Title: A Clinical Tool to Identify Incidental Meningioma for Early Outpatient Management

Authors: Abdurrahman I. Islim, MPhil, MRCS[1,2]; Christopher P. Millward, PhD, MRCS[3,4]; Rasheed Zakaria, PhD, FRCS (SN)[3,4]; Rory J. Piper, PhD, MRCS[5]; Daniel M. Fountain, DPhil, MRCS[5,6]; Shaveta Mehta, PhD, FRCR[3,7]; Ruwanthi Kolamunnage-Dona, PhD[8]; Usama Ali, DPhil[9]; Shelli D. Koszdin, PharmD[10]; Theo Georgious, MBiol[11]; Ryan K. Mathew, PhD, FRCS (SN)[12,13]; Samantha J. Mills, PhD, FRCR[3,14]; Andrew R. Brodbelt, PhD, FRCS (SN)[3,4]; Thomas Santarius, PhD, FRCS (SN)[15,16]; and Michael D. Jenkinson, PhD, FRCS (SN)[3,4]; on behalf of the IMPACT Study Investigators, International Consortium on Meningioma (ICOM) and British Neurosurgical Trainee Research Collaborative (BNTRC)

Affiliations:

1. Department of Neurosurgery, Geoffrey Jefferson Brain Research Centre, Northern Care Alliance NHS Foundation Trust, Manchester, UK.

2. Division of Immunology, Immunity to Infection and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

3. Institute of Systems, Molecular & Integrative Biology, University of Liverpool, Liverpool, UK

4. Department of Neurosurgery, The Walton Centre NHS Foundation Trust, Liverpool, UK

5. Department of Neurosurgery, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

6. MRC Weatherall Institute of Molecular Medicine, University of Oxford, Oxford, UK

7. Department of Clinical Oncology, The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, UK

8. Department of Health Data Science, Institute of Population Health, University of Liverpool, Liverpool, UK

9. Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

10. Veterans Affairs Healthcare System, Palo Alto, California, USA

11. Brain Tumor Charity, Fleet, UK

12. Leeds Institute of Medical Research at St James's, University of Leeds School of Medicine, Leeds, UK

13. Department of Neurosurgery, Leeds Teaching Hospitals NHS Trust, Leeds, UK

14. Department of Neuroradiology, The Walton Centre NHS Foundation Trust, Liverpool, UK

15. Department of Neurosurgery, Addenbrooke's Hospital, Cambridge, UK

16. Division of Clinical Neurosciences, University of Cambridge, Cambridge, UK

Corresponding author:

Dr Abdurrahman I. Islim

Division of Immunology, Immunity to Infection and Respiratory Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

Telephone and fax: 0161 206 8340. Email: Abdurrahman.Islim@manchester.ac.uk

Key points

Question: Is the Incidental Meningioma: Prognostic Analysis Using Patient Comorbidity and Magnetic Resonance Imaging Tests (IMPACT) tool valid for predicting the risk of incidental meningioma progression, stratifying patients into early intervention, serial monitoring, or safe discharge from outpatient care?

Findings: In this international multicenter cohort study including 1248 patients, the IMPACT tool accurately predicted the risk of incidental meningioma progression; 1 in 2 patients with high-risk disease progressed, compared with 1 in 4 with medium-risk and 1 in 25 low-risk disease. Accordingly, these groups can be stratified into early intervention, serial monitoring, or safe discharge.

Meaning: The IMPACT tool is an externally validated tool that may be used for the management of patients with incidental meningioma.

Abstract

Importance: Incidental meningiomas are common. There is a need for a validated clinical tool to stratify patients into early intervention, serial monitoring, or safe discharge from outpatient care.

Objective: To externally validate the Incidental Meningioma: Prognostic Analysis Using Patient Comorbidity and Magnetic Resonance Imaging Tests (IMPACT) tool.

Design, Setting, and Participants : This retrospective cohort study included 33 centers in 15 countries. Adult patients diagnosed with an incidental meningioma from January 2009 to December 2010 were included, up to the point of intervention, death, or last clinical encounter. Patients with radiation-induced meningioma and NF2-related

schwannomatosis were excluded. Data collection was completed on December 31, 2023. Statistical analysis was conducted between March 2024 and December 2024.

Main Outcomes and Measures: The primary outcome of the study was a composite end point comprising growth, symptom development, meningioma-related mortality, and end points related to loss of window of curability. Secondary end points included the occurrence of an intervention and nonmeningioma-related mortality.

Results: Overall, 1248 patients were included. The median (IQR) age was 66 (55-77) years and 999 were female individuals (80%). There were 945 patients (75.7%) who had 1010 treatment-naive meningiomas. During follow-up (median [IQR], 61 [17-108] months), 114 tumors (11.3%) in 113 patients (12%) progressed, 132 tumors (13.1%) in 126 patients (13.3%) underwent an intervention, and 383 patients (40.5%) died without progression or intervention, from a nonmeningioma-related cause. The 5- and 10-year progression-free survival rates were 88.1% (95% CI, 85.8%-90.5%) and 85.7% (95% CI, 83.2%-88.2%), respectively. A low-risk meningioma had a disease progression risk of 3.9%, compared with 24.2% in medium-risk meningioma, and 51.6% in high-risk meningioma (χ^2 test, $P < .001$). Measures of external validity were adequate (Brier score = 0.12; C-statistic = 0.80; 10-year area under the curve, 0.83) and the addition of other variables in a Cox regression analysis did not confound the statistical significance of the IMPACT tool. Patients with an age-adjusted Charlson Comorbidity Index score of 6 or higher (eg, a patient aged 80 years with type 2 diabetes and a previous myocardial infarction) and a performance status of 2 to 4 (unable to carry out any work activities or in a chair/bed for 50% or more of the day) were more likely to die of other causes than to receive intervention following diagnosis.

Conclusions and Relevance: This cohort study found that the IMPACT tool accurately predicted the risk of incidental meningioma progression and can be used to stratify patients into early intervention, serial monitoring, or safe discharge from outpatient care.

Introduction

Meningioma is the most common incidental finding on magnetic resonance imaging (MRI) of the brain.[1-4] The behavior of incidental meningiomas is variable with natural history studies reporting radiological growth in 38% to 75% of cases, and symptom development in 5% to 8%.[5-7] Patients with an incidental meningioma want to know if their meningioma will grow and require treatment within their lifetime. We previously developed the Incidental Meningioma: Prognostic Analysis Using Patient Comorbidity and MRI Tests (IMPACT) tool to predict disease progression and aid clinical decision-making.[8] The model estimates a risk of progression based on 4 imaging features: meningioma volume, T2-weighted MRI tumor hyperintensity, peritumoral edema, and proximity to critical neurovascular structures. It then estimates the risk of observing a progression event vs competing events such as death from actuarial models based on comorbidity burden and functional status. The aim of this study was to externally validate the IMPACT tool and determine which patients need early intervention, serial monitoring, or can be safely discharged.

Methods

Study design

A peer-reviewed study protocol was previously published.[9] We performed a retrospective cohort study, which included adult patients with an incidental intracranial

meningiomas, diagnosed in January 2009 and December 2010. Data collection started on January 12, 2020. An interim analysis took place in December 2022. Longitudinal clinical and imaging data were collected up to the point of intervention, death, or last recorded clinical encounter. Patients were excluded if they had radiation-induced meningioma, NF2-related schwannomatosis, or missing medical notes/imaging data. The risk of incidental meningioma progression in the development cohort was 10%, and for external validation studies, a minimum of 100 events is required.[8,10] Based on this, data for 1000 patients were sought. Centers were recruited through the British Neurosurgical Trainee Research Collaborative (BNTRC), International Consortium on Meningioma (ICOM), and through direct correspondence with researchers in the field of meningioma. Local institutional approval was obtained at each participating center, and the requirement for individual patient consent was waived. This study is reported according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines.[11]

Study End Points

Primary End Point

Disease progression was a composite end point comprising new symptom development, meningioma-specific mortality, meningioma growth (absolute growth rate [AGR] ≥2 cm^3/y or ≥1 cm^3/y + relative growth rate [RGR] ≥30%/y), development or increase of peritumoral edema, venous sinus invasion, and meningioma volume exceeding 10 cm^3. The first 2 criteria denote clinical progression, whereas the latter 3 are related to loss of window of curability. Venous sinus invasion and peritumoral edema can prevent complete surgical resection.[12,13] Peritumoral edema and a

meningioma volume greater than 10 cm^3 are relative contraindications to stereotactic radiosurgery (SRS).[14,15]

Secondary End Points

Intervention and mortality unrelated to the meningioma were secondary end points.

Data collection and recorded variables

Recorded baseline clinical variables included age, sex, the World Health Organization (WHO) performance status (PS), and age-adjusted Charlson Comorbidity Index (ACCI) score.[16] Baseline and longitudinal imaging data included number of meningiomas at diagnosis, tumor signal intensity on T2-weighted MRI (hypo/iso/hyper), peritumoral edema on T2-weighted MRI (0%-5% [no]/6%-100% [yes]; adapted from the Visually AcceSAble Rembrandt Images features for glioma[17]), meningioma volume (using the ABC/2 formula on contrast-enhanced T1-weighted MRI/computed tomography [CT]: (A) maximum meningioma diameter on axial plane, (B) diameter perpendicular to and (C) maximum height on coronal/sagittal plane, meningioma location (according to the ICOM classification system[18]), proximity to major dural venous sinuses (eg, superior sagittal sinus), categorized into separate (within 10 mm), in direct contact with its wall, or invading, and involvement of critical neurovascular structures (eg, internal carotid artery and optic apparatus). Meningiomas that fulfilled 1 of the 2 previous categories were said to be in proximity to critical neurovascular structures.

Statistical analysis

Details of statistical platforms and packages are provided in eTable 1 in Supplement 1. Demographic differences across groups were explored with the χ^2 test for

categorical variables and the Mann-Whitney U test, Kruskal-Wallis test, or Student *t* test for continuous variables. Differences were considered statistically significant at $P < .05$. All tests were 2 sided. The growth rate for each meningioma was determined using mixed modeling assuming a random intercept and slope for each tumor. Statistical analysis was conducted between March 2024 and December 2024.

IMPACT scores were calculated, and classified into low risk (<1), medium risk (1-3), and high risk (≥3). Kaplan-Meier curves were generated to assess the differences in progression-free and intervention-free survival across the risk groups, and statistical significance was examined using the log-rank test. AGR and RGR were also compared. Cox regression was performed to assess for an added benefit or confounding effect from other baseline variables not included in the IMPACT tool, and a sensitivity analysis was conducted to assess its performance based on center behavior. Predictive performance was assessed using the Brier score (overall accuracy, 0 = perfect and 1 = random), Harrell C-index (measure of the model's ability to discriminate between patients based on their predicted risk scores, 1 = perfect and 0.5 = random), Chambless and Diao time-dependent area under the curve (AUC) (accuracy over time, 1 = perfect and 0.5 = random) and a calibration curve (to visualize predicted vs observed risk). The proportional hazards assumption of the IMPACT tool was tested by examination of Schoenfeld residuals, and influential observations were examined with diagnostics using standardized β panels.

The 2 competing risk analyses performed as part of the IMPACT tool were repeated and plots of cumulative incidence rates (CIR) were formulated. Patients were split based on WHO PS into 0 to 1 (normal or limited activity) and 2 to 4 (unable to carry out any work activities or in a chair/bed for ≥50% of the day) and stratified by ACCI score into 0 to 2 (young patients with few or no comorbidities), 3 to 5 (older patients

with few comorbidities or younger patients with several comorbidities) and 6 or higher (older patients with comorbidities). One analysis assessed the CIR of an intervention following diagnosis, stratified by PS and ACCI score (competing event: mortality, either observed during follow-up or after being discharged from outpatient care). Another evaluated the CIR of disease progression (competing events: discharge from outpatient care, loss to follow-up, death, or an intervention before disease progression occurred). To test the equality across CIR groups, the Fine and Gray test was carried out.

If calibration and discrimination measures of external validation demonstrated a poor fit, the model was to be recalibrated and adjusted as described in the study protocol.[9]

Results

Study population and baseline characteristics

Data collection started on January 12, 2020. An interim analysis took place in December 2022, with data available for 831 patients (25 centers). This yielded 74 progression events. By December 31, 2023, 33 centers provided data, with 1248 patients and sufficient progression events (n = 114) (Figure 1A; eTable 2 in Supplement 1). The development and validation cohorts were balanced in most clinical characteristics, but the validation cohort was enriched for more aggressive meningiomas (T2-weighted MRI hyperintense, with edema and in contact with critical neurovascular structures) (eTable 3 in Supplement 1). The most common indications for scan were headaches (282 [22.6%]) and audiovestibular symptoms (150 [12%]). Seventy-seven patients (6.2%) had multiple incidental meningiomas, resulting in an overall cohort of 1336 tumors. Baseline characteristics are summarized in eTable 4 in Supplement 1.

Management strategies and overall outcomes

At initial diagnosis, 572 tumors (in 533 patients [42.7%]) were actively monitored, 438 tumors (412 patients [33%]) were discharged or lost to follow-up, 307 tumors (300 patients [24%]) underwent surgery, and 19 tumors (17 patients [1.4%]) underwent SRS or fractionated radiotherapy. Differences in baseline characteristics across the treatment groups are shown in eTable 4 in Supplement 1. Patients who had upfront treatment tended to be younger, with fewer comorbidities and larger tumors (eTable 4 in Supplement 1). By the end of the study, 388 patients (31.1%) died, 317 (25.4%) were discharged or lost to follow-up, 103 (8.3%) remained under follow-up, and 440 (35.3%) underwent an intervention (Figure 1B for tumor statistics). Of the 1010 treatment-naive meningiomas, in 945 patients (75.7%), the median (IQR) clinical follow-up was 61 (17-108) months. Of the 734 meningiomas, in 680 patients (54.5%) with longitudinal MRI data, the median (IQR) imaging follow-up duration was 72 (26-116) months.

Risk of disease progression and intervention

During follow-up, 114 meningiomas, in 113 patients (12%), progressed. The risk was 11.3%, considering all treatment-naive meningiomas, and 15.5% considering meningiomas with longitudinal clinical and imaging follow-up. End points reached were meningioma growth (63 [8.6%]), symptom development (51 [6.9%]), development or increase of peritumoral edema (26 [3.5%]), meningioma volume exceeding 10 cm^3 (42 [5.7%]), and venous sinus invasion (9 [1.2%]). Symptoms were weakness (19 [37.3%]), headache (17 [33.3%]), seizure (8 [15.7%]), cognitive decline (7 [13.7%]), sensory disturbance (6 [11.8%]), speech disturbance (5 [9.8%]), and others (9 [17.6%]). Five patients (0.5%) died due to a growing and symptomatic meningioma. The median (IQR) time to progression was 27.5 (12-58) months. Eighty-seven

progression events (76.3%) occurred by 5 years of follow-up, and 105 by 10 years (92.1%). The 5- and 10-year follow-up period, progression-free survival rates were 88.1% (95% CI, 85.8%-90.5%) and 85.7% (95% CI, 83.2%-88.2%), respectively. The growth curves for tumors separated by disease progression status are shown in Figure 2A; there was little to no growth in tumors that did not progress and exponential growth in tumors that did. During follow-up, 132 tumors (13.1%), in 126 patients (13.3%), underwent an intervention, and the rate of intervention was significantly lower in the nonprogression group (12.9% vs 45.6%; χ^2 test, $P < .001$). The median (IQR) time to intervention was 35.3 (18.4-73.8) months. The 5- and 10-year intervention-free survival rates were 86.6% (95% CI, 86.6%-89.3%) and 73.9% (95% CI, 69.8%-78.0%), respectively.

IMPACT model performance

The risks of disease progression and intervention were significantly different across the 3 IMPACT risk categories (log-rank test, $P < .001$; Figure 3A; eFigure 1 in Supplement 1). Low-risk meningiomas had a disease progression risk of 3.9%, compared with 24.2% and 51.6% in medium- and high-risk meningiomas, respectively (χ^2 test, $P < .001$). The risk of intervention was 12.9%, 26.5%, and 37.4% across the 3 risk groups (χ^2 test, $P < .001$). Growth statistics differed significantly across the 3 risk scores (χ^2 test, $P < .001$) (Figure 2B). In Cox regression analysis, the addition of factors such as age (HR, 1.01; 95% CI, 0.99-1.02; $P = .49$), sex (HR, 1.46; 95% CI, 0.94-2.29; $P = .09$), meningioma location (HR, 1.07; 95% CI, 0.99-1.15; $P = .69$), and study center (HR, 0.99; 95% CI, 0.96-1.01; $P = .36$) did not alter the statistical significance of IMPACT score. In a sensitivity analysis, the IMPACT tool performed well in all center groups, stratified by initial treatment decision behavior (Figure 1A; eFigure 2 in Supplement 1). The Brier score, C-index, and time-dependent AUC at 5

and 10 years, were 0.12, 0.80, 0.83, and 0.83, respectively. A calibration curve (Figure 3B) showed that for low-risk meningiomas, the model's predicted risk was similar to the observed risk. For medium- and high-risk meningiomas, the model slightly overestimated the risk of progression. The assumptions of a valid Cox model were not violated; the effect of the individual IMPACT variables was similar across the validation and development cohorts (eTable 5 in Supplement 1) and did not change over time (proportional hazard assumptions) (eFigure 3 in Supplement 1). None of the individual observations had a standardized β value of 2 or more, indicating the absence of any influential observations (eFigure 4 in Supplement 1). Recalibration of the Cox regression model was not necessary.

Association of Comorbidity and Performance Status With Progression and Intervention Risk

CIR plots of disease progression and intervention are shown in Figure 4; eFigure 5 and eTables 6 to 7 in Supplement 1. Stratified by comorbidity index, the rates of intervention were statistically different across the 3 groups (Fine and Gray test, $P < .001$), although the rates of disease progression were not (Fine and Gray test, $P = .46$). At 10 years, 71.9% of patients with an ACCI score of 6 or higher were discharged, deceased, or lost to follow-up, having not had disease progression or an intervention. Patients with an ACCI score of 6 or higher were also 6 times more likely to die after 10 years of follow-up than to receive an intervention. The rates of intervention and mortality did not differ in patients with an ACCI score of 3 to 5. The rates of disease progression and intervention were significantly different according to PS (Fine and Gray test, $P = .047$ and $P < .001$, respectively). At 10 years, patients with a PS of 2 to 4 were 13 times more likely to have been discharged, lost to follow-up, or dead, than to have experienced disease progression. They were also 6 times more

likely to have died than to have had an intervention. The rates of intervention and mortality did not differ in patients with a PS of 0 to 1. Recalibration of the CIR plots was not necessary.

Discussion

In this international multicenter study of incidental meningioma prognosis, 1 in 9 patients demonstrated clinical and radiological progression. The IMPACT tool was able to accurately predict the risk of progression, stratifying patients into high, medium, and low risk. Based on robust external validation findings, our previous treatment recommendations are updated as follows: early intervention for high-risk patients is recommended, given a progression risk of about 50%. Medium-risk patients may be serially monitored to identify the 24% of patients likely to progress within 5 years of diagnosis. Low-risk patients may be discharged from outpatient care, with safety netting (counseling about potential symptoms, what to watch for, and when to seek further medical attention). Patients with an ACCI score of 6 or higher and PS of 2 to 4 were highly unlikely to require an intervention for their incidental meningiomas during their estimated lifetime. A treatment pathway based on these findings is presented and could be used to aid clinicians and patients to reach a shared-care decision about management (https://www.impact-meningioma.com/).

The IMPACT tool combines meningioma volume, T2-weighted MRI meningioma intensity, the presence of edema, and proximity to critical neurovascular structures to predict a risk of a progression. Each individual MRI variable has previously been shown to correlate with the risk of incidental meningioma growth.[12,19-24] T2 hyperintense meningiomas have a softer consistency noted at surgery, which may reflect their growth potential, compared with firmer isointense and hypointense

meningiomas.[25,26] Peritumoral edema implies breach of the arachnoid plane and is associated with a higher meningioma grade and recurrence after surgery.[27] Slow growth of a meningioma in eloquent and skull base locations meningioma may pose a higher risk of causing major morbidity compared with convexity meningiomas, owing to their proximity to critical neurovascular structures.[28] A previously reported prognostic model (Asan Intracranial Meningioma Scoring System), combined MRI and CT features to predict a risk of progression but is yet to undergo adequate validation for clinical use.[24,29] Patient factors, such as age, comorbidity burden, and performance status, are integral to clinical decision-making. The effects of these, like in the development cohort, were assessed in competing risk analyses. We observed that patients with an ACCI scores of 6 or higher (eg, a patient aged 80 years with a previous myocardial infarction and chronic obstructive pulmonary disease) and PS of 2 to 4 (eg, in a chair/bed for ≥50% of a day) were less likely to receive an intervention for their meningiomas, despite having a similar progression risk to other groups. The reasons for this are 2-fold: (1) patients were 6 times more likely to die, from a nonmeningioma-related cause, than to receive an intervention at 10 years following diagnosis, highlighting their meningiomas were unlikely to lead to death or to require treatment and (2) the threshold for offering an intervention to these patients being much higher, due to the increased risk of intervention-related morbidity and mortality.[30,31]

In addition to identifying prognostic factors for growth and intervention, it is also important to predict the timing of incidental meningioma progression to guide follow-up imaging surveillance. Our study showed that most progression events occured within the first 5 years of follow-up, and this seemed to tail off with longer follow-up. A meta-analysis of 10 studies[5] showed that meningiomas that did not grow within the first 5 years of follow-up were unlikely to grow during extended follow-up beyond 5

years. In addition, a recent prospective study[32] of 62 patients showed despite initial growth during early follow-up, growth decelerated after 1.5 years, and tumors had either plateaued or shrunk after 8 years. One study reported growth, defined as more than 2 mm of progression in any unidimensional diameter, beyond 10 years; however, their definition of tumor growth was not clinically useful.[33]

We have updated our management algorithm based on the IMPACT score, ACCI and PS (Figure 5). Low- and medium-risk patients with an ACCI score of 6 or higher and/or PS of 2 to 4 can be discharged from outpatient follow-up with appropriate safety netting. High-risk patients with ACCI scores of 6 or higher and/or PS of 2 to 4 may be offered clinical monitoring because imaging changes alone may not prompt an intervention in such patients. For otherwise low-risk patients, discharge from outpatient care or low-frequency serial monitoring may be considered. For otherwise medium-risk patients, serial monitoring should be considered. For otherwise high-risk patients, early intervention or frequent serial monitoring may be considered. Reassessment of ACCI and PS at extended follow-up (beyond 10 years) is recommended because older patients with new comorbidities but who remain radiologically and clinically stable can be safely discharged from outpatient care. Patients with a longer life expectancy, on the other hand, may be offered infrequent clinical monitoring.

Strengths and Limitations

This cohort study had several strengths. First, it is an international study, with cohorts from several centers, countries, health care models, and continents, which make the results generalizable. Second, meningiomas included were diagnosed in 2009 and 2010, ensuring a long duration of follow-up. Finally, the study included a variety of meningioma anatomical locations and volumes, reflecting an actual clinical cohort.

Some limitations of this cohort study should be noted. First, data entry took place locally in each center, without central validation. However, training and an iterative assessment process was mandated for all study members. Second, there was a variety of nonstandardized management, such as the decision to perform intervention, and follow-up schedules, owing to the retrospective multicenter nature of the cohort. Third, it was not possible to ascertain the exact reasons for continued monitoring in cases of progression, but this may have been due to patient preference, considering factors such as employment, loss of driving license, and risk of complications such as epilepsy, new neurological deficit, and death. Also, data for socioeconomic status, which may have affected return to follow-up, was not available. Finally, a quarter of patients underwent an intervention at presentation for meningiomas that were noted to be larger, with a higher rate of edema and T2-weighted MRI tumor hyperintensity, thus excluding them from further observation. Therefore, the overall risk of progression for an incidental meningioma may be higher than observed. Moreover, the observed risk of progression for medium- and high-risk patients, if all patients were monitored, may be more like the slightly overestimated predicted risk in the calibration curve.

Conclusion

This cohort study found that the IMPACT tool is a robust risk stratification tool that, by incorporating routine clinical and imaging factors, facilitates personalized management of patients with incidental meningiomas. In this large multicenter study, we demonstrated that the IMPACT tool had good external validity and can be used to stratify clinical management (discharge from outpatient care vs active monitoring vs early intervention) and manage uncertainty about the need for future treatment.

References

1. Ostrom QT, Price M, Neff C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016—2020. *Neuro-Oncol*. 2023;25(Supplement_4):iv1-iv99. doi:10.1093/neuonc/noad149

2. Morris Z, Whiteley WN, Longstreth WT, et al. Incidental findings on brain magnetic resonance imaging: systematic review and meta-analysis. *BMJ*. 2009;339:b3016. doi:10.1136/bmj.b3016

3. Nakasu S, Notsu A, Nakasu Y. Prevalence of incidental meningiomas and gliomas on MRI: a meta-analysis and meta-regression analysis. *Acta Neurochir (Wien)*. 2021;163(12):3401-3415. doi:10.1007/s00701-021-04919-8

4. Bhala S, Stewart DR, Kennerley V, Petkov VI, Rosenberg PS, Best AF. Incidence of Benign Meningiomas in the United States: Current and Future Trends. *JNCI Cancer Spectr*. 2021;5(3):pkab035. doi:10.1093/jncics/pkab035

5. NAKASU S, NAKASU Y. Natural History of Meningiomas: Review with Meta-analyses. *Neurol Med Chir (Tokyo)*. 2020;60(3):109-120. doi:10.2176/nmc.ra.2019-0213

6. Islim AI, Mohan M, Moon RDC, et al. Incidental intracranial meningiomas: a systematic review and meta-analysis of prognostic factors and outcomes. *J Neurooncol*. 2019;142(2):211-221. doi:10.1007/s11060-019-03104-3

7. Islim AI, Millward CP, Mills SJ, et al. The management of incidental meningioma: An unresolved clinical conundrum. *Neuro-Oncol Adv*. 2023;5(Suppl 1):i26-i34. doi:10.1093/noajnl/vdac109

8. Islim AI, Kolamunnage-Dona R, Mohan M, et al. A prognostic model to personalize monitoring regimes for patients with incidental asymptomatic meningiomas. *Neuro-Oncol*. 2020;22(2):278-289. doi:10.1093/neuonc/noz160

9. Islim AI, Millward CP, Piper RJ, et al. External validation and recalibration of an incidental meningioma prognostic model - IMPACT: protocol for an international multicentre retrospective cohort study. *BMJ Open*. 2022;12(1):e052705. doi:10.1136/bmjopen-2021-052705

10. Kattan MW, Hess KR, Amin MB, et al. American Joint Committee on Cancer acceptance criteria for inclusion of risk models for individualized prognosis in the practice of precision medicine. *CA Cancer J Clin*. 2016;66(5):370-374. doi:10.3322/caac.21339

11. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD Statement. *BMC Med*. 2015;13(1):1. doi:10.1186/s12916-014-0241-z

12. Han MS, Kim YJ, Moon KS, et al. Lessons from surgical outcome for intracranial meningioma involving major venous sinus. *Medicine (Baltimore)*. 2016;95(35):e4705. doi:10.1097/MD.0000000000004705

13. Vignes JR, Sesay M, Rezajooi K, Gimbert E, Liguoro D. Peritumoral edema and prognosis in intracranial meningioma surgery. *J Clin Neurosci*. 2008;15(7):764-768. doi:10.1016/j.jocn.2007.06.001

14. Cai R, Pan C, Ghasemigharagoz A, et al. Panoptic imaging of transparent mice reveals whole-body neuronal projections and skull–meninges connections. *Nat Neurosci*. 2019;22(2):317-327. doi:10.1038/s41593-018-0301-3

15. Kollová A, Liscák R, Novotný J, Vladyka V, Simonová G, Janousková L. Gamma Knife surgery for benign meningioma. *J Neurosurg*. 2007;107(2):325-336. doi:10.3171/JNS-07/08/0325

16. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-682. doi:10.1093/aje/kwq433

17. VASARI Research Project - The Cancer Imaging Archive (TCIA) Public Access - Cancer Imaging Archive Wiki. Accessed July 26, 2025. https://wiki.cancerimagingarchive.net/display/Public/VASARI+Research+Project

18. Nassiri F, Wang JZ, Au K, et al. Consensus core clinical data elements for meningiomas (v2021.1). *Neuro-Oncol*. 2022;24(5):683-693. doi:10.1093/neuonc/noab259

19. Delgado-López PD, Montalvo-Afonso A, Martín-Alonso J, et al. Volumetric growth rate of incidental asymptomatic meningiomas: a single-center prospective cohort study. *Acta Neurochir (Wien)*. 2021;163(6):1665-1675. doi:10.1007/s00701-021-04815-1

20. Thomann P, Häni L, Vulcu S, et al. Natural history of meningiomas: a serial volumetric analysis of 240 tumors. *J Neurosurg*. 2022;137(6):1639-1649. doi:10.3171/2022.3.JNS212626

21. Häni L, Thomann P, Maragkou T, et al. Velocity and pattern of growth of intracranial meningiomas. *J Neurosurg*. 2025;142(1):206-213. doi:10.3171/2024.4.JNS2446

22. Nakamura M, Roser F, Michel J, Jacobs C, Samii M. The Natural History of Incidental Meningiomas. *Neurosurgery*. 2003;53(1):62. doi:10.1227/01.NEU.0000068730.76856.58

23. Oya S, Kim SH, Sade B, Lee JH. The natural history of intracranial meningiomas. *J Neurosurg*. 2011;114(5):1250-1256. doi:10.3171/2010.12.JNS101623

24. Lee EJ, Kim JH, Park ES, et al. A novel weighted scoring system for estimating the risk of rapid growth in untreated intracranial meningiomas. *J Neurosurg*. 2017;127(5):971-980. doi:10.3171/2016.9.JNS161669

25. Smith KA, Leever JD, Chamoun RB. Predicting Consistency of Meningioma by Magnetic Resonance Imaging. *J Neurol Surg Part B Skull Base*. 2015;76(3):225. doi:10.1055/s-0034-1543965

26. Yamada H, Tanikawa M, Sakata T, Aihara N, Mase M. Usefulness of T2 Relaxation Time for Quantitative Prediction of Meningioma Consistency. *World Neurosurg*. 2022;157:e484-e491. doi:10.1016/j.wneu.2021.10.135

27. Morin O, Chen WC, Nassiri F, et al. Integrated models incorporating radiologic and radiomic features predict meningioma grade, local failure, and overall survival. *Neuro-Oncol Adv*. 2019;1(1):vdz011. doi:10.1093/noajnl/vdz011

28. Nguyen M, Chen W, Mirchia K, Magill S, Morshed R, Raleigh D. EPID-09. THE NATURAL HISTORY AND MOLECULAR ARCHITECTURE OF INCIDENTAL MENINGIOMAS. *Neuro-Oncol*. 2024;26(Supplement_8):viii139. doi:10.1093/neuonc/noae165.0545

29. Brugada-Bellsolà F, Teixidor Rodríguez P, Rodríguez-Hernández A, et al. Growth prediction in asymptomatic meningiomas: the utility of the AIMSS score. *Acta Neurochir (Wien)*. 2019;161(11):2233-2240. doi:10.1007/s00701-019-04056-3

30. Bartek J, Sjåvik K, Förander P, et al. Predictors of severe complications in intracranial meningioma surgery: a population-based multicenter study. *World Neurosurg*. 2015;83(5):673-678. doi:10.1016/j.wneu.2015.01.022

31. Grossman R, Mukherjee D, Chang DC, et al. Preoperative charlson comorbidity score predicts postoperative outcomes among older intracranial meningioma patients. *World Neurosurg*. 2011;75(2):279-285. doi:10.1016/j.wneu.2010.09.003

32. Strømsnes TA, Lund-Johansen M, Skeie GO, Eide GE, Behbahani M, Skeie BS. Growth dynamics of incidental meningiomas: A prospective long-term follow-up study. *Neuro-Oncol Pract*. 2023;10(3):238-248. doi:10.1093/nop/npac088

33. Jadid KD, Feychting M, Höijer J, Hylin S, Kihlström L, Mathiesen T. Long-term follow-up of incidentally discovered meningiomas. *Acta Neurochir (Wien)*. 2015;157(2):225-230. doi:10.1007/s00701-014-2306-3

Figures

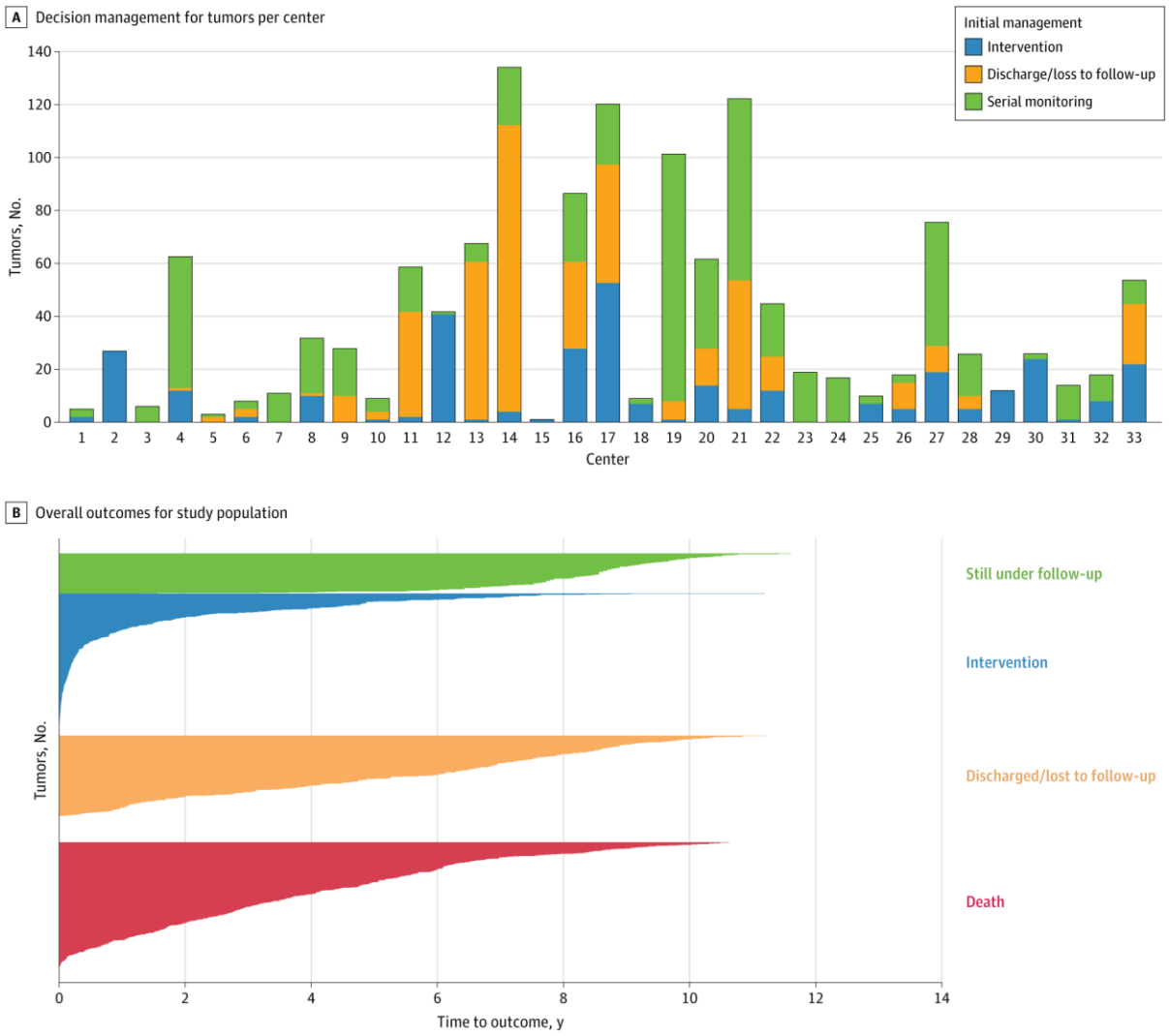


Figure 1. Overview of the participating centers and overall study outcomes. A, Bar chart of decision management for each tumor per each center. Centers 2,12, 25, 29 and 30 were more likely to offer upfront intervention (group 1). Centers 4, 7, 8, 9, 19, 23, 24, 27, 28 and 31 offered serial monitoring (group 2). Centers 11 and 14 primarily discharged patients (group 3). The remainder of the centers had a mix (group 4). B, Swimmer's plot demonstrating the overall outcomes for the study population. The x-axis represent time taken to reach the outcome and the y-axis corresponds to the number of tumors under each outcome.

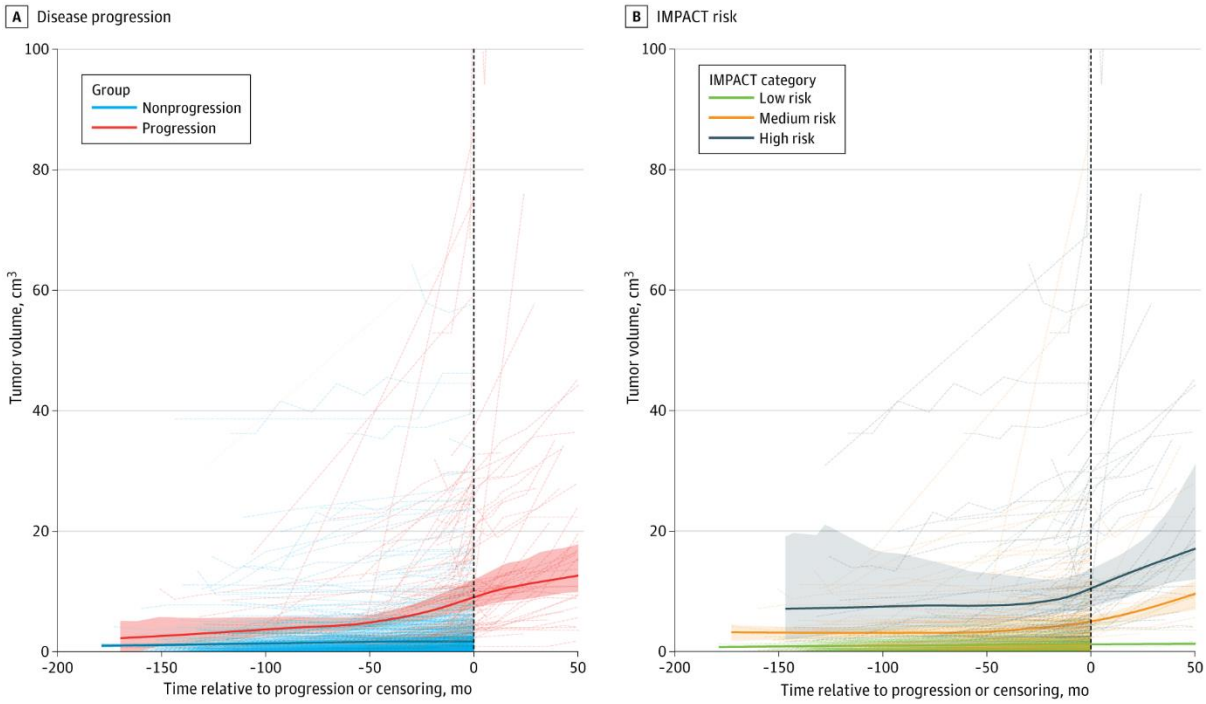


Figure 2. Growth characteristics of incidental meningioma. A, Locally fitted estimated scatterplot smoothing (LOESS) curves of tumor behavior, stratified by disease progression status. Nonprogressive tumors were static during follow-up. Progressive tumors grew exponentially before reaching progression. Growth slowed after progression in tumors that remained under observation. Nonprogressive tumors had an absolute growth rate (AGR) of 0.08 (0.4) cm3/year and a relative growth rate (RGR) of 9.6% (26.7%)/year; progressive tumors had an AGR of 3.8 (9.4) cm3/year and a RGR of 80% (375%)/year. B, LOESS curves by IMPACT risk category. Low-risk tumors (AGR 0.11 [0.3] cm3/year; RGR 11.9% [31.7%]/year) were static. Medium risk (AGR 0.52 [1.32] cm3/year; RGR 14.3% [32.3%]/year) and high risk (AGR 3.4 [10.5] cm3/year; RGR 74.5% [420%]/year) grew faster, especially the latter. Censoring or progression marked time 0. Summary statistics are presented as mean (SD). IMPACT indicates Incidental Meningioma: Prognostic Analysis Using Patient Comorbidity and Magnetic Resonance Imaging Tests.

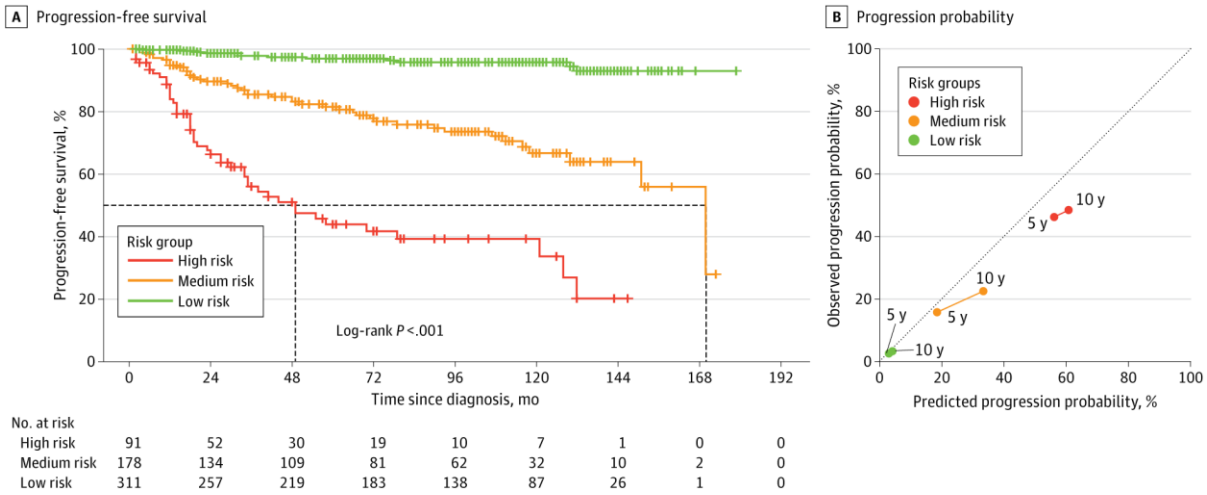
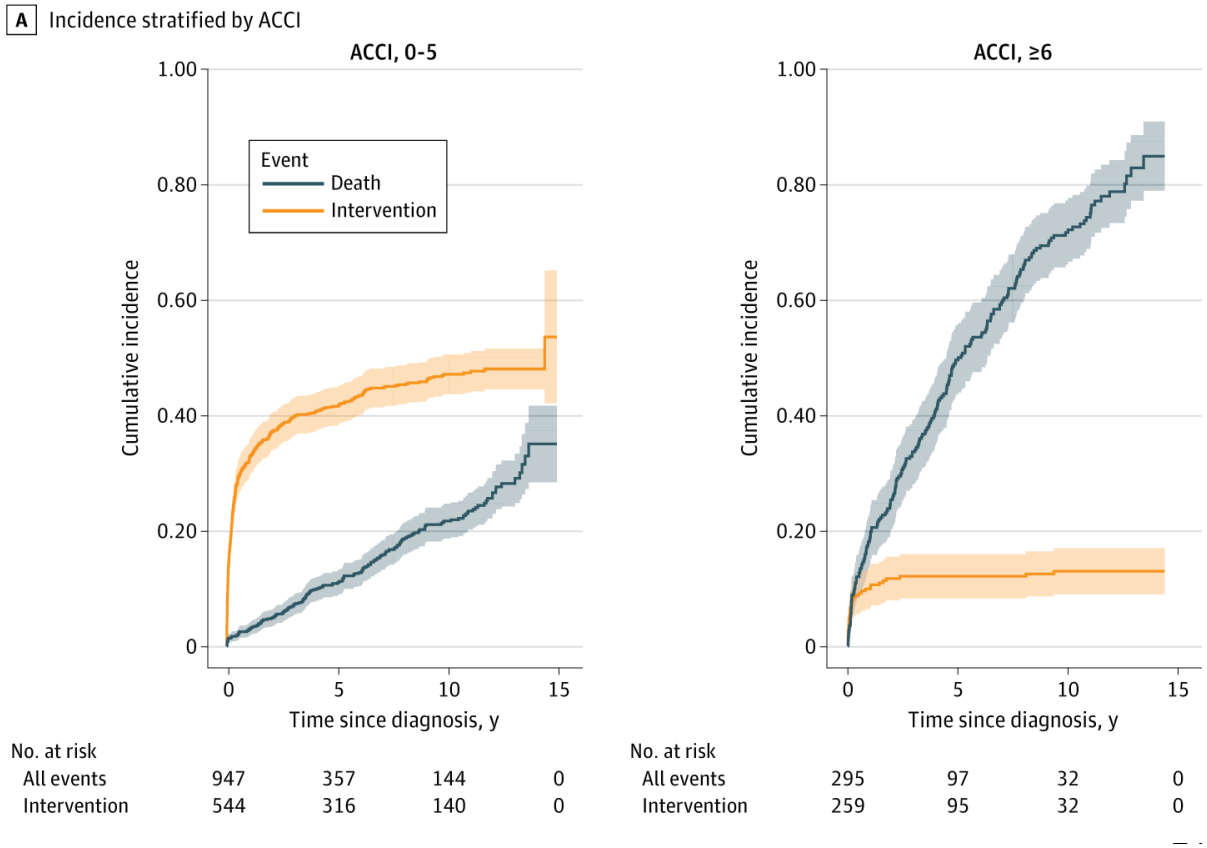


Figure 3. Performance of the IMPACT model. A, Kaplan-Meier curve demonstrating the difference in progression-free survival between the IMPACT risk categories. B, A calibration plot comparing the predicted risk by the IMPACT model and the observed risk. For low-risk patients, the predicted and observed risks were similar. For medium- and low-risk patients, the predicted risk at 5 and 10 years was slightly overestimated.



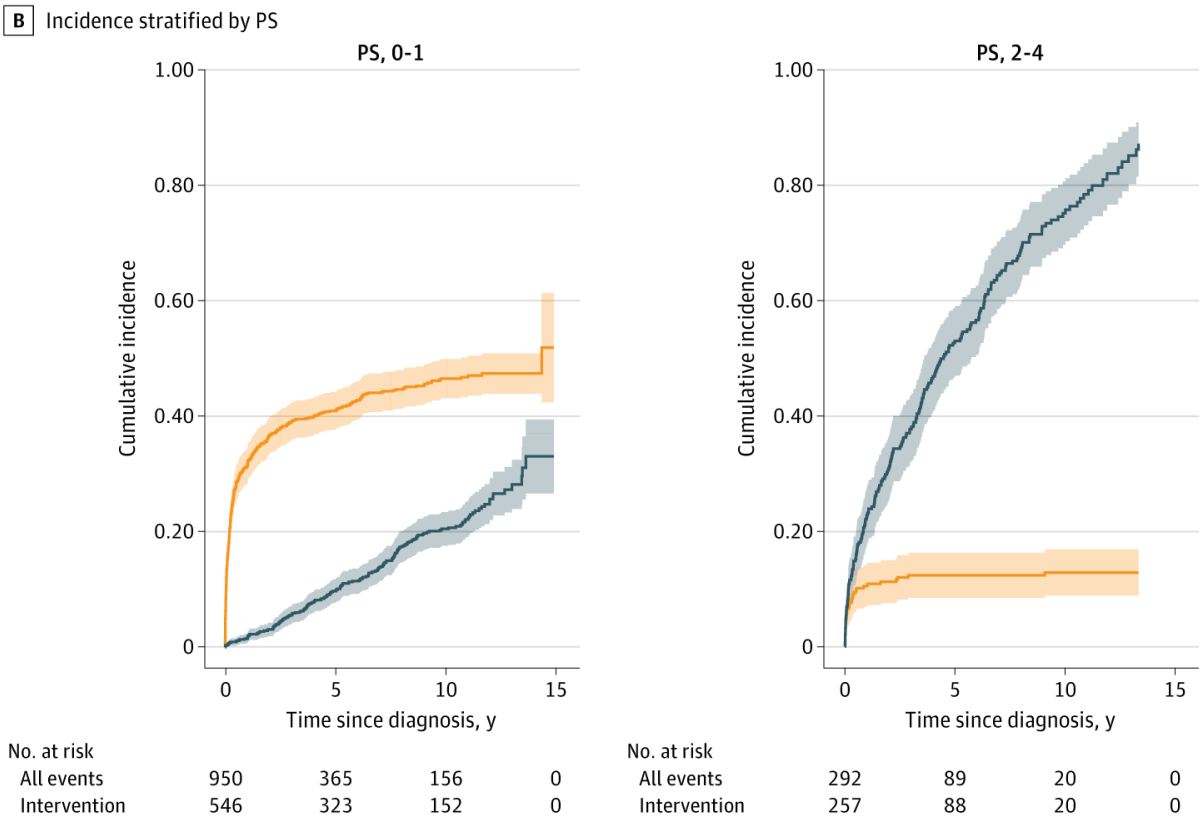


Figure 4. Results of the competing risks analysis for intervention vs mortality. A, Estimated cumulative incidence curves (solid lines) for intervention and mortality, with 95% CIs (shaded areas), stratified by ACCI score. B, Estimated cumulative incidence curves (solid lines) for intervention and mortality, with 95% CIs, stratified by PS. The full results are available in Supplement 1. ACCI indicates age-adjusted Charlson Comorbidity Index; PS, performance status.

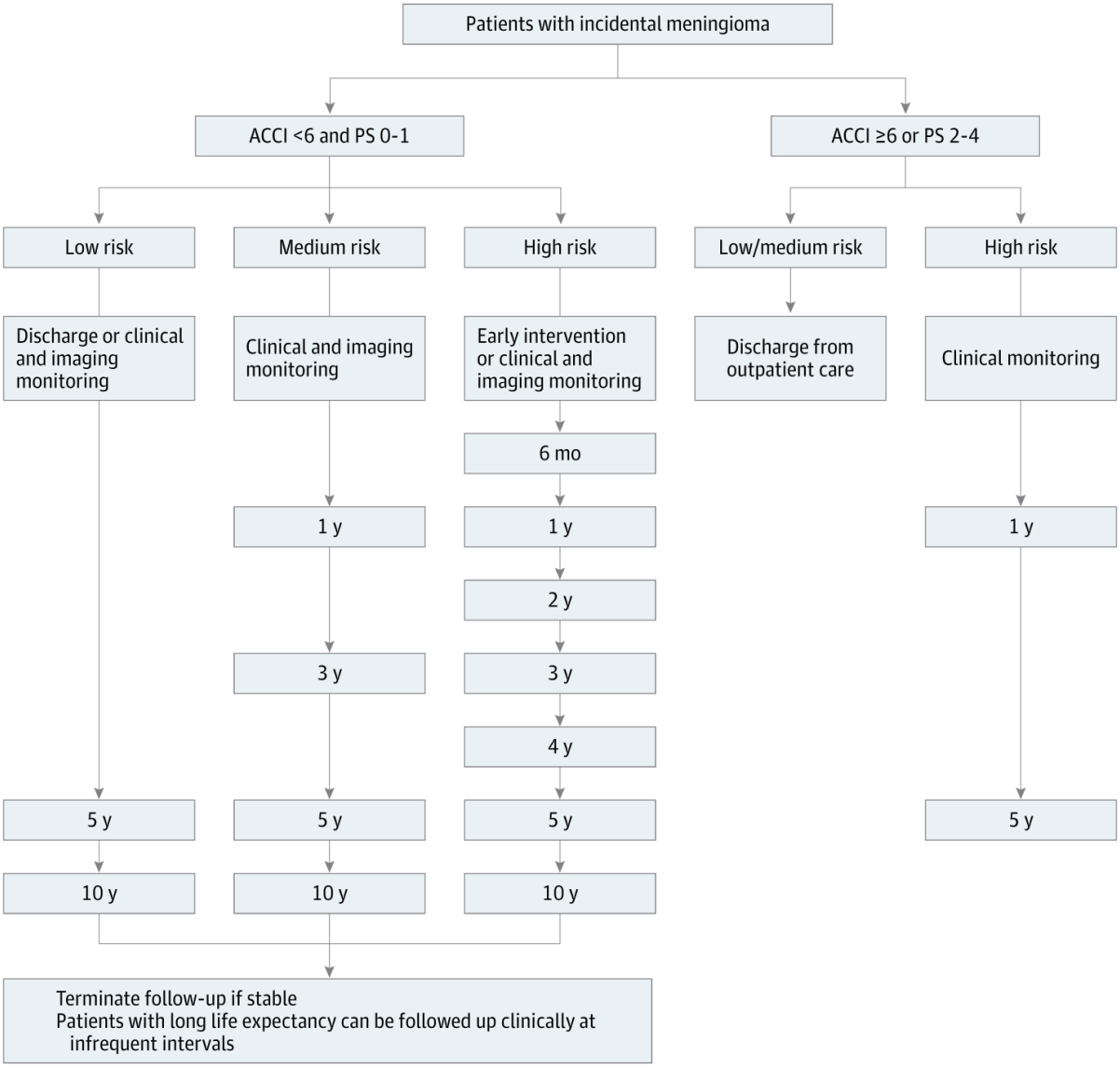


Figure 5. Proposed management strategies for patients with incidental meningioma.

Acknowledgements

Access to data and data analysis

Abdurrahman I. Islim and Michael D. Jenkinson had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Nonauthor collaborators (investigators) for groups

IMPACT Study investigators, International Consortium on Meningioma (ICOM): and British Neurosurgical Trainee Research Collaborative (BNTRC)

Non-author contributions

We would like to thank James Tovey and Janet Harrison, at the Liverpool Clinical Trials Centre, for their help setting up and maintaining the REDCap database for data collection.

Conflict of Interest Disclosures

There are no conflicts of interest to report.

Funding/Support

No funding.

Data sharing statement

The individual clinical data and data definition table file can be shared upon approval of the analysis proposal by the IMPACT study steering committee, and after a data-sharing agreement has been signed. Requests will be addressed within 4 weeks. Data availability after approval and signatory of the data-sharing agreement will depend on

the analysis to be performed and agreed upfront in the data-sharing agreement. Please contact the corresponding author for more information.

Online supplement

Contents: 7 eTables and 5 eFigures.

(solid lines) for intervention and mortality with 95% CIs (shading) stratified by (C) ACCI and (D) PS. LTFU: lost to follow-up.

eTable 1. Details of the statistical packages used			
Package	Version	Platform	Function
Stats	4.4.1	R v4.4.1	General statistics
Dplyr	1.1.4	R v4.4.1	Data manipulation
Survival	3.8.3	R v4.4.1	Survival analysis
Survminer	0.5.0	R v4.4.1	Survival plotting
Pec	2023.4.12	R v4.4.1	Brier score
Hmisc	5.2.3	R v4.4.1	C-index
TimeROC	0.4	R v4.4.1	Time-dependent AUC
Lme4	1.1.37	R v4.4.1	Mixed-effects modelling
Cmprsk	2.2.12	R v4.4.1	Competing risk analysis
Ggplot2	3.5.2	R v4.4.1	Visualisation
Matplotlib	3.7.1	Python v3.10	Visualisation

eTable 2. Details of the 33 participating centers			
Center	City	Country	Nature
Royal Melbourne Hospital	Melbourne	Australia	Academic hospital and a large referral center
Royal University Hospital	Saskatchewan	Canada	Academic hospital and a large referral center
Wingat Royal Hospital	Alexandria	Egypt	Community Hospital
University Hospital Regensburg	Regensburg	Germany	Academic hospital and a large referral center
Beaumont Hospital	Dublin	Ireland	Academic hospital and a large referral center
Sapienza University of Rome	Rome	Italy	Academic hospital and a large referral center
Mater Dei Hospital	Msida	Malta	Academic hospital and a large referral center
Haukeland University Hospital	Bergen	Norway	Academic hospital and a large referral center
Hospital Universitari Germans Trias i Pujol	Barcelona	Spain	Academic hospital and a large referral center
Hospital Universitario de Burgos	Burgos	Spain	Academic hospital and a large referral center

University of Khartoum	Khartoum	Sudan	Academic and community hospital
Sahlgrenska University Hospital	Göteborg	Sweden	Academic hospital and a large referral center
University Hospital of Geneva	Geneva	Switzerland	Academic hospital and a large referral center
Leiden University Medical Center	Leiden	The Netherlands	Academic hospital and a large referral center
The Walton Center	Liverpool	UK	Academic hospital and a large referral center
Royal Sussex County Hospital	Brighton	UK	Academic hospital and a large referral center
Salford Royal Hospital	Manchester	UK	Academic hospital and a large referral center
The National Hospital for Neurology and Neurosurgery	London	UK	Academic hospital and a large referral center
John Radcliffe Hospital	Oxford	UK	Academic hospital and a large referral center
Royal Preston Hospital	Preston	Uk	Academic hospital and a large referral center
Ninewells Hospital	Dundee	UK	Academic hospital and a large referral center
Queen Elizabeth University Hospital	Glasgow	UK	Academic hospital and a large referral center
Leeds General Infirmary	Leeds	UK	Academic hospital and a large referral center
Queen Elizabeth Hospital	Birmingham	UK	Academic hospital and a large referral center
Addenbrooke’s Hospital	Cambridge	UK	Academic hospital and a large referral center
Derriford Hospital	Plymouth	UK	Academic hospital and a large referral center
The James Cooke University Hospital	Middlesbrough	UK	Academic hospital and a large referral center
Queen’s Hospital	Romford	UK	Academic hospital and a large referral center

King’s College Hospital	London	UK	Academic hospital and a large referral center
Royal Stoke University Hospital	Stoke	UK	Academic hospital and a large referral center
Royal Victoria Infirmary	Newcastle	UK	Academic hospital and a large referral center
John’s Hopkins Hospital	Baltimore	USA	Academic hospital and a large referral center
University of California, San California,	California	USA	Academic hospital and a large referral center

eTable 3. Baseline characteristics of the development and validation cohorts			
		Validation (1248 patients, 1336 tumors)	Development (441 patients, 459 tumors)
Median age (IQR)		66 years (55-77)	63.3 years (55-73)
Female: male		999:294 (4:1)	348:93 (4:1)
Median WHO performance status (range)		1 (0-4)	0 (0-3)
Median age-adjusted Charlson comorbidity index (ACCI) (IQR)		4 (2-5)	4 (3-6)
Median meningioma volume (IQR)		2.1 cm^3 (0.7-8.2)	1.6 cm^3 (0.6-4.0)
Anatomical location (%)	Non-skull base	947 (70.9%)	322 (70.2%)
	Skull base	389 (29.1%)	137 (29.8)
Meningioma hyperintensity on T2 (%)		342 (25.6%)	75 (16.3%)
Peri tumoural hyperintensity on T2 (%)		193 (14.4%)	31 (6.8%)
Venous sinus involvement (%)		554 (41.5%)	168 (36.7%)
In contact with critical neurovascular structures (%)		199 (14.9%)	35 (7.6%)

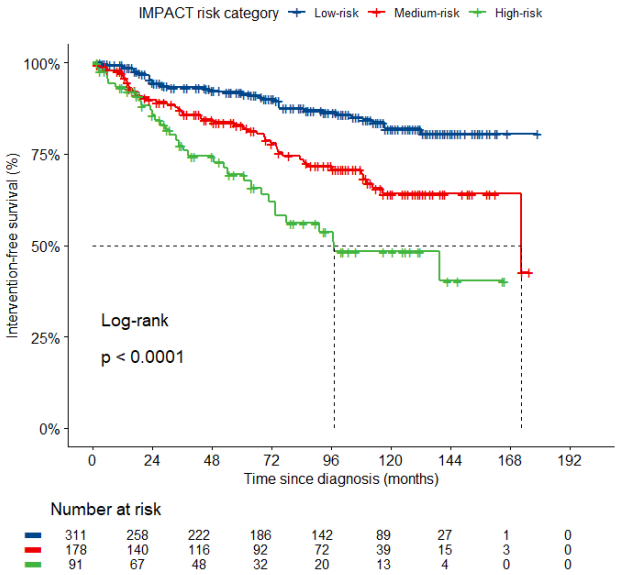
eTable 4. Baseline clinical and imaging characteristics for the study population, 1336 tumors in 1248 patients

		Overall	Active monitoring (533 patients, 572 tumors)	Discharge/Loss to follow-up (412 patients, 43(8 tumors)	Intervention (317 patients, 326 tumors)	P
Median age (IQR)		66 years (55-77)	63 (53-73)	77 (66-84)	58 (49-69)	<0.001
Female: male		999:294 (4:1)	3.7:1	3.3:1	2.9:1	0.340
Median WHO performance status (range)		1 (0-4)	1 (0-1)	1 (1-2)	1 (0-1)	<0.001
Median age-adjusted Charlson comorbidity index (ACCI) (IQR)		4 (2-5)	3 (2-5)	5 (4-7)	2 (1-4)	<0.001
Median meningioma volume (IQR)		2.1 cm^3 (0.7-8.2)	1.6 cm^3 (0.6-4)	1.0 cm^3 (0.4-3.4)	12.5 cm^3 (4.3-28.2)	<0.001
Anatomical location (%)	Non-skull base	947 (70.9%)	397 (69.4%)	337 (76.9%)	213 (65.3%)	0.001
	Convexity	*470 (35.2%)*	*191 (33.4%)*	*188 (42.9%)*	*91 (27.9%)*	
	Parafalcine/parasagittal	*363 (27.2%)*	*152 (26.6%)*	*123 (28.1%)*	*88 (27%)*	
	Tentorial	*99 (7.4%)*	*50 (8.7%)*	*20 (4.6%)*	*29 (8.9%)*	
	Intraventricular	*12 (0.9%)*	*3 (0.5%)*	*5 (1.1%)*	*4 (1.2%)*	
	Pineal region	*3 (0.2%)*	*1 (0.2%)*	*1 (0.2%)*	*1 (0.3%)*	
	Skull base	389 (29.1%)	175 (30.6%)	101 (23.1%)	113 (34.7%)	
	Posterior fossa	*150 (11.2%)*	*72 (12.6%)*	*42 (9.6%)*	*36 (11%)*	
	Sphenoid wing	*134 (10%)*	*59 (10.3%)*	*33 (7.5%)*	*42 (12.9%)*	
	Anterior midline	*105 (7.9%)*	*44 (7.7%)*	*26 (5.9%)*	*35 (10.7%)*	
Meningioma hyperintensity on T2-MRI (%)		342 (25.6%)	146 (25.5%)	38 (8.7%)	158 (48.5%)	<0.001
Peri tumoural hyperintensity on T2-MRI (%)		193 (14.4%)	42 (7.3%)	25 (5.7%)	126 (38.7%)	<0.001
Venous sinus involvement (%)	Separate (within 10 mm)	219 (16.4%)	105 (18.4%)	60 (13.7%)	54 (16.6%)	<0.001
	In direct contact	255 (19.1%)	108 (18.9%)	64 (14.6%)	83 (25.5%)	
	Invading	80 (6%)	35 (6.1%)	6 (1.4%)	39 (12%)	
In contact with critical neurovascular structures (%)		199 (14.9%)	86 (15%)	34 (7.8%)	79 (24.2%)	<0.001

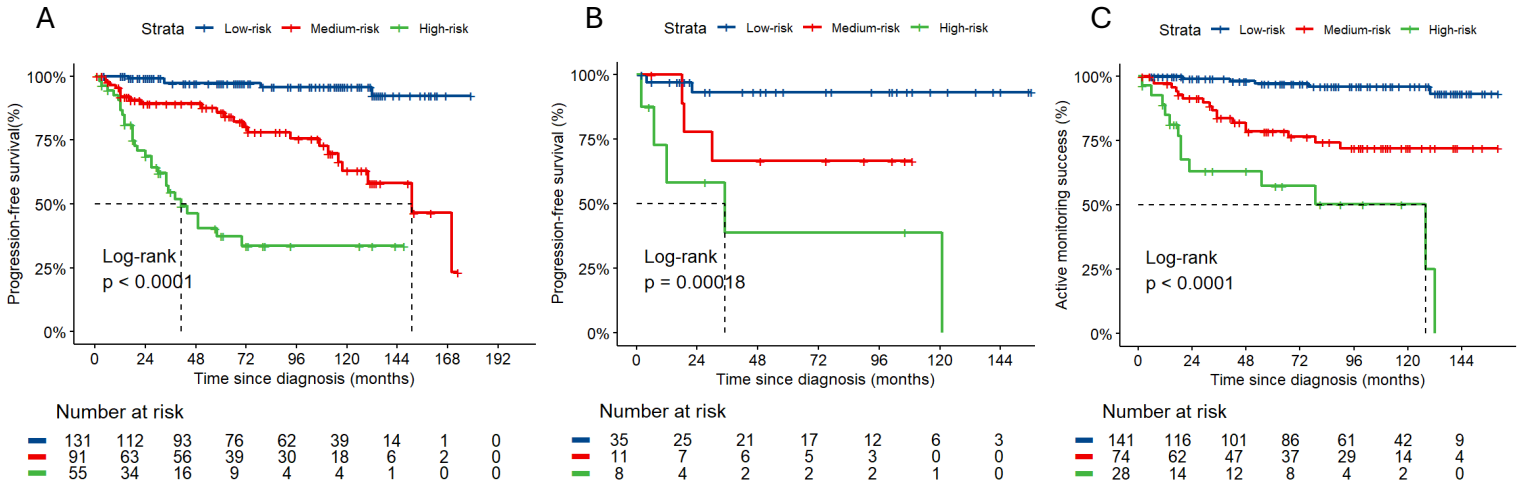
eTable 5. Results of a Cox regression analysis to assess the association between the individual IMPACT variables and disease progression		
Variable	HR (95% CI)	P-value
Meningioma volume	1.07 (1.05-1.09)	<0.001
T2 signal intensity	4.7 (3.1-7.0)	<0.001
T2 peritumoral signal intensity	1.3 (0.8-2.3)	0.287
Proximity to critical neurovascular structure	1.2, (0.8-1.8)	0.464

eTable 6. Cumulative incidence rates of intervention and its competing event at 5 and 10 years.					
Event	Factor		At 5 years	At 10 years	P
Intervention	ACCI	0-2	57.7%	66.8%	P<0.001
		3-5	29.6%	32.7%	
		>5	12.1%	13%	
	PS	0-1	41.6%	47.3%	P<0.001
		2-4	12.3%	12.8%	
Mortality	ACCI	0-2	1.4%	3.6%	P<0.001
		3-5	18%	35%	
		>5	49.6%	71.7%	
	PS	0-1	9.9%	20.8%	P<0.001
		2-4	53%	75.1%	
ACCI=age-adjusted Charlson comorbidity index; PS=performance status					

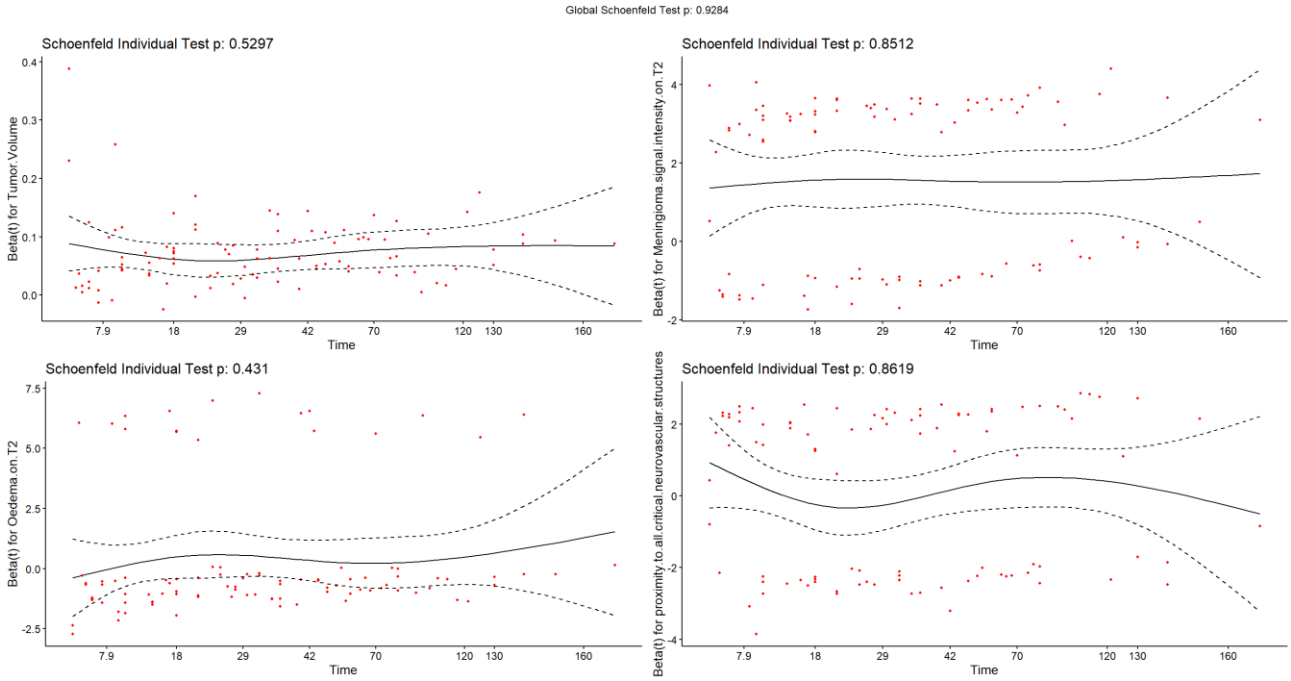
eTable 7. Cumulative incidence rates of disease progression and its competing events at 5 and 10 years.					
Event	Factor		5 years	10 years	P
Disease progression	ACCI	0-2	7.2%	8.7%	P=0.465
		3-5	7.1%	8.7%	
		>5	6.1%	7.4%	
	PS	0-1	7.4%	9.2%	P=0.047
		2-4	5.4%	5.8%	
HD/LTFU/DDFU	ACCI	0-2	17.2%	25.6%	P<0.001
		3-5	27.4%	47.6%	
		>5	51.8%	71.9%	
	PS	0-1	22%	36.7%	P<0.001
		2-4	54.5%	75.8%	
Intervention	ACCI	0-2	48%	51%	P<0.001
		3-5	25%	26.9%	
		>5	10.1%	10.1%	
	PS	0-1	35.1%	37.3%	P<0.001
		2-4	10.6%	11%	
ACCI=age-adjusted Charlson comorbidity index; DDFU=deceased during follow-up; HD=hospital discharge; LTFU=lost to follow-up; PS=performance status.					



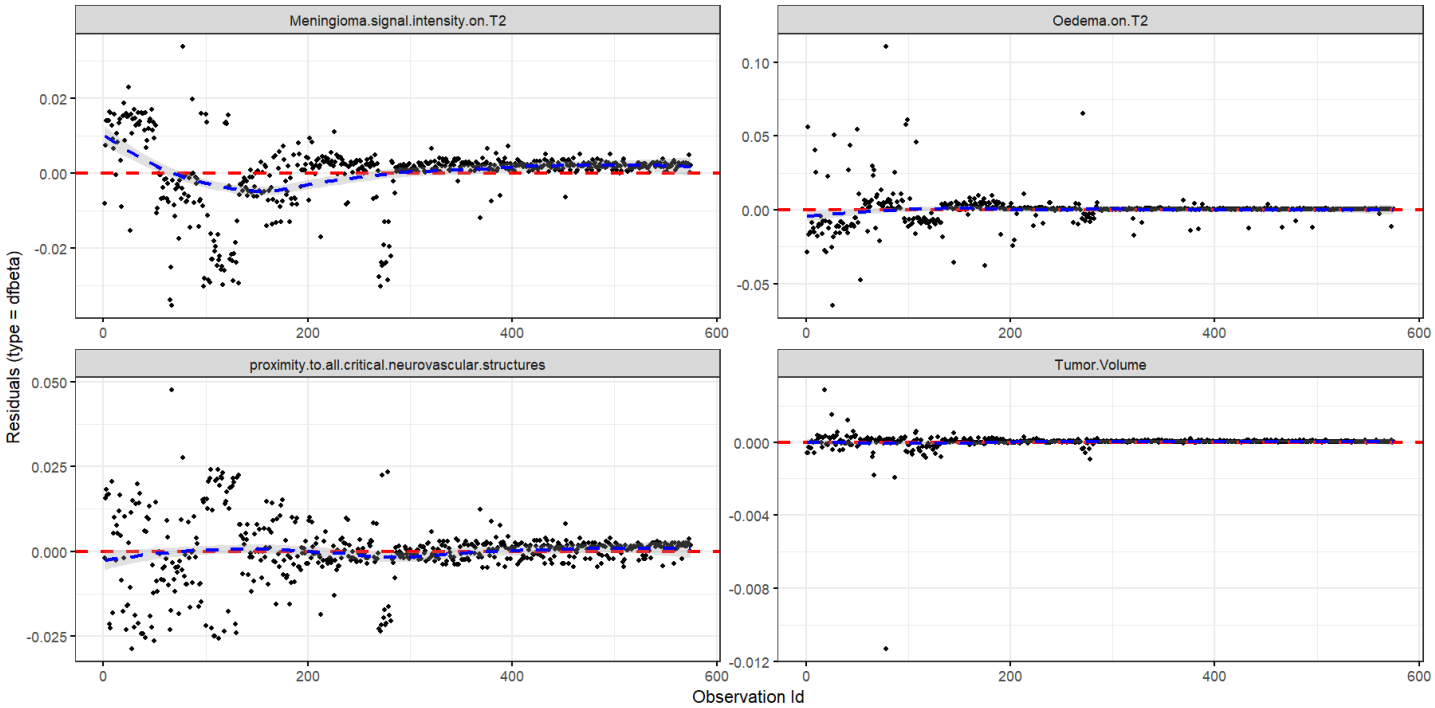
eFigure 1. Kaplan Meier curve showing difference in intervention-free survival between IMPACT risk categories



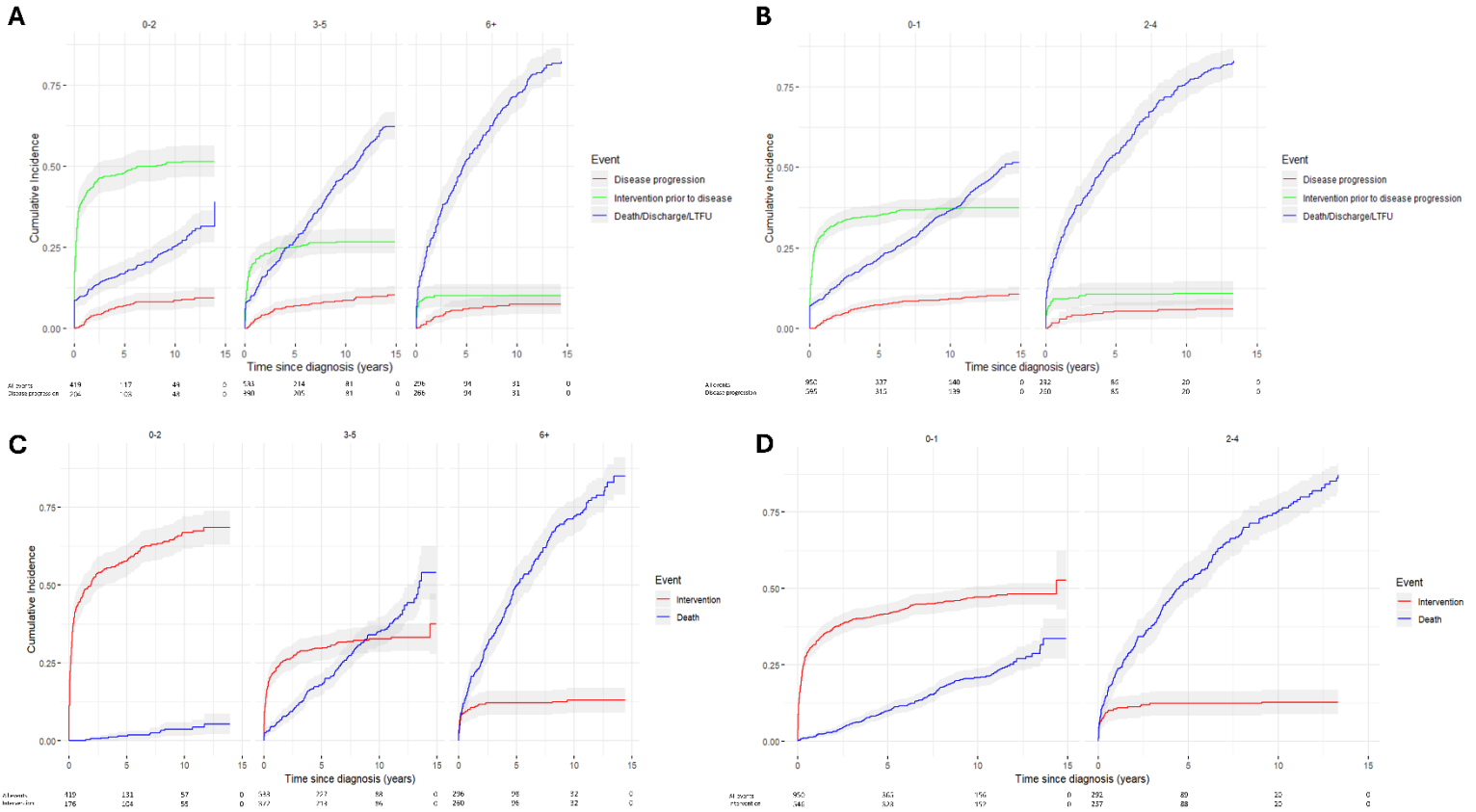
eFigure 2. Kaplan Meier curves showing difference in progression-free survival between IMPACT risk categories across A) centre group 2, B) center group 3 and C) center group 4.



eFigure 3. Schoenfeld residual plot for each of the covariates included in IMPACT. The solid line is a smoothing spline fit to the plot, with the dashed lines representing a ± 2-standard-error band around the fit. None of the plots demonstrated a regular pattern with time, and tests were all not statistically significant. The proportional hazards assumption in model the prognostic model were



eFigure 4. DFBETA panels for each of the covariates included in IMPACT. None of the observations under any covariate had a value of 2 or more indicating the absence of influential observations.



eFigure 5. (A–B) Estimated cumulative incidence curves (solid lines) for disease progression and its competing events with 95% confidence intervals (CIs) (shading) stratified by (A) ACCI and (B) PS. (C–D) Estimated cumulative incidence curves (solid lines) for intervention and mortality with 95% CIs (shading) stratified by (C) ACCI and (D) PS. LTFU: lost to follow-up.