence supported and consensus-based recommendations addressing individual patient IIM-associated cancer risk stratification, cancer screening modalities, and screening frequency.

The recommendations provide practical guidance for clinicians serving IIM populations across varying countries and health systems. Implementation of the recommendations aim to facilitate early IIM-associated cancer detection, especially in those with high risk, thus potentially improving outcomes, including survival. The recommendations can help standardise cancer screening practices for IIM patients across the globe, especially benefitting those without access to specialist services. Recommendations can foster open and clear clinician-patient discussions regarding individualised cancer risk and facilitate shared decision making.

There are a number of strengths of this guideline. Firstly, recommendations were developed via a process that assimilated current evidence, results of a meta-analysis, and experts’ experience and expertise, thus maximising the applicability of recommendations into clinical care. Secondly, recommendations were formed by a large (N=75) Expert Group with academic expertise in IIM management (rheumatology, neurology, respiratory medicine, and dermatology) and cancer screening. Members of the Expert Group were located in a wide variety of countries with varying health systems and populations, thus ensuring international applicability. Thirdly, formation of recommendations via an online questionnaire using the Delphi process conferred a number of benefits: 1) assurance of anonymity, thus reducing peer influence, 2) equal weighting of each response, 3) practicality of response collation, thus facilitating involvement of international Expert Group members without the need for a face-to-face meeting. Finally, input from three patient partners allowed for the guidelines to be assessed from a practical perspective with the added benefit of improving engagement and integration into clinical systems.

This study has a number of limitations. Firstly, the evidence base pertaining to the utility of IIM-associated cancer screening approaches is markedly limited, thus reducing the strength

of recommendations. Indeed, no recommendation had “high (A)” quality of supporting evidence, thus highlighting the pressing need for high quality studies that can strengthen the evidence base and inform future iterations of this guideline. Secondly, although the Expert Group comprised members from 22 countries, geographic diversity was limited with representation from a limited number of countries/regions (27 members from USA, 30 from Europe). Specifically, no Expert Group member practiced in any country from Africa, only one member was from China, one from South America, and no members were from Indonesia or Pakistan, which have the fourth and fifth largest populations in the world. This disparity illustrates the international distribution of IIM specialists and future iterations of this guideline should ensure wider inclusion, where possible. Indeed, implementation of recommendations may not be possible in all countries and health systems, especially in resource-challenged areas; future iterations of the guideline should aim to address identified disparities. Finally, the definition of cancer risk groups was based on available evidence, not empirical research. Future research focusing upon the ability of the risk stratification groups to accurately differentiate and predict cancer development is warranted and will influence subsequent iterations of this guideline.

The guideline development process has highlighted a number of unmet needs, thus facilitating the formation of a research agenda. Firstly, the utility of the cancer screening recommendations have not been empirically investigated; research addressing this topic could guide future iterations and improve clinicians’ ability to detect cancer. Secondly, no study investigated the utility of repeated screening or determined optimal screening frequency; research specifically addressing the optimal frequency and/or interval of screening, especially CT scanning of the thorax, abdomen, and pelvis, could greatly enhance cancer detection. Thirdly, future research investigating complications or harm resulting from this guideline’s recommendations is vital; for example, identification of the number of false-positive cancer diagnoses and any resulting harm via recommended screening will be key in the formation of future iterations of the guideline.

It is anticipated that revision of this guideline after a five year period will be appropriate, thus allowing inclusion of emerging research and findings into the evidence base upon which recommendations can be revised and created.

An audit tool, developed by the Steering Committee, is included (Supplementary Material) to allow clinicians and clinical teams to measure their concordance with recommendations, thus aiding service quality improvement.

In conclusion, this International Guideline for IIM-Associated Cancer Screening provides guidance to clinicians and patients regarding individual patient risk stratification, cancer screening modalities, and screening frequency. The guideline standardises patient care and provides a foundation upon which future IIM-cancer screening research can build.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was developed and conducted under the auspices of the International Myositis Assessment and Clinical Studies Group (IMACS). R.A. conceived the guideline development process. A.G.S.O carried out survey question design, distribution, and response collation. A.G.S.O and R.A. led preparation of the manuscript, which was critically appraised and amended by all co-authors. All co-authors completed surveys that led to recommendation formation.

The authors would like to acknowledge the input of the following, who provided input on the systematic literature review and meta-analysis, which formed as key evidence for recommendation development: Dr Andrew B. Allard, Dr Michael D. George, Dr Kate Kolstad, Dr Drew J. B. Kurtzman, and Dr Anna Postolova.

The authors would like to acknowledge the invaluable input from three patient partners (two listed as authors, one anonymous) during the guideline planning, development, and manuscript writing.

The authors would like to thank members of the IMACS Scientific Committee for critical reading of the manuscript.

The authors would like to thanks Dr Hanna Kim and Dr Iago Pinal Fernández for critical reading the manuscript and providing helpful comments as part of the NIH internal review process.

Funding

This report includes independent research supported by the National Institute for Health Research Biomedical Research Centre Funding Scheme. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research or the Department of Health and Social Care.

A.G.S.O is supported by funding from the National Institute for Health Research Clinical Lectureship Scheme.

A.G.S.O, H.C., E.J.C., D.G.R.E., L.McW., and P.A.J.C are supported by the NIHR Manchester Biomedical Research Centre (NIHR203308).

P.M.M is supported by funding from the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

S.T. is supported by funding from the Bath Institute of Rheumatic Diseases.

E.J.C. is supported by a National Institute for Health Research Advanced Fellowship (NIHR300650).

This research was supported in part by the Intramural Research Programs of the NIH, National Institute of Environmental Health Sciences (to L.G.R., F.W.M., and A.S.), and National Institute of Arthritis and Musculoskeletal and Skin Diseases (to A.M.).

J.J.P. is supported by funding from the NIH (K23AR073927).

M.VDM. is supported by funding from Fondo de Desarrollo Científico (FODECIJAL) 2019 from Consejo Estatal de Ciencia y Tecnología de Jalisco (COECYTJAL, 1702512-8152).

J.V. is supported by funding from the Czech Ministry of Health - Conceptual Development of Research Organization 00023728 (Institute of Rheumatology).

International Myositis Assessment and Clinical Studies Group Cancer Screening Expert Group

Anthony A. Amato^{18, 23}, Helena Andersson²⁴, Lilia Andrade-Ortega^{25, 26}, Dana Ascherman²², Olivier Benveniste^{27, 28}, Lorenzo Cavagna^{29, 30}, Christina Charles-Shoeman³¹, Benjamin F. Chong³², Lisa Christopher-Stine³³, Jennie T. Clarke³⁴, Emma J. Crosbie^{1, 35, 36}, Philip A. J. Crosbie^{1, 37}, Sonye Danoff³⁸, Maryam Dastmalchi³⁹, Marianne De Visser⁴⁰, Paul Dellaripa^{18, 41}, Louise Pyndt Diederichsen^{42, 43}, Mazen M. Dimachkie

⁴⁴, Erik Ensrud ⁴⁵, Floranne Ernste ⁴⁶, D. Gareth R. Evans ^{1, 47}, Manabu Fujimoto ⁴⁸, Ignacio Garcia-De La Torre ⁴⁹, Abraham Garcia-Kutzbach ⁵⁰, Zoltan Griger ⁵¹, Latika Gupta ^{3, 52, 53}, Marie Hudson ⁵⁴, Florenzo Iannone ⁵⁵, David Isenberg ^{10, 12, 56}, Joseph Jorizzo ⁵⁷, Helen Kurtz ⁵⁸, Masataka Kuwana ⁵⁹, Vidya Limaye ^{60, 61}, Ingrid E. Lundberg ³⁹, Andrew L. Mammen ^{33, 62}, Herman Mann ^{63, 64}, Frank Mastaglia ⁶⁵, Lorna McWilliams ^{1, 66}, Christopher A. Mecoli ³³, Federica Meloni ^{29, 67}, Frederick W. Miller ⁶⁸, Siamak Moghadam-Kia ²², Sergey Moiseev ⁶⁹, Yoshinao Muro ⁷⁰, Melinda Nagy-Vincze ⁷¹, Clive Nayler ⁵⁸, Merrilee Needham ^{72, 73, 74}, Ichizo Nishino ^{75, 76}, Chester V. Oddis ²², Julie J. Paik ³³, Joost Raaphorst ⁴⁰, Lisa G. Rider ⁶⁸, Jorge Rojas-Serrano ^{77, 78}, Lesley Ann Saketkoo ^{79, 80, 81, 82}, Adam Schiffenbauer ⁶⁸, Samuel Katsuyuki Shinjo ⁸³, Vineeta Shobha ⁸⁴, Yeong-Wook Song ⁸⁵, Tania Tillett ⁸⁶, Yves Troyanov ^{87, 88}, Anneke J. van der Kooi ⁴⁰, Mónica Vázquez-Del Mercado ^{89, 90}, Jiri Vencovsky ^{63, 64}, Qian Wang ⁹¹, Steven Ytterberg ⁴⁶

²³ Department of Neurology, Brigham and Women's Hospital, Boston, Massachusetts, USA

²⁴ Department of Rheumatology, Oslo University Hospital, Oslo, Norway

²⁵ Department of Rheumatology, Centro Médico Nacional 20 de Noviembre, ISSSTE, Mexico City, México

²⁶ Universidad Nacional Autónoma de México, Mexico City, México

²⁷ Department of Internal Medicine and Clinical Immunology, Assistance Public Hôpitaux de Paris, Paris, France

²⁸ Sorbonne Université, Pitié-Salpêtrière University Hospital, Paris, France

²⁹ Department of Internal Medicine and Therapeutics, Università di Pavia, Pavia, Italy

³⁰ Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

³¹ Department of Medicine, Division of Rheumatology, University of California, Los Angeles, California, USA

³² Department of Dermatology, University of Texas Southwestern Medical Center, Dallas, Texas, USA

³³ Department of Medicine, Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

³⁴ Department of Dermatology, University of Utah School of Medicine, Salt Lake City, Utah, USA

³⁵ Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom

36 Department of Obstetrics and Gynaecology, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

37 Division of Infection, Immunity, and Respiratory Medicine, University of Manchester, Manchester, UK

38 Department of Medicine, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

39 Division of Rheumatology, Department of Medicine, Solna, Karolinska Institutet, and Karolinska University Hospital, Stockholm, Sweden

40 Department of Neurology, Amsterdam University Medical Centres, locatie AMC, University of Amsterdam, Neuroscience institute, Amsterdam, Netherlands

41 Division of Rheumatology, Brigham and Women's Hospital, Boston, Massachusetts, USA

42 Centre for Rheumatology and Spine Diseases, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

43 Department of Rheumatology, Odense University Hospital, Odense, Denmark

44 Department of Neurology, The University of Kansas Medical Center, Kansas City, Kansas, USA

45 Department of Neurology, Department of Physical Medicine and Rehabilitation, University of Missouri School of Medicine, Columbia, Missouri, USA

46 Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA

47 Manchester Centre for Genomic Medicine, Manchester Academic Health Science Centre, Division of Evolution and Genomic Medicine, University of Manchester, St Mary's Hospital, Manchester Universities NHS Foundation Trust, Manchester, UK

48 Department of Dermatology, Osaka University Graduate School of Medicine, Osaka, Japan

49 Department of Immunology and Rheumatology, Hospital General de Occidente and Universidad de Guadalajara, Guadalajara, Mexico

50 Internal Medicine Rheumatology Secion, Francisco Marroquín University, Guatemala City, Guatemala

51 Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

- 52 Department of Rheumatology, Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, UK
- 53 Department of Rheumatology, City Hospital, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
- 54 Division of Rheumatology and Department of Medicine, Jewish General Hospital and McGill University, Montreal, Canada
- 55 Rheumatology Unit, Department of Emergency and Organ Transplantation, University of Bari, Bari, Italy
- 56 Department of Rheumatology, University College London Hospitals NHS Foundation Trust, London, UK.
- 57 Wake Forest University School of Medicine, Winston Salem, North Carolina, USA
- 58 Patient Partner
- 59 Department of Allergy and Rheumatology, Nippon Medical School, Tokyo, Japan
- 60 Rheumatology Department, Royal Adelaide Hospital, Adelaide, South Australia, Australia
- 61 Discipline of Medicine, University of Adelaide, Adelaide, South Australia, Australia
- 62 Muscle Disease Unit, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA
- 63 Institute of Rheumatology, Prague, Czech Republic
- 64 Department of Rheumatology, 1st Medical Faculty, Charles University, Prague, Czech Republic
- 65 Perron Institute for Neurological and Translational Science, Perth, Western Australia, Australia
- 66 Manchester Centre for Health Psychology, Division of Psychology and Mental Health, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK
- 67 Respiratory Disease Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
- 68 Environmental Autoimmunity Group, Clinical Research Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Bethesda, Maryland, USA
- 69 Tareev Clinic of Internal Diseases, Sechenov First Moscow State Medical University, Moscow, Russia

70 Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan

71 Division of Clinical Immunology, Faculty of Medicine, University of Debrecen, Debrecen, Hungary

72 Department of Neurology, Fiona Stanley Hospital, Perth, Western Australia, Australia

73 Centre for Molecular Medicine and Innovative Therapeutics, Murdoch University, Murdoch, Western Australia, Australia

74 School of Medicine, University of Notre Dame, Fremantle, Perth, Western Australia, Australia

75 Department of Neuromuscular Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Tokyo, Japan

76 Department of Genome Medicine Development, Medical Genome Center, National Center of Neurology and Psychiatry, Tokyo, Japan

77 Clínica de Reumatología, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico

78 Programa de Maestría y Doctorado en Ciencias Médicas, Facultad de Medicina, Universidad Nacional Autónoma de México, Mexico City, Mexico

79 Scleroderma and Sarcoidosis Patient Care and Research Center, Department of Medicine, Section of Rheumatology, LSU Health Sciences Center, New Orleans, Louisiana, USA

80 Comprehensive Pulmonary Hypertension Center, University Medical Center, New Orleans, Louisiana, USA

81 Tulane University School of Medicine, New Orleans, Louisiana, USA

82 Louisiana State University School of Medicine, New Orleans, Louisiana, USA

83 Division of Rheumatology, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Sao Paulo, Brazil

84 Department of Clinical Immunology and Rheumatology, St John's Medical College Hospital, St John's National Academy of Medical Sciences, Bangalore, India

85 Department of Internal Medicine, College of Medicine, Medical Research Center, Institute of Human-Environment Interface Biology, Seoul National University, Seoul, South Korea

86 Department of Oncology, Royal United Hospitals NHS Foundation Trust Bath, Bath, UK

87 Department of Medicine, University of Montreal, Montreal, Québec, Canada

88 Division of Rheumatology, Hôpital du Sacré-Coeur, Montreal, Québec, Canada

89 Servicio de Reumatología, Hospital Civil Dr. Juan I. Menchaca, Guadalajara, Mexico

90 Instituto de Investigación en Reumatología y del Sistema Músculo Esquelético, Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Guadalajara, Mexico

91 Department of Rheumatology and Clinical Immunology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

References

1. Oldroyd A, Lilleker J & Chinoy H Idiopathic inflammatory myopathies - a guide to subtypes, diagnostic approach and treatment. *Clin. Med. (Northfield. Il)* 17, (2017).
2. Chinoy H & Cooper RG Polymyositis and dermatomyositis. in *Oxford Textbook of Rheumatology 1009–1020* (Oxford University Press, 2013). doi:10.1093/med/9780199642489.003.0124_update_001
3. Qiang JK, Kim WB, Baibergenova A & Alhusayen R Risk of malignancy in dermatomyositis and polymyositis: A systematic review and meta-analysis. *J. Cutan. Med. Surg* 21, 131–136 (2017). [PubMed: 27534779]
4. Dobloug GC, Garen T, Brunborg C, Gran JT & Molberg Ø Survival and cancer risk in an unselected and complete Norwegian idiopathic inflammatory myopathy cohort. *Semin. Arthritis Rheum* 45, 301–308 (2015). [PubMed: 26190563]
5. Kang EH et al. Temporal relationship between cancer and myositis identifies two distinctive subgroups of cancers: impact on cancer risk and survival in patients with myositis. *Rheumatology (Oxford)*. 55, 1631–41 (2016). [PubMed: 27247435]
6. Hočvar A. et al. Survival of Patients With Idiopathic Inflammatory Myopathies in Slovenia. *Front. Med* 8, 801078 (2021).
7. Dobloug GC, Svensson J, Lundberg IE & Holmqvist M Mortality in idiopathic inflammatory myopathy: Results from a Swedish nationwide population-based cohort study. *Ann. Rheum. Dis* 77, 40–47 (2018). [PubMed: 28814428]
8. Nuño-Nuño L. et al. Mortality and prognostic factors in idiopathic inflammatory myositis: a retrospective analysis of a large multicenter cohort of Spain. *Rheumatol. Int* 37, 1853–1861 (2017). [PubMed: 28866745]
9. Oldroyd AGS et al. A systematic review and meta-analysis to inform cancer screening guidelines in idiopathic inflammatory myopathies. *Rheumatology* 60, 2615–2628 (2021). [PubMed: 33599244]
10. Moher D, Liberati A, Tetzlaff J & Altman DG Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med.* 6, e1000097 (2009). [PubMed: 19621072]
11. Scottish Intercollegiate Guidelines Network. SIGN 50 - A Guideline Developer's Handbook. (2011).
12. Gunawardena H. et al. Clinical associations of autoantibodies to a p155/140 kDa doublet protein in juvenile dermatomyositis. *Rheumatology* 47, 324–328 (2007).
13. Sato JDO et al. A Brazilian registry of juvenile dermatomyositis: Onset features and classification of 189 cases. *Clin. Exp. Rheumatol* 27, 1031–1038 (2009). [PubMed: 20149327]
14. Na SJ, Kim SM, Sunwoo IN & Choi YC Clinical characteristics and outcomes of juvenile and adult dermatomyositis. *J. Korean Med. Sci* 24, 715–721 (2009). [PubMed: 19654958]
15. Dawkins MA et al. Dermatomyositis: a dermatology-based case series. *J. Am. Acad. Dermatol* 38, 397–404 (1998). [PubMed: 9520020]
16. Sun C. et al. Juvenile dermatomyositis: A 20-year retrospective analysis of treatment and clinical outcomes. *Pediatr. Neonatol* 56, 31–39 (2015). [PubMed: 24985888]

17. Ponyi A. et al. Cancer-associated myositis: clinical features and prognostic signs. *Ann. N. Y. Acad. Sci* 1051, 64–71 (2005). [PubMed: 16126945]
18. Morris P & Dare J Juvenile dermatomyositis as a paraneoplastic phenomenon: An update. *J. Pediatr. Hematol. Oncol* 32, 189–191 (2010). [PubMed: 20057323]
19. Limaye V. et al. The incidence and associations of malignancy in a large cohort of patients with biopsy-determined idiopathic inflammatory myositis. *Rheumatol. Int* 33, 965–971 (2013). [PubMed: 22833242]
20. Greenberg SA, Pinkus JL, Amato AA, Kristensen T & Dorfman DM Association of inclusion body myositis with T cell large granular lymphocytic leukaemia. *Brain* 139, 1348–1360 (2016). [PubMed: 26920676]
21. Greenberg SA et al. Highly differentiated cytotoxic T cells in inclusion body myositis. *Brain* 142, 2590–2604 (2019). [PubMed: 31326977]
22. Ebell MH, Thai TN & Royalty KJ Cancer screening recommendations: An international comparison of high income countries. *Public Health Reviews* 39, (2018).
23. Yang H. et al. Identification of multiple cancer-associated myositis-specific autoantibodies in idiopathic inflammatory myopathies: A large longitudinal cohort study. *Arthritis Res. Ther* 19, (2017).
24. Ichimura Y. et al. Anti-nuclear matrix protein 2 antibody-positive inflammatory myopathies represent extensive myositis without dermatomyositis-specific rash. *Rheumatology* 61, 1222–1227 (2022). [PubMed: 34152410]
25. Fujimoto M. et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. *Arthritis Rheum.* 64, 513–522 (2012). [PubMed: 21987216]
26. Oldroyd A. et al. The temporal relationship between cancer and adult onset anti-transcriptional intermediary factor 1 antibody-positive dermatomyositis. *Rheumatol. (United Kingdom)* 58, (2019).
27. Targoff IN et al. A novel autoantibody to a 155-kd protein is associated with dermatomyositis. *Arthritis Rheum.* 54, 3682–3689 (2006). [PubMed: 17075819]
28. Ikeda N. et al. Clinical significance of serum levels of anti-transcriptional intermediary factor 1- γ antibody in patients with dermatomyositis. *J. Dermatol* 47, 490–496 (2020). [PubMed: 32103537]
29. Ly NTM et al. Clinical and laboratory parameters predicting cancer in dermatomyositis patients with anti-TIF1 γ antibodies. *J. Dermatol. Sci* 104, 177–184 (2021). [PubMed: 34772582]
30. Loarce-Martos J, Lilleker JB, Parker M, McHugh N & Chinoy H Polymyositis: is there anything left? A retrospective diagnostic review from a tertiary myositis centre. *Rheumatology* (2020). doi:10.1093/rheumatology/keaa801
31. Mariampillai K. et al. Development of a New Classification System for Idiopathic Inflammatory Myopathies Based on Clinical Manifestations and Myositis-Specific Autoantibodies. *JAMA Neurol.* 75, 1528–1537 (2018). [PubMed: 30208379]
32. Allenbach Y. et al. High risk of cancer in autoimmune necrotizing myopathies: Usefulness of myositis specific antibody. *Brain* 139, 2131–2135 (2016). [PubMed: 27086869]
33. Maliha PG, Hudson M, Abikhzer G, Singerman J & Probst S ¹⁸F-FDG PET/CT versus conventional investigations for cancer screening in autoimmune inflammatory myopathy in the era of novel myopathy classifications. *Nucl. Med. Commun* 40, 377–382 (2019). [PubMed: 30664602]
34. Selva-O'Callaghan A. et al. Conventional Cancer Screening versus PET/CT in Dermatomyositis/Polymyositis. *Am. J. Med* 123, 558–562 (2010). [PubMed: 20569766]
35. Trallero-Araguás E. et al. Cancer screening in idiopathic inflammatory myopathies: Ten years experience from a single center. *Semin. Arthritis Rheum* 53, 151940 (2022). [PubMed: 35051890]
36. Li Y, Zhou Y & Wang Q Multiple values of ¹⁸F-FDG PET/CT in idiopathic inflammatory myopathy. *Clin. Rheumatol* 36, 2297–2305 (2017). [PubMed: 28831580]
37. Bradhurst P, Limaye S & Kane B Review of Cancer Screening Investigations in New Diagnoses of Idiopathic Inflammatory Myopathies at a Single Tertiary Hospital. *J. Clin. Rheumatol* 28, E274–E277 (2022). [PubMed: 33264255]
38. Leatham H. et al. Evidence supports blind screening for internal malignancy in dermatomyositis: Data from 2 large US dermatology cohorts. *Medicine (Baltimore)*. 97, e9639 (2018). [PubMed: 29480875]

39. Sparsa A. et al. Routine vs extensive malignancy search for adult dermatomyositis and polymyositis: A study of 40 patients. *Arch. Dermatol* 138, 885–890 (2002). [PubMed: 12071815]
40. Irekeola AA et al. Prevalence of nasopharyngeal carcinoma in patients with dermatomyositis: A systematic review and meta-analysis. *Cancers* 13, (2021).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

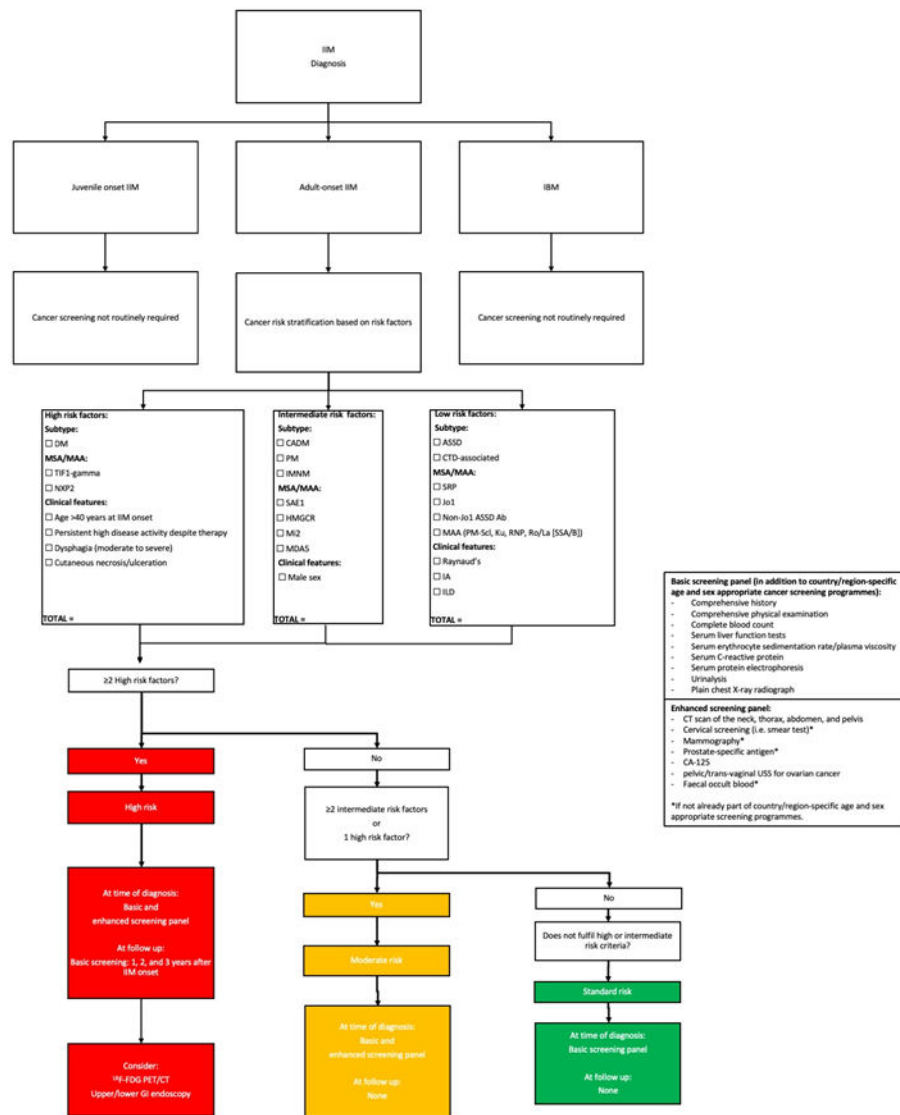


Figure 1 –. Flowchart of cancer risk stratification and frequency of screening

Abbreviations:

DM = dermatomyositis

PM = polymyositis

IMNM = immune-mediated necrotising myopathy

CADM = clinically amyopathic dermatomyositis

NXP2 = nuclear matrix protein 2

TIF1-gamma = transcriptional intermediary factor 1

SAE1 = small ubiquitin-like modifier-1 activating enzyme

HMGCR = 3-hydroxy 3-methylglutaryl coenzyme A reductase

MDA5 = melanoma differentiation-associated gene 5

IIM = idiopathic inflammatory myopathy

SRP = signal recognition particle

ASSD = anti-synthetase syndrome

RNP = ribonucleoprotein

CT = computed tomography

USS = ultrasound scan

^{18}F -FDG PET/CT = [^{18}F]-fluoro-deoxy-glucose positron emission tomography/computed tomography

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1 -

Summary of all recommendations from the International Guideline for Idiopathic Inflammatory Myopathy-Associated Cancer Screening

Recommendation	Strong/ conditional	Level of evidence (GRADE) [†]	Consensus	
			No. responses	Median score (IQR)
1 - Screening for IIM-associated cancer is not routinely required in patients with juvenile-onset IIM	Strong	Moderate	62	8 (8, 9)
2 - Screening for IIM-associated cancer is not routinely required in patients with verified inclusion body myositis	Strong	Moderate	62	8 (7, 9)
3 - All IIM patients, irrespective of cancer risk, should continue to participate in country/region-specific age and sex appropriate cancer screening programmes	Strong	Moderate	64	9 (9, 9)
4 - All adult patients with new onset IIM should be tested for myositis-specific autoantibodies and myositis-associated autoantibodies to assist stratification of cancer risk.	Strong	Moderate	64	9 (8, 9)
5 - Underlying cancer risk of adult IIM patients should be stratified according to IIM subtype, autoantibody status, and clinical features in the following manner: High risk - a. DM b. Anti-TIF1-gamma positivity c. Anti-NXP2 positivity d. Age >40 years at the time of onset e. Features of persistent high disease activity despite immunosuppressive therapy (including relapse of previously controlled disease) f. Dysphagia (moderate to severe) g. Cutaneous necrosis/ulceration Intermediate risk - a. CADM b. PM c. IMNM d. Anti-SAE1 positivity e. Anti-HMGCR positivity f. Anti-Mi2 positivity g. Anti-MDA5 positivity h. Male sex Low risk - a. ASSD b. Overlap IIM/connective tissue disease-associated myositis c. Anti-SRP positivity d. Anti-Jo1 positivity e. Non-Jo1 ASSD antibody positivity f. Myositis-associated antibody positivity (PM-Scl, Ku, RNP, Ro/La [SSA/B]) g. Raynaud's phenomenon	Strong	Moderate	52	8 (7, 9)

Recommendation	Strong/ conditional	Level of evidence (GRADE) [†]	Consensus	
			No. responses	Median score (IQR)
h. Inflammatory arthropathy i. Interstitial lung disease				
6 - Adult IIM patients with two or more “high risk” factors (subtype, autoantibody, or clinical feature) should be considered to have a “high risk for IIM-related cancer”. [§]	Strong	Moderate	67	8 (8, 9)
7 - Adult IIM patients with two or more “intermediate risk” factors (subtype, autoantibody, or clinical feature) or only one “high risk” factor (subtype, autoantibody, or clinical feature) should be considered to have an “moderate risk for IIM-related cancer”. [§]	Strong	Moderate	67	7 (7, 9)
8 - Adult IIM patients that do not fulfil the “high” or “moderate risk” definitions should be considered to have “standard risk for IIM-related cancer”. [§]	Strong	Moderate	67	8 (7, 9)
9 - “Basic cancer screening” should include the following investigations (in addition to country/region-specific age and gender appropriate cancer screening programmes for the general population): a. Comprehensive history b. Comprehensive physical examination c. Complete blood count d. Serum liver function tests e. Serum erythrocyte sedimentation rate/plasma viscosity f. Serum C-reactive protein g. Serum protein electrophoresis and free light chains measurement h. Urinalysis i. Plain chest X-ray radiograph	Strong	Low	50	7 (6, 8)
10 - “Enhanced cancer screening” should include the following investigations: a. CT scan of the neck, chest, abdomen, and pelvis b. Cervical screening (i.e. smear test) [*] c. Mammography [*] d. Prostate-specific antigen [*] e. CA-125 f. Pelvic/trans-vaginal USS for ovarian cancer g. Faecal occult blood [*] *If not already part of country/region-specific age and sex appropriate screening programmes.	Strong	Low	51	8 (7, 8)
11 - Adult IIM patients at “standard risk of IIM-related cancer” should undergo “basic cancer screening” at the time of IIM diagnosis. This is in addition to country/region-specific age and sex appropriate screening programmes for the general population.	Strong	NA [*]	67	8 (7, 9)
12 - Adult IIM patients at “moderate risk of IIM-related cancer” should undergo “basic screening” and “enhanced screening” at the time of IIM diagnosis.	Strong	NA [*]	66	8 (7, 9)
13 - Adult IIM patients at “high risk of IIM-related cancer” should undergo “enhanced screening” and “basic screening” at the time of diagnosis and “basic screening” annually for three years.	Strong	NA [*]	67	8 (7, 9)

Recommendation	Strong/ conditional	Level of evidence (GRADE) †	Consensus	
			No. responses	Median score (IQR)
14 - Clinicians should consider carrying out an ¹⁸ F-FDG PET/CT scan for adult IIM patients at “high risk of IIM-related cancer” where underlying cancer has not been detected by investigations at the time of IIM diagnosis.	Conditional	Low	67	8 (7, 9)
15 - Clinicians should consider carrying out an ¹⁸ F-FDG PET/CT scan as a single screening investigation for anti-TIF1-gamma positive DM patients with disease onset >40 years with ≥1 additional high risk clinical feature.	Conditional	Low	67	8 (7, 9)
16 - Clinicians should consider carrying out upper and lower gastro-intestinal endoscopy for adult IIM patients at “high risk of IIM-related cancer” where underlying cancer has not been detected by investigations at the time of IIM diagnosis.	Conditional	Very low	67	8 (7, 9)
17 - Clinicians should consider carrying out naso-endoscopy at the time of diagnosis in adult IIM patients in geographical regions where risk of nasopharyngeal carcinoma is increased.	Conditional	Very low	67	8 (7, 9)
18 - Clinicians should consider cancer screening in all IIM patients with the following “red-flag” symptoms/clinical features, regardless of risk category: • Unintentional weight loss • Family history of cancer • Smoking • Unexplained fever • Night sweats	Conditional	Very low	66	9 (7, 9)

† According to Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology

IQR = interquartile range

DM = dermatomyositis

PM = polymyositis

IMNM = immune-mediated necrotising myopathy

CADM = clinically amyopathic dermatomyositis

NXP2 = nuclear matrix protein 2

TIF1-gamma = transcriptional intermediary factor 1

SAE1 = small ubiquitin-like modifier-1 activating enzyme

HMGCR = 3-hydroxy 3-methylglutaryl coenzyme A reductase

MDA5 = melanoma differentiation-associated gene 5

IIM = idiopathic inflammatory myopathy

SRP = signal recognition particle

ASSD = anti-synthetase syndrome

RNP = ribonucleoprotein

CT = computed tomography

USS = ultrasound scan

¹⁸F-FDG PET/CT = [18F]-fluoro-deoxy-glucose positron emission tomography/computed tomography

* These recommendations had no corresponding evidence base and were formed via expert consensus only

[§]Risk categories are in comparison to the IIM population, not the general population

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript